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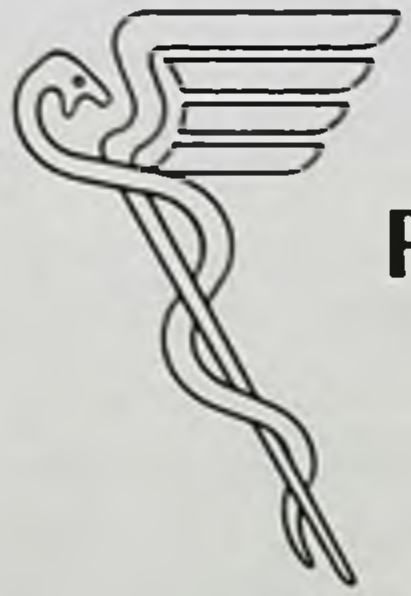

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The YEAR BOOK of

Pediatrics®

1984

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American Journal of Ophthalmology
American Journal of Pediatric Hematology/Oncology
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1. The Newborn

1–1 **Making Heel Pricks Less Painful.** The heel prick technique is frequently used to obtain blood samples from newborn infants. The usual method employing a metal stylet is painful for the infant, and more than one prick may be necessary to obtain adequate blood. Many mothers find the procedure distressing. V. A. Harpin and N. Rutter (Nottingham, England) compared a mechanical lancet, the Autolet, with a manual heel prick in 36 newborns undergoing routine sampling for the Guthrie test and hypothyroid screening. The stylet is in a spring-loaded cartridge that is held against the skin and pierces the skin for 2.4 mm. Both methods were applied by midwives. The results are given in the table. Three infants in the Autolet group did not wake during the procedure, and 2 others remained quiet though awake. A second prick was necessary in 3 infants in the manual group and 2 in the Autolet group.

The Autolet is superior to the manual heel prick for obtaining blood samples from newborn infants. Successful sampling is as likely with the Autolet, and less distress apparently results from this method than from the manual heel prick. The Autolet method is virtually painless. Repeat sampling is less likely to cause soreness of the heel. The Autolet method also could be used on postnatal wards and in neonatal intensive care units.

▶ [The Autolet, or similar spring-loaded lancets, have taken the pain out of finger punctures for children with diabetes. It makes good sense to extend the same courtesy to newborns. The Aug. 15, 1983, issue of *Time Magazine* had an infant on the cover and the feature story was "Babies: What Do They Know? When Do They Know It?" The article summarized all the information that indicates the normal neonate is aware of his surroundings. Harpin and Rutter, the authors of the article presented here, previously demonstrated that emotional sweating occurs in newborns (*Arch. Dis. Child*. 57:691, 1982). They used this technique to determine if the heel pricks elicited an emotional response in the babies. The palms of the infants' hands began to sweat after the babies were stuck with the regular lancet blade but not with the Autolet.

While we have the foot in our hands, it is worth reminding you of the study and illustrations of T. A. Blumenfeld et al. (*Lancet* 1:230, 1979) that demonstrate the safest heel puncture site that will reduce the risk of bone injury developing in the baby. Calcified nodules on the heel are another complication of this oft-repeated procedure (1981 YEAR BOOK, pp. 120–121).

Get your nursery to start using the Autolet.—Remind them that only a "heel" would puncture the foot of a baby painfully.

For more on pain, see the following article.—F.A.O.] ◀

1–2 **Physiologic Stress Reduction by a Local Anesthetic During Newborn Circumcision.** To evaluate the effectiveness of the dorsal penile nerve block in reducing the stress of circumcision on newborns,

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(1–1) Arch. Dis. Child. 58:226–228, March 1983.
(1–2) Pediatrics 71:36–40, January 1983.

Paul S. Williamson and Marvel L. Williamson (Univ. of Iowa, Iowa City) monitored physiologic measurements in 30 healthy full-term infants (including transcutaneous oxygen pressure [PO_2] levels, crying time, heart rate, and respiratory rate) continuously before, during, and after the operation. The mean values for each of the screening criteria by group are shown in the table.

Twenty infants receiving the dorsal penile nerve block with lidocaine (1% Xylocaine) experienced significantly less stress, as evidenced by smaller decreases in transcutaneous PO_2 levels, less time spent crying, and smaller increases in heart rate, than 10 infants circumcised in an identical manner without anesthetic. No complications were observed from injection of the local anesthetic or from cir-

RESULTS FOR THE TWO METHODS OF OBTAINING BLOOD SAMPLES

	Manual heel prick (n = 18)	*Autolet (n = 18)*
Time taken to obtain sample (mean and range)	3 minutes 33 seconds (1 minute–6 minutes 30 seconds)	2 minutes 54 seconds (1 minute–7 minutes)
Time taken for palmar water loss to return to resting levels (mean and range in g/m² per hour)	6 minutes (2 minutes 20 seconds–10 minutes)	2 minutes 54 seconds* (0–8 minutes 40 seconds)
Initial palmar water loss with infant quiet or asleep (mean and range g/m² per hour)	20 (12–31)	18·3 (10–30)
Maximum palmar water loss (mean and range g/m² per hour)	60·7 (27–114)	37·3* (18–85)

*$P < .005$.

(Courtesy of Harpin, V. A., and Rutter, N.: Arch. Dis. Child. 58:226–228, March 1983.)

Selection Criteria	Screening Data* Anesthetized Group (N = 20)	Control Group (N = 10)
Apgar score		
1 min	8.1 ± 0.5	7.9 ± 0.9
5 min	8.9 ± 0.4	9.2 ± 0.4
Birth weight (g)	3,652 ± 384	3,368 ± 250
Age at operation (h)	38.9 ± 9.4	39.0 ± 11.4
Systolic BP before operation (mm Hg)	57.3 ± 13.1	55.2 ± 11.8
Gestational age by Dubowitz score (wk)	39.7 ± 1.2	39.4 ± 1.2
Base line transcutaneous Po_2 (torr)	74.8 ± 9.4	77.4 ± 9.1

*Values are means ± SD.

(Courtesy of Williamson, P. S., et al.: Pediatrics 71:36–40, January 1983. Copyright American Academy of Pediatrics, 1983.)

cumcision. The time of first postoperative voiding was sooner for the anesthetized group than for controls.

The physiologic changes reported show that newborns are responsive to pain, but these changes do not reflect fully all aspects of the pain response. Inasmuch as dorsal penile nerve block has a low complication rate, is simple to learn, and adds little time or expense to the procedure, it should be considered for every infant undergoing circumcision if it proves to be as effective as the physiologic data indicate.

The physiologic changes induced by preoperative handling were greater than the physiologic response to injection of the anesthetic. Perhaps changing the method of restraint to swaddling instead of strapping to a restraint board or warming the scrub solution would reduce the response. Inasmuch as the difference between the anesthetized group and controls for the 30-second interval during the injection was significant only in crying and did not extend beyond the immediate event, pain caused by the injection is not sufficient to condemn its use.

This study has implications for other procedures performed on unanesthetized infants.

▶ [Speaking of sweaty palms, efforts to demonstrate psychological consequences for the newborn infant as a result of this barbaric procedure have produced equivocal results (Marshall, R. E., et al.: *Early Hum. Dev.* 7:367, 1982), but that should not justify the continued "rape of the phallus." Providing information to the parents regarding the risks of the procedure and the fact that there are no valid medical indications for circumcision apparently does not deter families from requesting circumcision for their sons (Maisels, M. J., et al.: *Pediatrics* 71:454, 1983). Studies suggest that parents usually state that medical reasons and their own personal preference for the child were the major reasons for deciding in favor of circumcision (Stein, M. T., et al.: *J. Fam. Pract.* 15:47, 1982).

Maybe if we labeled this procedure for what it really is—cosmetic surgery—the insurance companies would no longer reimburse physicians for performing the circumcision. Then we could see its real popularity. Nevertheless, if it is going to be done, it should be done as painlessly as possible, and the idea of a nerve block seems reasonable.—F.A.O.] ◀

1–3 **Optimal Position for a Spinal Tap in Preterm Infants.** Christine A. Gleason, Richard J. Martin, John V. Anderson, Waldemar A. Carlo, Kathleen J. Sanniti, and Avroy A. Fanaroff (Cleveland) attempted to determine the best position for performing spinal taps on preterm infants in order to minimize resultant morbidity. Seventeen healthy preterm infants, 6 boys and 11 girls with a mean birth weight of 1.5 kg and a mean gestational age of 31.5 weeks, were studied. At the time of study they weighed 1.6 kg and were aged 6–46 days. They were placed in three spinal tap positions, the conventional lateral recumbent position with hip and neck flexion or with partial neck extension, and the sitting position with head support and flexion of the spine and hips, for 5-minute periods. Five other infants were monitored during an actual spinal tap to rule out meningitis. Three were examined in the flexed position and 2 while upright. Their mean birth weight was 1.5 kg, and the mean gestational age was 31 weeks. They were examined 1–12 days after birth.

The transcutaneous P_{O_2} decreased as the infants were placed in each of the three study positions (table). The mean reduction was greatest in the flexed position (Fig 1–1). The transcutaneous P_{CO_2} showed a small but significant increase in the flexed position only. The increase exceeded 5 mm Hg in 4 infants. Values recovered slowly, in contrast to the rapid recovery of P_{O_2} levels. Positioning had highly variable effects on ventilation, and the greater fall in P_{O_2} in the flexed position was not associated with a greater decrease in ventilation compared with the upright position. Comparable blood gas changes were noted in the infants monitored during an actual spinal tap. The transcutaneous P_{O_2} fell 10–27 mm Hg in infants in the flexed position, while the P_{CO_2} increased by 3.0–3.5 mm Hg. The P_{O_2} remained stable in infants tapped while upright, and the P_{CO_2} rose by 1 mm Hg.

A consistent adverse effect on transcutaneous P_{O_2} is noted in the flexed position for the spinal tap. Spinal taps done in the widely ac-

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EFFECT OF SPINAL TAP POSITION ON TRANSCUTANEOUS P_{O_2} (TcP_{O_2}), TRANSCUTANEOUS P_{CO_2} (TcP_{CO_2}), AND MINUTE VENTILATION ($\dot{V}_I$)*

	$TcPO_2$ (n = 17) [mm Hg]		$TcPCO_2$ (n = 17) [mm Hg]		$\dot{V}_I$ (n = 7) [mL/min]	
	Control	Study	Control	Study	Control	Study
Flexed	72 ± 12	44 ± 12†	55 ± 7	58 ± 9‡	660 ± 260	600 ± 340
Extended	71 ± 11	53 ± 15†	57 ± 9	57 ± 9	690 ± 170	620 ± 190
Upright	73 ± 12	58 ± 13†	56 ± 8	57 ± 9	710 ± 360	670 ± 270

*Means ± SD.
†$P < .001$.
‡$P < .005$.
(Courtesy of Gleason, C. A., et al.: Pediatrics 71:31–35, January 1983. Copyright American Academy of Pediatrics, 1983.)

(1–3) Pediatrics 71:31–35, January 1983.

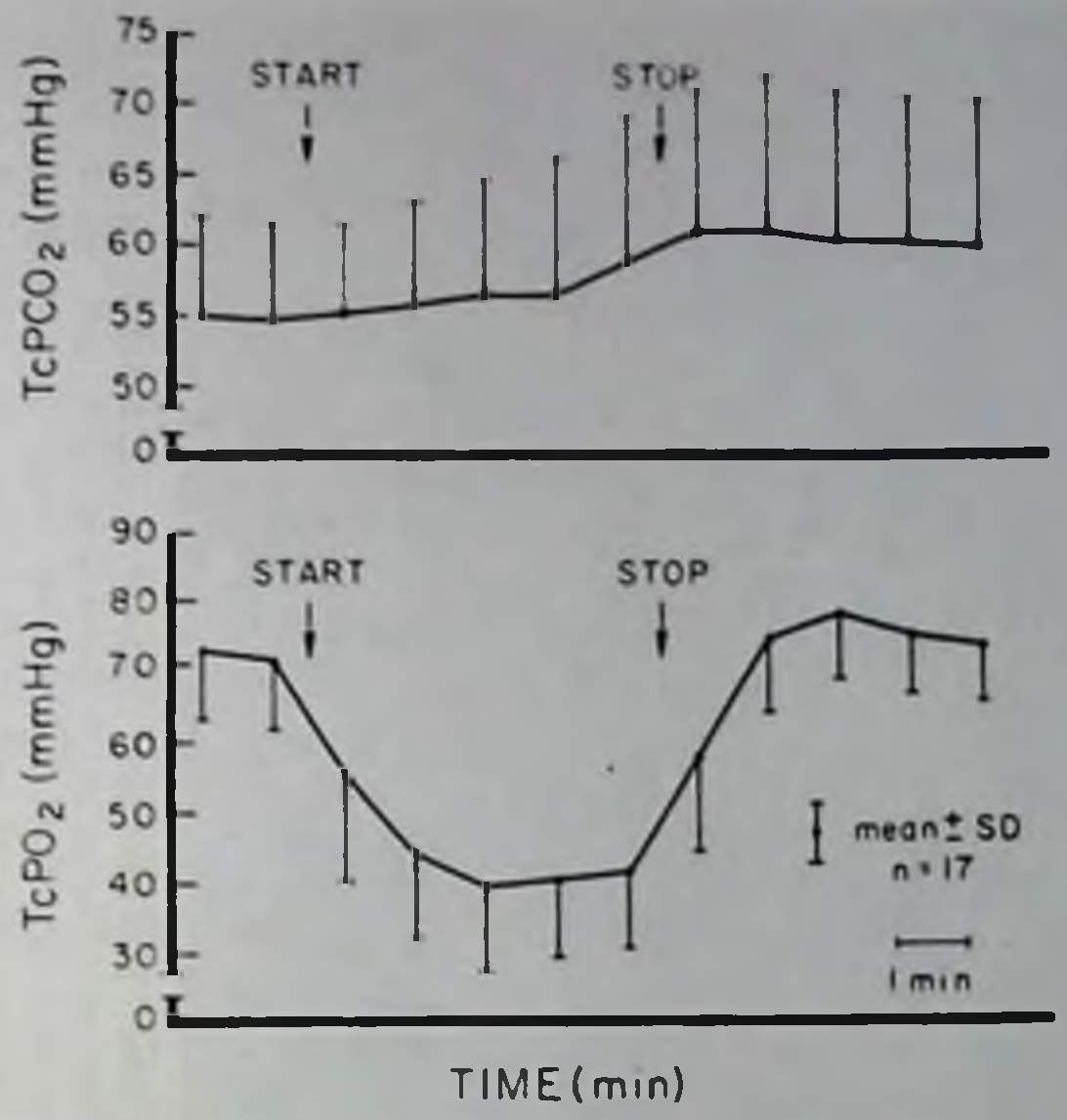

Fig 1–1.—Overall effect of placement in lateral recumbent flexed position on mean transcutaneous P_{O_2} (TcP_{O_2}) and P_{CO_2} (TcP_{CO_2}) in 17 preterm infants. Position was maintained for the 5-minute period indicated between arrows. (Courtesy of Gleason, C. A., et al.: Pediatrics 71:31–35, January 1983. Copyright American Academy of Pediatrics, 1983.)

cepted lateral position with the neck flexed carry a real risk of morbidity in preterm infants. Either neck extension should be used or the tap be done with the infant upright.

▶ [Anyone who has had the unpleasant experience of having a small infant suddenly stop breathing while a lumbar puncture is being performed will welcome the wisdom and recommendations of this study.

Speaking of cerebrospinal fluid, there is a growing appreciation, as a result of the use of cytocentrifuge techniques, that the predominant cell in the cerebrospinal fluid of most infants is the macrophage (Pappu, L. D., et al.: *Am. J. Dis. Child.* 136:297, 1982); and Dalens, B., et al.: *Acta Cytol. (Baltimore)* 26:395, 1982). These macrophages, or histiomonocytes, may be "activated" or "inactive," and the number of inactive forms may be an indicator of long-term brain damage. The recognition of the predominance of the macrophage was made possible by the use of low-speed cytocentrifugation that leaves these cells intact. I suspect that cytology of cerebrospinal fluid will become an art and will be used in conjunction with brain imaging techniques to make more accurate neurologic predictions.—F.A.O.] ◀

1–4 **Ultrasonic Detection of Complications Following Umbilical Arterial Catheterization in the Neonate.** David A. Oppenheimer, Barbara A. Carroll, and Karen E. Garth (Stanford Univ.) report that 71 neonates with umbilical arterial catheters received serial real-time ultrasound examinations in order to identify catheter-associated thrombosis and prospectively study its natural history. Patients were scanned at the cribside with minimal disturbance.

Twelve (17%) of the infants had clinically evident signs of vascular compromise. Catheters had been in place for 2–35 days (average, 11 days) before ischemic symptoms developed. Ultrasound detected ab-

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(1–4) Radiology 145:667–672, December 1982.

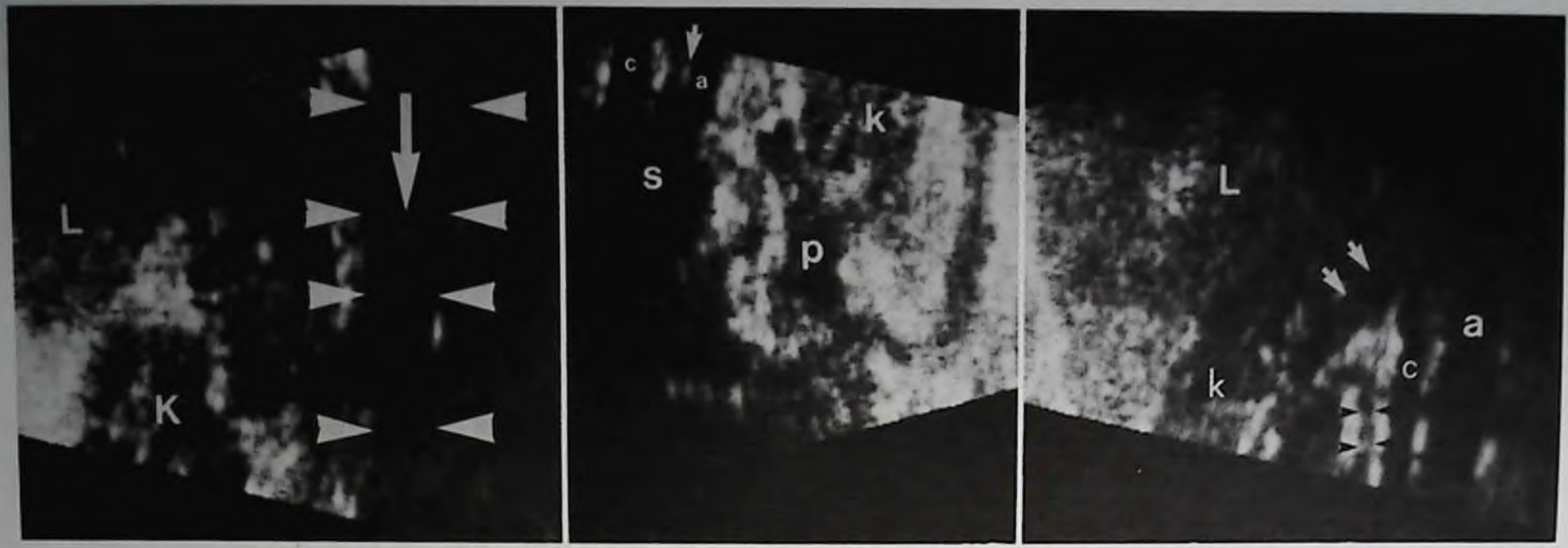

Fig 1–2.—Ultrasound scan taken after removal of catheter in newborn boy with hypertension and microhematuria. **Left,** coronal scan through the right flank reveals a thin, linear, intraluminal echo *(arrow)* within the aorta *(arrowheads)*. On real-time examination, this "flap" oscillated to and fro in the pulsatile aorta; *K*, right kidney; *L*, liver. **Center,** transverse scan through the left flank reveals a persistent linear echo *(arrow)* within the aortic lumen *(a)*. On real-time examination, this "flap" oscillated from left to right within the aortic lumen; *c*, inferior vena cava; *s*, spine; *p*, psoas muscle; *k*, left kidney. **Right,** coronal scan through the right flank 3 days later reveals an echo-free aortic lumen; *a*, aorta; *c*, inferior vena cava; *k*, right kidney; *L*, liver; *white arrows*, right renal vein; *arrowheads*, ureter. (Courtesy of Oppenheimer, David A., et al.: Radiology 145:667–672, December 1982.)

normal intravascular echoes or lack of expansile pulsation in 10 of these 12 infants (83%). Nine patients had fixed echogenic collections along the vascular wall. Fixed lesions appeared as flat echogenic plaques or as focal convex bumps on the vascular wall. A single mobile abnormality was identified in the aortic lumen (Fig 1–2); this echogenic flap intermittently occluded the renal artery origins and may have caused the hypertension noted in this patient. Abnormal echogenic foci were consistent with thrombus and intimal dissection.

Two infants had normal ultrasound examinations despite clinical symptoms of ischemia. Two infants without clinical evidence of vascular compromise had ultrasonic findings consistent with thrombus. The ultrasonically detected abnormalities persisted from 2 to 70 days; many persisted long after the clinical signs of ischemia had resolved.

Real-time ultrasound is a valuable tool with which to assess thrombotic complications associated with umbilical arterial catheterization.

1–5 **Anticoagulant Therapy by Continuous Heparinization in Newborn and Older Infants.** Thrombotic complications of intensive therapy are relatively common in newborn and older infants. Marilyn M. McDonald and Wm. E. Hathaway (Univ. of Colorado) examined the metabolism and anticoagulant effect of heparin in 15 infants (12 neonates and 3 older infants), who received continuous infusions for up to 4 weeks for large-vessel thrombosis. Heparin and antithrombin III assays were performed, and the clotting time was measured with Laidlaw tubes as shown in Figure 1–3.

Infants with the most significant thromboses, many of them delivered near term, had the highest heparin clearance rates. Laidlaw clotting times did not correlate significantly with size at birth or with postnatal age. The coefficient of correlation of the Laidlaw clotting time with the plasma heparin concentration was 0.47 (Fig 1–4). Base-

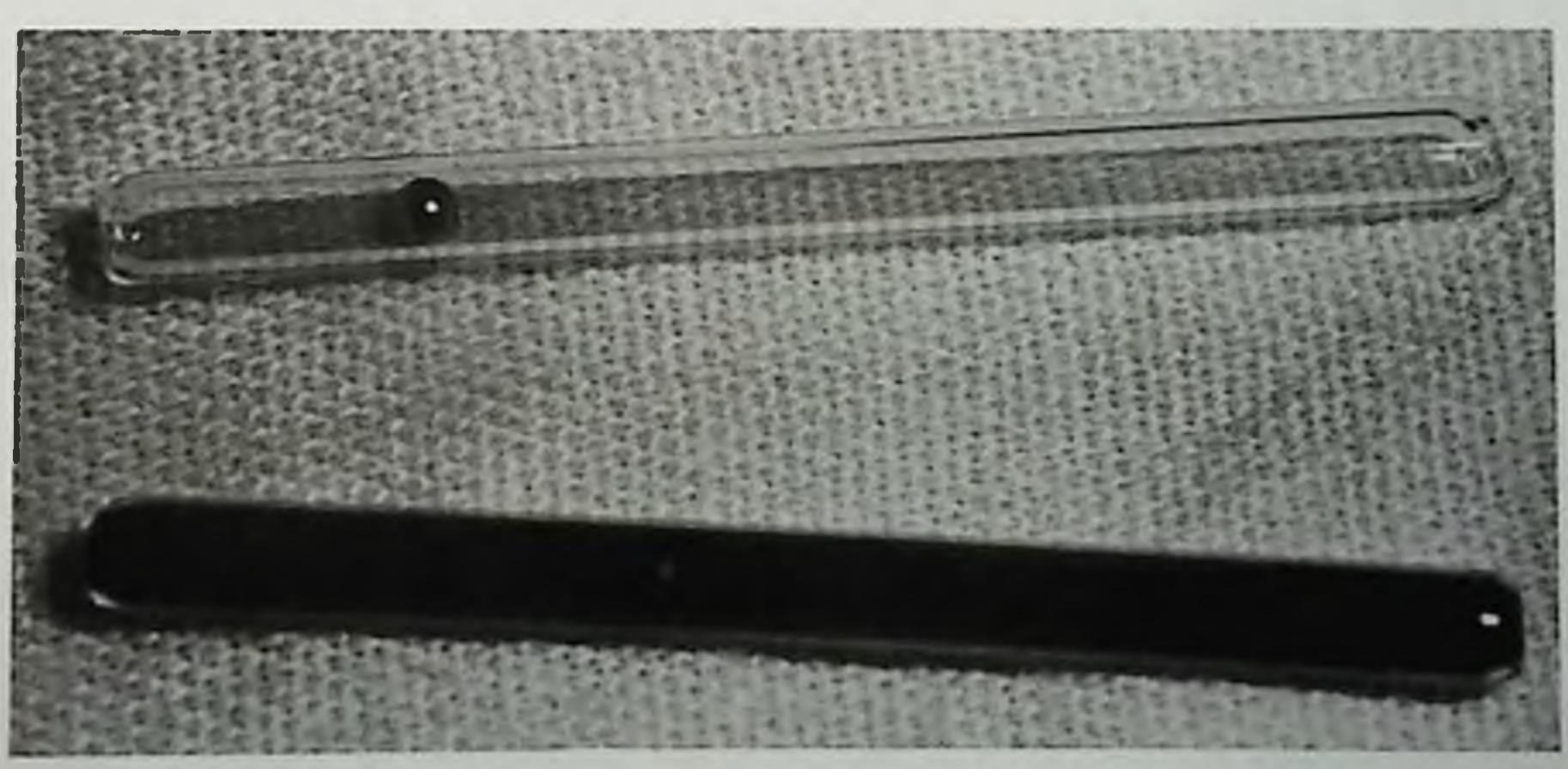

Fig 1–3.—Laidlaw clotting time tubes. Note metal ball in both empty and blood-filled tubes. (Courtesy of McDonald, M. M., and Hathaway, W. E.: J. Pediatr. 101:451–457, September 1982.)

(1–5) J. Pediatr. 101:451–457, September 1982.

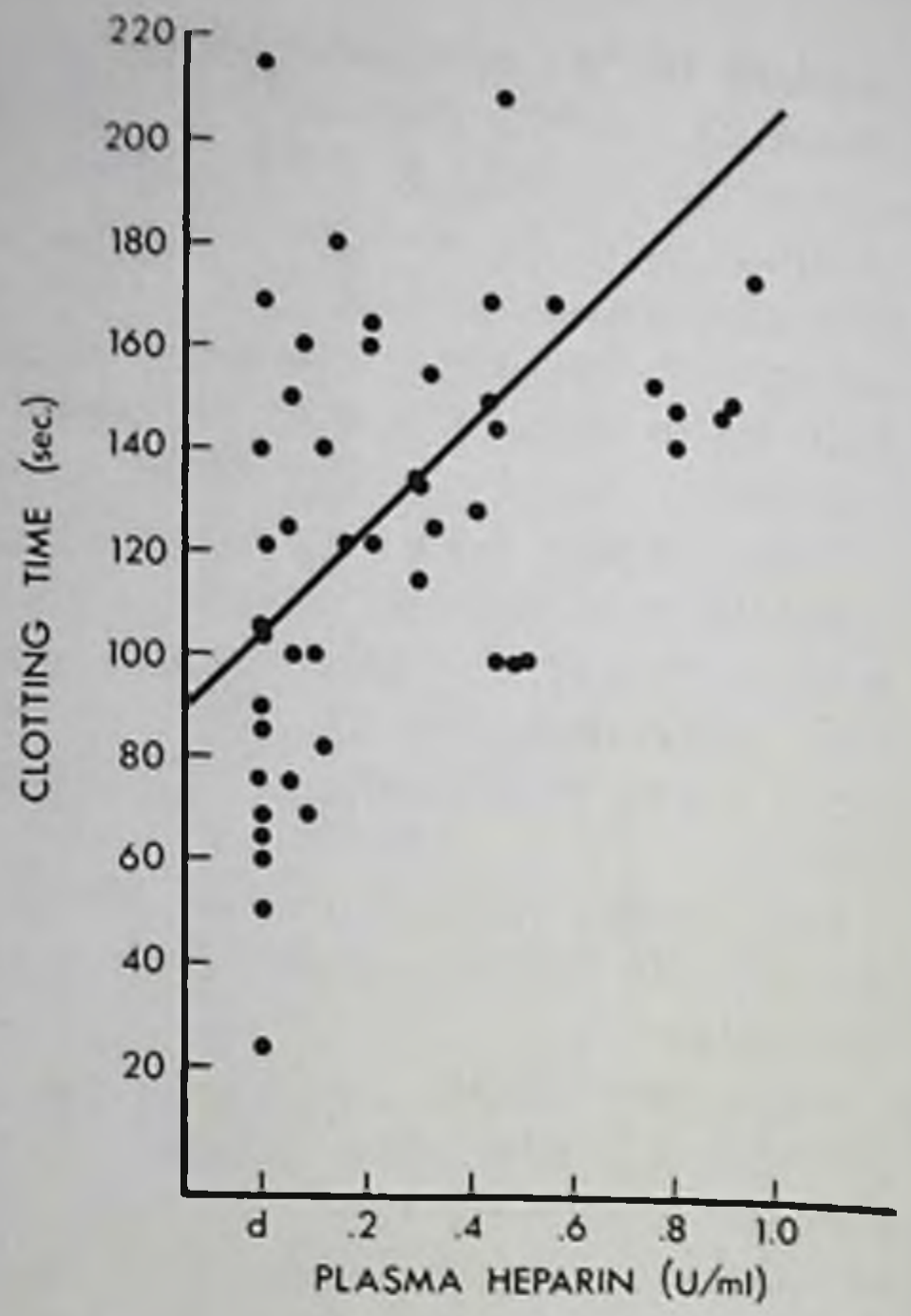

Fig 1–4.—Relation of Laidlaw clotting time to plasma heparin concentrations in study infants; $r = .47$. (Courtesy of McDonald, M. M., and Hathaway, W. E.: J. Pediatr. 101:451–457, September 1982.)

line clotting times usually were shortened in the face of active major thrombosis, except when consumption coagulopathy was present, as in 2 infants. In several instances, when the clotting time was not prolonged despite an apparently adequate infusion, subtherapeutic to undetectable plasma heparin concentrations were documented. All patients but 1 had resolution of thrombi. Only 1 infant received an excessive dose of heparin and had oozing from puncture sites. Catheter-related thrombosis continued to resolve after heparin was discontinued in this infant.

After baseline coagulation values are obtained, a bolus of 50 units of heparin per kg is given, followed by 20 units per kg per hour for small preterm infants and 25 units per kg per hour for larger preterm and older infants. If a definite heparin effect is not observed at 5 hours, the dose is increased by 5 units per kg per hour. Clotting tests are repeated daily as soon as an effect is evident. Heparin should be continued for 48 hours after thrombus resolution. The Laidlaw clotting time is used as a guide to the heparin effect and to prevent excessive anticoagulation, but it cannot be used to indicate heparin concentrations.

► [Doctor James J. Corrigan, Jr., Professor of Pediatrics and Chief, Section of Pediatric Hematology-Oncology, the University of Arizona Health Sciences Center, prepared the following comment:

"This very nice investigation provides us with data about therapeutic heparinization of newborns with thrombotic disease. By using a bolus dose followed by continuous intravenous administration of heparin, these investigators have given us insight into the metabolism of the drug in newborns with thrombosis. They also have described a clotting time method using a neat capillary glass tube that contains a small movable metal ball (Laidlaw tube). Doctor Hathaway tells me that just about anybody

can be taught to use this method, with the exception of those with severe presbyopia, the author notwithstanding. In their laboratory, less than 100 seconds meant too little heparin and greater than 200 seconds, too much heparin. Unfortunately, there was no correlation of the clotting times in between these numbers with the actual heparin concentration; thus, more sensitive tests are needed when desired. Nevertheless, the Laidlaw clotting time would seem to be an easy, reproducible screening test for the extremes. (As far as I am aware, the tubes are not manufactured in the United States; you must obtain them from R and G Finnie, 16 Binghill Road, Milltimber, Aberdeen, Scotland.)

"By using a heparin assay, the authors' goal was to achieve a plasma heparin concentration of 0.3–0.5 units/ml. This concentration has been recommended by other investigators to be necessary to provide optimal anticoagulation in patients with thrombotic disease. To achieve this, McDonald and Hathaway found it necessary to administer 27 units/kg/hour (range, 16–25) as a continuous infusion after a bolus of 50 units/kg. By using clinical response and heparin concentration, they found that infants with the most significant thrombosis had the highest clearance rates for heparin. Although the authors measured the partial thromboplastin time (PTT), they found it unreliable in their patients.

"Heparin, a negatively charged polysaccharide of 3,000–5,700 molecular weight, must interact with a plasma α_2-globulin (antithrombin III) in order to exhibit its anticoagulant properties. Although it is a very potent inhibitor of thrombin, it also neutralizes other activated coagulation factors, such as factors XIIa, XIa, Xa, and IXa. It has been known for over 30 years that less heparin is required to prevent clotting (i.e., 0.5–0.15 units/ml of plasma) than to treat thrombotic disease (0.3–0.5 units/ml). The metabolism of heparin is also dose dependent, in that the higher the dose, the longer the anticoagulant activity lasts in the plasma. Thus, plasma levels of antithrombin III, the presence of thrombosis, and the dose participate in the actual anticoagulant level achieved. I agree with the authors that the PTT is difficult to use to monitor heparin activity in the newborn. The PTT is very sensitive to heparin and is influenced by the levels of a number of coagulation factors that may be low physiologically or because of disease in the preterm and term infant. If an assay for heparin is not available, the thrombin clotting time (TCT) is reliable except in disseminated intravascular coagulation (DIC). The TCT is not influenced by the levels of plasma coagulation factors except fibrinogen. There is a linear relationship between the prolongation of the TCT and the heparin concentration; it will be moderately prolonged when heparin is within the anticoagulant range. An abnormal TCT will occur in patients with hypofibrinogenemia and/or very high levels of fibrin split products as may be seen in DIC. In this circumstance, serial determination of the consumption factors (i.e., fibrinogen) and clinical assessment will be a better guide to the effectiveness of heparinization.

"Although there are no studies that show that continuous administration of heparin is any better than an intermittent schedule for treating thrombotic disease, there do appear to be less side effects, especially bleeding, when using the continuous schedule."] ◀

1–6 **Clinical Estimation of Liver Size in the Normal Neonate.** Leonard E. Weisman, Nancy Cagle, Richard Mathis, and Gerald B. Merenstein (Fitzsimons Army Med. Center, Aurora, Colo.) established norms for the clinical estimation of liver size in 100 consecutive healthy neonates of 37–42 weeks' gestational age, at age 24–72 hours of life. Nearly 90% were white. Overall, 20% were delivered by cesarean section. Twenty-three percent were large and 7% were small for gestational age. Estimates were made independently by a pediatrician and a pediatric nurse practitioner, using percussion, palpation, and scratch test techniques.

Intraobserver variability of estimates on days 1 and 3 was least with either percussion of the upper border and palpation of the lower

(1–6) Clin. Pediatr. 21:596–598, October 1982.

border or with percussion of both borders. With the latter method, coefficients of correlation were 0.72 and 0.74 for the 2 workers, respectively. Interobserver variability was least with the same methods. The coefficient of correlation with percussion of both borders was 0.78. Liver span could not be related to birth weight or length, head circumference at age 3 days, chest or abdominal circumferences, gestational age, surface area, or ponderal index. No significant sex effect was apparent. On day 1 the liver span was 5.65 cm, with 95% confidence limits of 4.25–7.00 cm. In 3 infants the lower border could not be determined by percussion. The spleen was palpable in 23% of the neonates.

The mean liver span in healthy term neonates in this study on the first day of life was 5.65 cm. The liver span is best assessed by percussing both borders, or by percussing the upper border and palpating the lower border.

1–7 **Transient Fetal Hydrops and "Prune Belly" in One Identical Female Twin.** Prune belly is most common in males and is usually accompanied by urinary tract abnormalities. Mark Lubinsky and Peggy Rapoport (Children's Meml. Hosp., Omaha, Neb.) observed this condition in one female twin with a normal urinary tract.

CASE 1.—Firstborn girl weighed 1.52 kg and had a length of 43 cm and a head circumference of 28.5 cm when born at 34 weeks' gestation. One-minute Apgar score was 5, with bradycardia, irregular breathing, cyanosis, and prune-belly abdomen (Fig 1–5). Disorders occurring during the 5-week hospital course included hyaline membrane disease, anemia, hyperbilirubinemia, right-sided pneumothorax, and patent ductus arteriosus. At 21 months, height was 85 cm and weight was 11.34 kg. The rectus abdominis was normal but the lateral abdominal musculature was hypoplastic, with bulging flanks. Motor and language skills were similar to those of her sister. Pyelography showed normal kidneys, pelvicaliceal system, and bladder. The ureters showed some tortuosity but no dilatation.

CASE 2.—Secondborn girl weighed 2.2 kg and had a length of 48.5 cm and head circumference of 32.5 cm. Both Apgar scores were 8. After a few minor problems, her health has been good and growth and development normal. She is now slightly smaller than her sister.

Polyhydramnios was present from late in the second trimester until about 5 weeks before delivery. Three episodes of painful bleeding occurred. After premature rupture of the membranes and labor at 34 weeks' gestation, the twins were delivered vaginally. Ultrasound studies performed serially after the 22d week showed transient fetal hydrops in the twin with prune belly.

This case showed several remarkable features. There is only one previous report of fetal ascites with prenatal resolution. Prune belly in females is rare, and the absence of urinary tract anomalies is unusual. The discordance for ascites and prune belly in identical twins is of interest. The findings can be explained as sequelae of a twin-twin transfusion, a common event in monochorionic twins. The findings implicate prenatal abdominal distention in at least some cases of abdominal muscle laxity. Prune belly may not always be a resid-

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(1–7) N. Engl. J. Med. 308:256–257, Feb. 3, 1983.

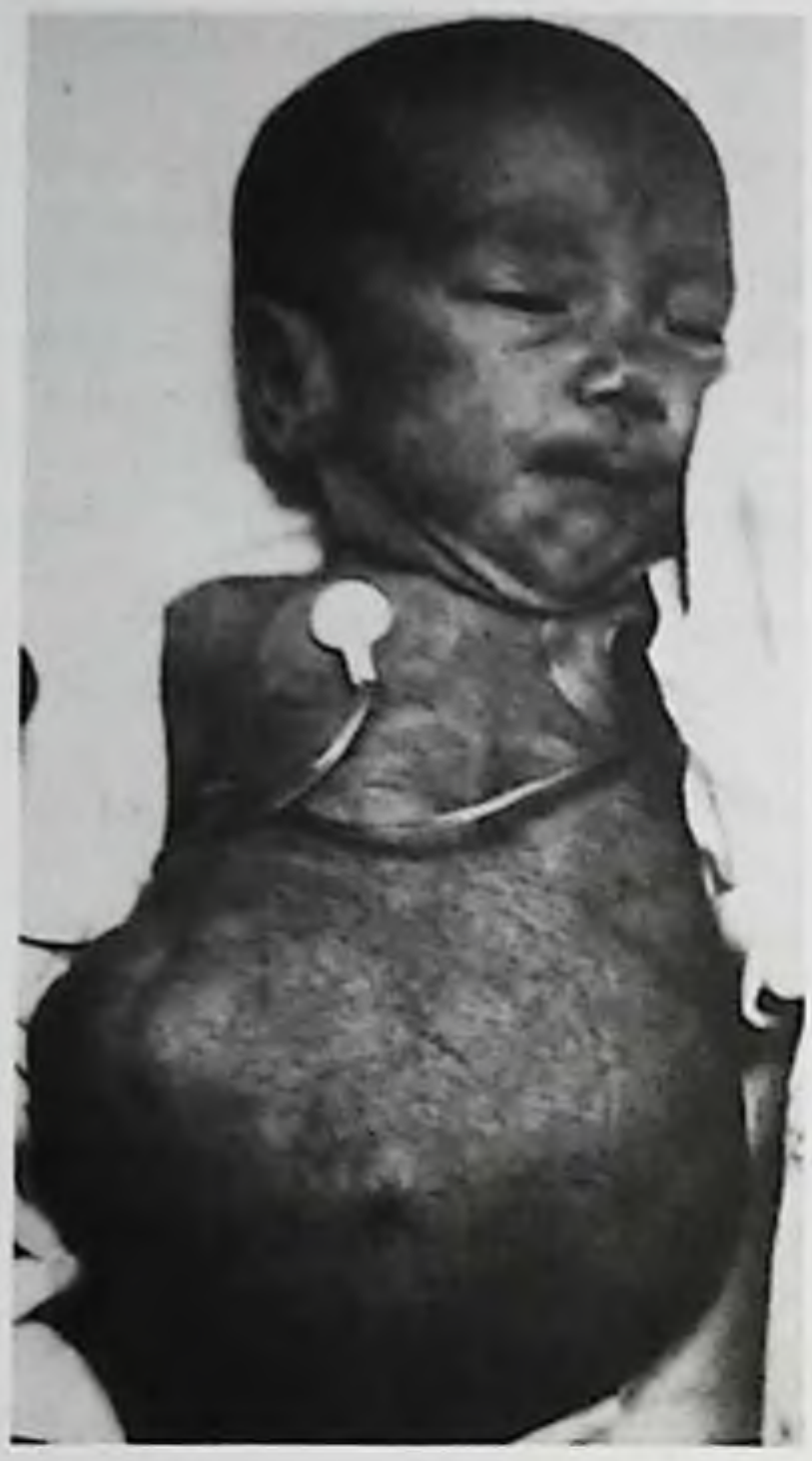

Fig 1–5.—Abdominal distention in Twin 1 at age 1 month. (Courtesy of Lubinsky, M., and Rapoport, P.: N. Engl. J. Med. 308:256–257, Feb. 3, 1983.)

uum. The degree and type of damage may depend on the rapidity of the change, fetal age, or other predisposing factors.

► [This is an important observation, transient fetal hydrops, and an imaginative hypothesis to explain the "prune belly." At least two other examples of this phenomenon have been described. E. Mueller-Heubach and J. Mazer (*Obstet. Gynecol.* 61:253, 1983) reported data on two patients with sonographically documented fetal ascites that subsequently disappeared. At birth, the infants had loose abdominal walls with diastasis of the rectus muscles and protruding flanks. The genitourinary tracts of both infants were normal. No obvious reason was apparent to explain what happened. With the increasing use of sonography during the course of pregnancy, more and more amazing things will be discovered.

For more, much more, on nonimmune fetal hydrops, see the 1983 YEAR BOOK, pages 9–11 and 237–238. For more on "prune belly," see the review of data on 47 boys with this syndrome by C. R. J. Woodhouse (*Arch. Dis. Child.* 57:856, 1982) and Chapter 6, "The Genitourinary Tract," in this edition.—F.A.O.] ◄

1–8 **Hematocrit of Reconstituted Blood for Exchange Transfusion in Newborn Infants** was investigated by Cirilo Sotelo-Avila, Robert T. Brouillette, Jr., and Sherri D. Gould (Northwestern Univ.). Maintenance of an adequate hematocrit is necessary in newborn infants given exchange transfusions because of the increased metabolic rate of neonates, which may be augmented by prematurity or illness, and because anemia may exacerbate left-to-right shunting and contribute to heart failure in infants with congenital heart disease. The hematocrit immediately after a standard double blood volume exchange transfusion closely approximates that of donor blood. The hematocrit

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(1–8) J. Pediatr. 100:971–972, June 1982.

of fresh whole blood is often too low, whereas that of packed red blood cells is often too high for exchange transfusion.

Packed red blood cells can be reconstituted with fresh frozen plasma to achieve a desired hematocrit. Reconstitution was done on 35 packed red blood cell units with hematocrits of 65% to 92%, and a value within 3% of the desired hematocrit always was obtained. The weight (volume) of fresh frozen plasma (W_{FFP}) needed is: $W_{FFP} = \left(\frac{H_{PRC}}{H_{RB}} - 1\right)W_{PRC}$, where H_{PRC} is the hematocrit of packed red blood cells, H_{RB} is the desired hematocrit of reconstituted blood, and W_{PRC} is the weight of packed red blood cells. The mean difference between the predicted and the measured hematocrits was 1.1.

This approach permits precise control of the hematocrit of donor blood used in exchange transfusion and therefore of the neonate's hematocrit after transfusion. Reconstituted blood is a suitable alternative to fresh whole blood for use in exchange transfusion.

1–9 **Serum Potassium Changes Following Packed Red Cell Transfusions in Newborn Infants.** Hyperkalemia in neonates can lead to serious cardiac arrhythmias and reportedly may develop after exchange transfusion of banked blood. Elevated potassium levels also can occur in fresh whole blood and in packed cells reconstituted with

TABLE 1.—Effect of Packed Cell Transfusions on Serum Potassium and Hematocrit in Infants

Infant	Transfusion	Potassium (mEq per l) Before Transfusion	Potassium (mEq per l) After Transfusion	Hematocrit (%) Before Transfusion	Hematocrit (%) After Transfusion
A	1	5.9	6.0	40	45
	2	7.8	7.9	41	40
	3	3.8	4.2	36	37
B	1	4.3	3.9	42	46
	2	6.1	4.4	42	50
	3	4.7	4.9	42	49
	4	4.4	3.7	44	47
C	1	5.5	5.0	38	33
	2	4.4	4.8	36	46
D	1	4.3	5.3	45	50
E	1	5.7	4.3	41	51
Mean		5.1	4.9*	41	45†
± SD		±1.2	±1.2	±2.9	±5.8

*$P > .05$.
†$P > .01$.
(Courtesy of Batton, D. G., et al.: Transfusion 23:163–164, Mar.–Apr. 1983.)

(1–9) Transfusion 23:163–164, Mar.–Apr. 1983.

TABLE 2.—POTASSIUM INCREASES IN STORED PACKED RED BLOOD CELLS

	Day After Drawing						
	1	2	3	4	5	6	7
Numbers of units	4	11	6	10	8	5	3
Potassium* (mEq per liter)	7.6 ± 1.3	16.2 ± 4.3	14.2 ± 5.1	18.1 ± 4.7	21.3 ± 7.2	19.9 ± 5.6	23.1 ± 7.0
Range	(6.5–9.1)	(10.1–25.6)	(7.3–20.6)	(13.5–27.0)	(12.0–32.5)	(11.8–25.5)	(15.4–30.3)

*Mean ± SD.
(Courtesy of Batton, D. G., et al.: Transfusion 23:163–164, Mar.–Apr. 1983.)

fresh frozen plasma. D. G. Batton, M. J. Maisels, and G. Shulman (Hershey Med. Center, Hershey, Pa.) examined the effect of packed red blood cell transfusions on serum potassium levels in infants having umbilical or radial artery catheters in place. Transfusions were given to correct anemia through either the umbilical artery or a peripheral vein. The 5 infants in the study had a mean gestational age of 33 weeks and a mean birth weight of 1,920 gm.

The results of 11 transfusions in the 5 infants are presented in Table 1. The mean pretransfusion and posttransfusion potassium levels were 5.1 and 4.9 mEq/L, respectively. Infant A had an intraventricular hemorrhage that probably explains the elevated potassium level

present before the second transfusion. The plasma potassium concentrations in 47 gravity-sedimented units of banked blood are shown in Table 2. A marked increase with age was noted, but even blood less than 48 hours old had a significantly elevated potassium concentration. The mean hematocrit of the infants increased significantly after the transfusions.

Markedly elevated plasma potassium levels occur in gravity-sedimented packed cells, even in blood less than 48 hours old. The effect of transfusions on the serum potassium level, however, was negligible in infants in the present study. Hyperkalemia may occur from packed red blood cell transfusions, but it would not appear to be a significant problem in newborn infants who receive transfusions of 10 ml of packed red blood cells per kg.

1–10 **Acquired Immunodeficiency in an Infant: Possible Transmission by Means of Blood Products.** There is concern about the possible role of a transmissible agent in the etiology of acquired immunodeficiency syndrome (AIDS) in hemophilic patients who repeatedly receive blood products. Arthur J. Ammann, Morton J. Cowan, Diane W. Wara, Peggy Weintrub, Selma Dritz, Howard Goldman, and Herbert A. Perkins (San Francisco) describe an infant with features of AIDS and *Mycobacterium avium intracellulare* infection who received multiple blood products in the neonatal period.

Boy, aged 20 months, had been delivered by cesarean section at 33 weeks' gestation, weighing 2,850 gm, to a woman with a history of Rh sensitization. He was jaundiced at birth and received 6 two-volume exchange transfusions in the first 5 days. Besides platelet transfusions and partial transfusions to correct anemia, the infant received blood products from 18 donors during 8 weeks in the hospital. All blood was irradiated before being administered. Hepatosplenomegaly was present at age 4 months, and recurrent otitis media, thrush, and *Candida* dermatitis were present at 6 months, when weight loss and developmental retardation were first observed. Vomiting and diarrhea began at 10 months, when hepatitis was diagnosed. Jaundice developed at age 13 months. Immunologic findings are given in the table. Liver biopsy showed periportal fibrosis with some giant cells but no evidence of active hepatitis. Malabsorption, Coombs-positive hemolytic anemia, neutropenia, and thrombocytopenia with antiplatelet antibodies were found at age 15 months. Bleeding and hemolysis were controlled by prednisone therapy. At age 18 months the infant was admitted for treatment of *M. avium* infection. He died at age 2 years with *Pneumocystis carinii* pneumonia. Cultures had remained positive for *M. avium*.

This patient had several features of AIDS, which is attributed to transmission of an infectious agent through administration of blood products. It is possible, however, that the infant was born with a primary immunodeficiency disorder. Prospective studies are needed to determine the incidence of AIDS in patients receiving transfusions, particularly infants, immunosuppressed patients, and those given multiple blood products. Avoidance of the use of blood products obtained from persons with the potential to transmit AIDS should be seriously considered.

(1–10) Lancet 1:956–958, Apr. 30, 1983.

Age (mo)	%OKT4	%OKT8	OKT4/8	PHA (cpm)	MLC (cpm)
10	ND	ND	ND	ND	ND
14	ND	ND	ND	6800	900
18	34	34	1·2	11 230	480
Normal range	29±8	29±8	1·9±0·7	>15 000	>5000

•OKT4, helper-inducer cells; OKT8, suppressor-cytotoxic cells; PHA, phytohemagglutinin stimulation of peripheral blood lymphocytes; MLC, mixed lymphocyte culture; ND, not done.
†Values are normal at 10 months and increased at 14 months.
(Courtesy of Ammann, A. J., et al.: Lancet 1:956–958, Apr. 30, 1983.)

IMMUNOLOGIC EVALUATION•

Age (mo)	Immunoglobulin (g/l) † IgG	IgM	IgA	%T cells	%OKT4
10	7·8	0·8	0·4	ND	ND
14	18·7	3·2	8·9	23	ND
18	ND	ND	ND	7	40
Normal range	..	..	..	>65	51±7

•OKT4, helper-inducer cells; OKT8, suppressor-cytotoxic cells; PHA, phytohemagglutinin stimulation of peripheral blood lymphocytes; MLC, mixed lymphocyte culture; ND, not done.
†Values are normal at 10 months and increased at 14 months.
(Courtesy of Ammann, A. J., et al.: Lancet 1:956–958, Apr. 30, 1983.)

▶ [News about acquired immune deficiency syndrome (AIDS) is available to you on an almost daily basis, so that anything that I write now in August 1983 will clearly be ancient history by the time you read it in February 1984.

Pediatricians must be aware that AIDS can occur in infants and children. It may be acquired transplacentally, by blood transfusions, or by intimate household contact. Nobody really knows for sure. Both James Oleske and co-workers (*JAMA* 249:2345, 1983) and Arye Rubinstein and associates (ibid., p. 2350) have described infants and young children who fulfill the clinical and laboratory criteria for the diagnosis. The

patients have come from the Newark and New York City areas, but it is clear that this disease is not just a local problem.

The clinical manifestations may include any, or all, of the following: birth weight small for gestational age, failure to thrive, lymphadenopathy, hepatosplenomegaly, interstitial pneumonia, recurrent febrile illnesses, parotitis, and eczema-like rash. Laboratory findings include: mild thrombocytopenia, hypergammaglobulinemia, hypogammaglobulinemia, a decrease in the absolute number of T_4 (helper) lymphocytes and a reversal of the T_4 to T_8 (suppressor) lymphocyte ratio. Lymphocytes from these patients are usually hyporesponsive to antigenic stimuli. Infections described in the infants have been caused by *Pneumocystis*, Epstein-Barr virus, cytomegalovirus, and *Candida*.

Household contacts may include prostitutes, intravenous drug abusers, male homosexuals, or immigrants from Haiti.

All this should give one pause when making decisions regarding blood transfusions—particularly in the immature, immunocompromised infant. Woody Hayes, the ex-football coach at Ohio State University, reportedly said that he avoided the forward pass because when you threw a pass, three things could happen and only one of them was good. In a similar fashion, many things can occur after a blood transfusion and only one of them is good.—F.A.O.] ◄

1–11 **Late Prognosis in Untreated Neonatal Polycythemia With Minor or No Symptoms.** Although neonatal polycythemia may cause clinical manifestations and permanent sequelae, most polycythemic neonates are asymptomatic, and whether they require partial exchange transfusion is uncertain. A. Høst and M. Ulrich (Univ. of Odense) investigated whether untreated neonatal polycythemia with minor symptoms or none is followed by developmental or neurologic sequelae. Data were reviewed on 635 single, nonmalformed newborn infants with gestational ages of 35 to 43 weeks. Follow-up ranged up to 6 years. A venous hematocrit of 60% or above was found in 18% of infants, and 30 neonates (4.7%) had hematocrits above 65%. Seven of these had values above 70%.

Only 13 infants developed minor symptoms possibly attributable to polycythemia. All the polycythemic infants survived. Hemodilution was used in none. Of 113 children followed, 92% were considered to be normal. None had epilepsy or cerebral palsy. Abnormalities could not be related to hematocrit values or possible polycythemic symptoms in the neonatal period. All 7 children who as neonates had had a venous hematocrit above 70% were normally developed and without health problems on follow-up at age 6 years.

Preventive hemodilution does not appear to be indicated in neonates who have polycythemia with only minor symptoms or none. No infant in this series had an extremely high hematocrit and the prevalence of symptoms was low, probably because of routine clamping of the cord within a minute after birth. Clamping should be done without delay in selected groups of neonates at increased risk of polycythemia, such as infants small for gestational age, infants large for gestational age, postterm neonates, and infants with perinatal asphyxia.

► [Another controversial subject—the management of the polycythemic infant. Doctor Alfred W. Brann, Jr., Professor of Pediatrics, Emory University School of Medicine, supplied the following comment:

(1–11) Acta Paediatr. Scand. 71:629–633, July 1982.

"The data collected and analyzed from the study population of 113 essentially asymptomatic or only mildly symptomatic neonates with untreated hematocrits between 60% and 72% show that seizures, cerebral palsy, or severe mental retardation was not present at age 2.5 years or age 6 years in any greater frequency than in an unidentified reference population. In my opinion, the generalizations regarding the association between polycythemia and neurologic sequelae that can be made from this study are very limited because of problems in the study's research design.

These problems include:

"1. The failure to use adequate tools to assess the *functional status of the nervous system.*

"The classic neurologic examination and age-specific tests are now available to delineate dysfunction of the nervous system more completely than the tests used in this study. I agree that gross seizures, severe "cerebral palsy," and severe mental retardation, if present, could have been identified or at least strongly suspected by the tests used. However, subtle but significant signs of motor dysfunction, mild but definite mental retardation, or certain degrees of hearing loss would have been missed. In addition, signs of central nervous system dysfunction such as short attention span, distractibility, and disorders in abstract reasoning would not have been identified. Thus, because of the incompleteness of the evaluation of the nervous system, it cannot be assumed that the children in this study were free of all significant neurologic dysfunction. This significantly reduces the validity of the major conclusion of this study, which is: Untreated polycythemic neonates with no symptoms or only minor ones do not have neurologic or developmental sequelae.

"2. The failure to document the percentage of patients with hyperviscosity.

"Since the largest group of patients are those with hematocrits between 60% and 65%, a large number of study patients could possibly be at no unusual risk for developing signs of central nervous system dysfunction. The inclusion of a large number of such patients would increase the chance of showing no neurologic sequelae in this population of "polycythemic" patients.

"3. The failure to explore the entire range of clinical symptomatology seen in consecutively admitted polycythemic patients.

"In one study, asymptomatic and symptomatic polycythemic neonates had an equal chance of developing neurologic sequelae (*Pediatrics* 69:426, 1982). The present study does not supply data in enough detail to give the clinician the needed information for him to make a clinical decision regarding the risk status of an individual asymptomatic patient.

"Polycythemia/hyperviscosity (P/H) may be due to more than one disease; in addition, there can be secondary metabolic derangements such as hypoglycemia and hypocalcemia. It is important that future studies clearly delineate the etiology of P/H and associated metabolic derangements. This is important, since the nervous system potentially can be harmed directly by some of the causes of P/H or the associated metabolic derangements.

"As yet, there are no data on which to base a conclusive care plan for patients with polycythemia. It is my opinion that, at present, the data indicate that a significant number of patients, regardless of symptomatology, who have hematocrits greater than 65% or who are hyperviscous at any hematocrit may benefit from a partial exchange transfusion. The benefit to the patient may be during either the neonatal period or later childhood. The reader is urged to continue to review data for the purpose of creating a more definitive patient care plan for the neonate with P/H."] ◀

1–12 **Leukemoid Reaction Associated With Antenatal Dexamethasone Administration.** Steroids stimulate fetal lung maturation and reduce the risk of respiratory distress in premature infants, but they also result in neutrophilic leukocytosis. Endla K. Anday and Mary Catherine Harris (Univ. of Pennsylvania, Philadelphia) report data on 5 infants whose mothers received dexamethasone and who had a

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(1–12) J. Pediatr. 101:614–616, October 1982.

leukemoid reaction shortly after birth. All were girls, weighing 800–2,100 gm at birth, with a mean gestational age of 31.4 weeks. No mother had chorioamnionitis. Three mothers received their last dose of dexamethasone a week before delivery and 2 within 24 hours before delivery. All the infants had an uncomplicated postnatal course. Mild respiratory distress occurred in 2 cases, resolving within 24 hours. Absolute white blood cell counts increased over 24–72 hours postnatally, with neutrophils and neutrophil precursors predominating (table). Bone marrow examination, done on day 3 in 1 case, showed a hypercellular bone marrow.

Steroid-induced leukemoid reaction should be considered when other causes are ruled out. Although most studies indicate that glucocorticoid is not measurable in cord blood 72 hours after maternal injection, fetal adrenal function may be suppressed for up to 2 weeks. The rise in neutrophils is due to both accelerated release from the bone marrow pool of mature neutrophils and reduced egress of neutrophils from the circulation. Hormonal factors may account for a lesser response to corticosteroids in male fetuses. The leukocytosis induced by maternal glucocorticoid administration may be difficult to

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LEUKEMOID REACTION ASSOCIATED WITH ANTENATAL DEXAMETHASONE ADMINISTRATION

% of total leukocyte counts

Infant	*Day*	*Total leukocytes counts/mm³ blood*	*Neutrophils*		*Lymphocytes*	*Monocytes*	*Eosinophils*	*Other immature forms*	*Nonsegmented Segmented*
			Polymorphonuclear leukocytes	*Bands*					
1	0	9,900	25	14	54	3	0	4	0.72
	1	29,600	38	5	45	10	1	3	0.16
	2	45,800	48	23	16	5	0	3	0.54
	3	42,000	70	15	3	7	0	5	0.28
	4	25,100	52	4	38	6	0		0.07
	6	14,300	52	2	33	12	2		0.04
2	0	23,300	20	6	56	13	1	4	0.50
	1	32,100	54	7	14	16	0	9	0.29
	2	36,800	54	7	14	16	0		0.13
	3	42,500	39	5	39	16	0	1	0.15
	4	21,500	47	2	40	9	1	1	0.06
	5	18,900	47	0	42	10	1		0
3	0	46,500	16	20	26	8	2	28	3.00
	1	73,100	28	20	25	3	1	23	1.54
	2	86,100	47	23	8	4	0	18	0.87
	3	112,000	43	19	10	6	3	19	0.88
	4	88,000	62	14	18	4	0	2	0.26
	5	35,000	57	8	31	3	1		0.14
	6	15,400	60	6	31	3	0		0
4	0	46,300	44	15	27	10	0	4	0.43
	1	60,000	52	14	18	9	5	2	0.30
	2	54,400	30	16	33	1	0	20	1.20
	3	39,600	58	4	17	6	4	11	0.26
	4	36,300	37	10	27	16	3		0.27
	5	29,200	56	6	23	11	4		0.10
	6	28,200	36	11	28	19	6		0.30
	7	20,200	34	4	35	17	7		0.12
5	0	42,400	15	38	24	17	0	6	2.90
	1	48,400	26	26	20	16	1	11	1.42
	2	38,600	54	3	26	16	1		0.05
	3	57,200	63	10	11	10	1	5	0.24
	4	51,500	61	4	28	7	0		0.06
	5	22,400	42	1	35	3	3		0.02

(Courtesy of Anday, E. K., and Harris, M. C.: J. Pediatr. 101:614–616, October 1982.)

distinguish from that produced by coexisting infection, especially with premature rupture of the membranes. Appropriate cultures should be obtained in all cases, and other causes of leukemoid reaction should be excluded before it is attributed to maternal steroid therapy.

▶ [Two previous examples of dexamethasone-induced leukemoid reactions in low birth weight infants have been described (Bielawski, D., et al.: *Lancet* 1:219, 1978; and Orero, L., et al.: *Pediatrics* 68:778, 1981). White blood cell counts tend to peak in these infants on the second or third day of life, but leukocytosis persists for 1 week. It can be confusing.

The prenatal administration of dexamethasone does not appear to impair the postnatal pituitary-adrenal function as reflected by ACTH responses in these infants (Huhtaniemi, I., et al.: *Acta Paediatr. Scand.* 71:425, 1982).—F.A.O.] ◀

1–13 **Granulocyte Transfusions in Neonates With Bacterial Infection, Neutropenia, and Depletion of Mature Marrow Neutrophils.** The small neutrophil reserve of the neonate may be exhausted rapidly during bacterial infection, rendering the infant neutropenic. Robert D. Christensen, Gerald Rothstein, Harold B. Anstall, and Blair Bybee (Univ. of Utah) correlated bone marrow neutrophil reserves with clinical outcome in a series of 26 infected, neutropenic neonates. All had positive cultures or Gram stains and fewer than 7% polymorphonuclear-band forms-metamyelocytes in a bone marrow aspirate. Transfused granulocytes were obtained from normal adult donors by intermittent flow centrifugation.

Ten infants had moderate or no depletion of marrow neutrophil reserves. The degree of neutropenia did not correlate with that of marrow neutrophil depletion. All these infants lived. Nine infants with severe depletion of the marrow neutrophil reserve received no transfusions. Only 1 of these infants lived. In this group also, the blood neutrophil count did not correlate with the size of marrow reserves. Seven neonates with severe depletion of marrow reserves received granulocyte transfusions; all lived. No adverse reactions to granulocyte transfusions were apparent. No cultures were positive for cytomegalovirus. All the infants who received transfusions had blood neutrophil counts exceeding the lower limit of normal for age 12 to 18 hours after the granulocyte transfusion. The number of neutrophils given ranged from 0.2 to 1.0/kg.

Depletion of marrow neutrophil reserves in infected neonates is associated with a poor prognosis because of a high risk of death from sepsis. Granulocyte transfusions appear to improve survival of these infants. Adverse reactions to transfused granulocytes have been reported in both children and adults, although none occurred in this study. The transfused volume has been limited to 10 to 15 ml/kg. Granulocytes are irradiated to prevent graft-versus-host disease. The urine is cultured for cytomegalovirus.

▶ [Certain neonates with infections, even when promptly recognized, will not survive with appropriate antimicrobial therapy and the best that intensive care has to offer. This group of septic infants can benefit from leukocyte transfusions. How does one recognize the infant at risk so that treatment may be instituted promptly? Infants must be neutropenic as defined by the criteria of Manroe and associates (*J. Pediatr.*

(1–13) Pediatrics 70:1–6, July 1982.

95:89, 1979; in 1981 YEAR BOOK, pp. 11–16). White blood cell counts should be performed on venous or capillary blood and not blood obtained from an arterial sample. Blood obtained from arteries normally has a lower white blood cell count (see 1981 YEAR BOOK, pp. 17–19). The white blood cell count must be interpreted in terms of the age, in hours, of the infant. A neutrophil count that might be regarded as normal for a 2-hour-old infant may well be diagnostic of neutropenia in a 6-hour-old infant. The blood sample, preferably, should not be obtained within 1 hour of a painful procedure. The pain stimulus may raise the leukocyte count and temporarily mask the presence of neutropenia.

Once it has been established that the infant has neutropenia, the authors advocate that therapy be reserved for patients who also have evidence of bone marrow depletion, bone marrow depletion being defined as fewer than 7% of the nucleated cells in a bone marrow aspirate being polymorphonuclear leukocytes, band form, and metamyelocytes. Their results appear to justify this approach.

In some institutions, rapid aspiration and interpretation of bone marrow may not be possible, so some septic infants without bone marrow depletion, in whom the prognosis appears to be much better, may be treated unnecessarily. Leukocytes for transfusion are not always available. It would seem that two-volume exchange transfusions using fresh blood will provide adequate numbers of leukocytes.

H. Togari and associates (*Acta Paediatr. Scand.* 72:87, 1983) suggest that exchange transfusion be used in the management of infants with sepsis and shock because exchange transfusion could be demonstrated to clear the blood of circulating endotoxin. Endotoxin was present in 8 of 10 infants in septic shock and was removed completely from 6 by exchange transfusion. All 6 infants with no endotoxin after exchange transfusion survived, but the 2 who remained positive for the presence of endotoxin died despite the exchange transfusion.

R. D. Christensen and associates have demonstrated, in neonatal rats, that the proliferative rate of granulocytic stem cells is already maximal even when the rats are not infected, and these stem cells cannot increase their output significantly even when bacterial infections are present (*Pediatr. Res.* 17:278, 1983).

In summary, it would appear advisable to have leukocyte transfusions, or fresh whole blood, available to assist in the treatment of the septic infant who is neutropenic and in whom the bone marrow is exhausted from attempts to produce sufficient neutrophils to control the offending agent. For those who wish to read still more, see the article by R. D. Christensen and G. Rothstein (*J. Calif. Perinatal Assoc.* 2:31, 1982).—F.A.O.] ◀

1–14 **Breast-Feeding, Weight Loss, and Jaundice.** M. Jeffrey Maisels and Kathleen Gifford (Pennsylvania State Univ.) studied the weight loss experienced by fully breast-fed infants and its association with jaundice and fever. Consecutive charts were reviewed until 25 infants were identified in each of four birth weight groups (2,501–3,000, 3,001–3,500, 3,501–4,000, and more than 4,000 gm) who had been fully breast-fed without water or formula supplements.

The table and Figure 1–6 show the changes in weight and the cumulative weight loss by day 3 of life for infants in each weight group. Mean weight loss for all 100 infants was 5.8% (range, 1.4%–13.4%); 7 infants lost more than 10% of their birth weight. There were no significant differences in cumulative weight loss or in mean serum bilirubin concentrations between any of the groups. When all serum bilirubin values were plotted against the cumulative weight loss for each infant, no relation was found. Three infants became febrile; they were in three different weight groups, their percentage weight losses were 1.5, 4.1, and 6.9, and their maximum bilirubin concentrations were 6.8, 8.0, and 8.5 mg/dl, respectively.

(1–14) J. Pediatr. 102:117–118, January 1983.

CUMULATIVE WEIGHT LOSS BY DAY THREE AND TOTAL SERUM BILIRUBIN CONCENTRATIONS (MEANS ± SD)

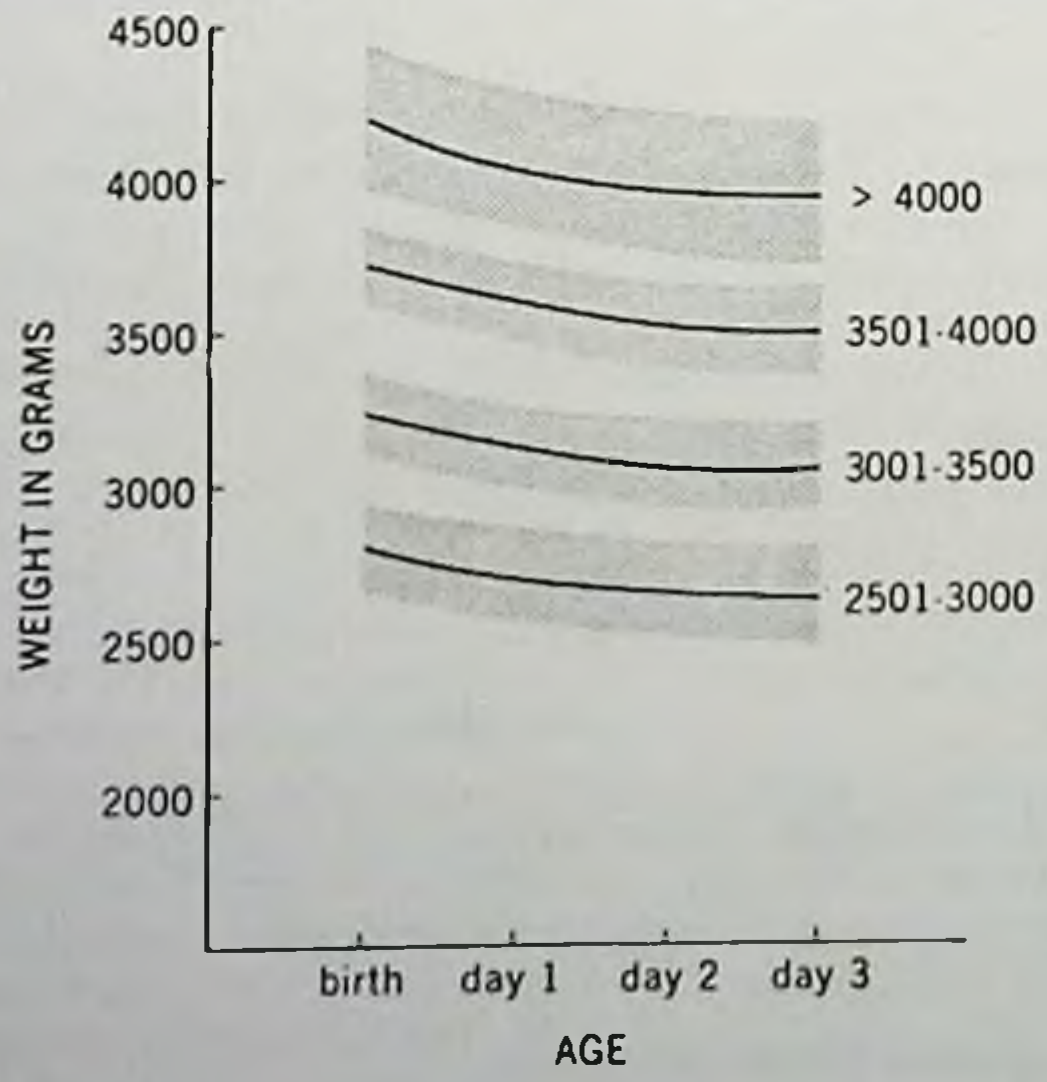
Birth weight (gm)	*Cumulative weight loss Day 3 (%)*	*Serum bilirubin Day 3 (mg/dl)*
2501 to 3000	5.4 ± 3.3	7.5 ± 3.5
3001 to 3500	5.9 ± 3.3	7.0 ± 3.4
3501 to 4000	6.0 ± 3.2	6.2 ± 3.6
> 4000	6.0 ± 3.0	7.1 ± 3.7

(Courtesy of Maisels, M. J., and Gifford, K.: J. Pediatr. 102:117–118, January 1983.)

Because the average weight loss for all groups was 5.8%, the suggestion that a weight loss in excess of 5% requires evaluation is refuted; rather, loss of more than 12% of birth weight (more than 2 SD above the mean) can be considered to be excessive. The 3 infants who became febrile did not have excessive weight loss and therefore could not have been identified earlier as infants likely to show "breast milk fever." Because it is widely believed that neonatal jaundice is associated with inadequate intake, breast-fed infants who become jaundiced frequently are given supplements of formula and water. No relation was found, however, between serum bilirubin concentrations and weight loss.

▶ [This and the following five articles all deal with some aspect of neonatal jaundice. If you are already sick and tired of the subject, I suggest that you jump ahead. A clearer picture of the problem gradually is emerging. Mild degrees of hyperbilirubinemia are becoming more common, while severe hyperbilirubinemia is becoming a rarity.

Fig 1–6.—Changes in birth weight for 100 fully breast-fed infants (n = 25 for each weight group). Lines indicate means; stippled areas represent 1 SD from mean (smoothed curves). (Courtesy of Maisels, M. J., and Gifford, K.: J. Pediatr. 102:117–118, January 1983.)



As demonstrated in this study by Maisels and Gifford, as well as in the following article by Saigal and co-workers, there was no correlation between the degree of weight loss in the breast-fed infant and the peak bilirubin concentration. M. Kuhr and N. Paneth (*J. Pediatr. Gastroenterol. Nutr.* 1:485, 1982) also examined this problem by studying the rates of early neonatal jaundice in 135 consecutive well newborns in relation to feeding practice. Breast-fed infants had significantly higher rates of jaundice than bottle-fed infants. Breast-fed infants with high sugar water intake in the first 3 days of life, and low breast milk intake on the fourth day, tended to have higher rates of jaundice. The authors' findings raise the possibility that the practice of giving sugar water to breast-fed babies may reduce their stimulus to nurse and thus increase their risk of developing hyperbilirubinemia.

If the supreme neonatologist wanted breast-fed infants to have sugar water, he would have provided nursing mothers with a third nipple that was for water only.—F.A.O.] ◄

1–15 **Serum Bilirubin Levels in Breast- and Formula-Fed Infants in the First 5 Days of Life.** Saroj Saigal, Ola Lunyk, Kathryn J. Bennett, and Maxwell C. Patterson (Hamilton, Ont.) conducted a prospective study in a level II maternity unit to investigate the incidence of hyperbilirubinemia in healthy, term, breast-fed and formula-fed infants. Serum bilirubin levels were determined for 176 breast-fed and 164 formula-fed infants in cord blood and on days 1, 2, 3, and 5 after birth.

There were no differences in mean cord-blood bilirubin levels between breast-fed and formula-fed infants (Table 1). Mean total and peak bilirubin levels were significantly higher on each postnatal day in breast-fed infants, as was the proportion of infants with peak levels above 12 mg/dl (26% vs. 7%, Table 2). However, only 9 infants in the breast-fed group and 1 formula-fed infant had peak levels above 15 mg/dl. Phototherapy was used on 17 breast-fed and 3 formula-fed infants; 6 breast-fed and 2 formula-fed infants had bilirubin levels less than 10 mg/dl at the onset of phototherapy. There was a statistically significant correlation between bilirubin in cord blood and bilirubin levels on day 3.

Breast-fed infants had significantly higher proportional weight losses on each postnatal day than formula-fed infants (Table 3). In

TABLE 1.—TOTAL SERUM BILIRUBIN LEVELS FROM BIRTH TO POSTNATAL DAY 5

	Infant group; mean level ± SD (mg/dl)	
Sample	Breast-fed	Formula-fed
Cord blood	1.8 ± 0.7	1.7 ± 0.6
Heel-prick blood		
Day 1	7.2 ± 2.8	6.1* ± 2.7
Day 2	8.3 ± 3.7	6.2* ± 3.3
Day 3	8.1 ± 4.1	5.9* ± 3.5
Day 5	8.3 ± 4.1	5.7* ± 6.5
Peak	8.8 ± 4.0	6.9* ± 5.4

*Significantly different from mean for breast-fed group at $P < .001$.

(Courtesy of Saigal, S., et al.: Can. Med. Assoc. J. 127:985–989, Nov. 15, 1982.)

(1–15) Can. Med. Assoc. J. 127:985–989, Nov. 15, 1982.

TABLE 2.—DISTRIBUTION OF PEAK BILIRUBIN LEVELS IN INFANTS

Level (mg/dl)	Infant group; no. (and %) Breast-fed		Formula-fed	
< 10	104	(59)	134	(82)
10–11.9	26	(15)	19	(12)
≥ 12	46	(26)	11*	(7)

*Significantly different from the proportion of breast-fed infants (χ^2 = 25.97, $P < .001$).

(Courtesy of Saigal, S., et al.: Can. Med. Assoc. J. 127:985–989, Nov. 15, 1982.)

TABLE 3.—CUMULATIVE WEIGHT LOSS AS A PERCENTAGE OF BIRTH WEIGHT

Day	Infant group; mean loss ± SD (%) Breast-fed	Formula-fed
1	2.9 ± 1.9	2.1* ± 1.7
2	4.5 ± 2.2	2.8* ± 2.6
3	5.0 ± 2.4	2.6* ± 2.6
4	4.8 ± 2.6	2.3* ± 2.7
5	4.9 ± 2.9	2.0* ± 2.9

*Significantly different from mean for breast-fed group at $P < .001$.

(Courtesy of Saigal, S., et al.: Can. Med. Assoc. J. 127:985–989, Nov. 15, 1982.)

28% of breast-fed and 9% of formula-fed infants, the cumulative weight loss was more than 6% of the birth weight. There was no correlation between the cumulative weight loss on day 3 and bilirubin levels on the same day with either feeding regimen.

No infant needed an exchange transfusion or prolonged hospitalization for hyperbilirubinemia.

▶ [This study tends to confirm what pediatricians have claimed all along—breast-fed infants have somewhat higher serum bilirubin concentrations. M. J. Maisels and K. Gifford looked at the same problem in their nursery in Hershey, Pennsylvania (*Am. J. Dis. Child.* 137:561, 1983). Serum bilirubin determinations were performed in 264 consecutively delivered term infants. Serum bilirubin values exceeded 12 mg/dl in 15.5% of this group. On the third hospital day, unlike the findings of Saigal et al., the mean serum bilirubin values in the breast-fed and bottle-fed groups were identical and averaged 6.9 mg/dl in the breast-fed group and 6.5 mg/dl in the bottle-fed infants.

In the group in whom the bilirubin level exceeded 12 mg/dl, no cause could be found for the hyperbilirubinemia in 56%. In 8 infants in whom bilirubin values exceeded 12 mg/dl on day 3, 4 were being bottle-fed and 4 were being breast-fed. In 15 infants, the elevated bilirubin level occurred on day 4 or 5—in this group, 14 of the 15 were being breast-fed. The authors concluded that breast-feeding does not appear to effect the total serum bilirubin concentration in the first 3 days of life but may be associated with an increased incidence of subsequent hyperbilirubinemia, and the incidence in their nursery was approximately 15%.

I'd like to see a study that compares bilirubin values in breast-fed infants who are rooming-in with those in infants kept in the nursery. I suspect that the rooming-in babies who are fed more frequently by their mothers would have lower bilirubin values. But in the end, so what if the bilirubin value averages out to be 8, 10, or even 16 mg/dl? No harm is done unless this results in a prolonged hospital stay or unnecessary laboratory determinations.—F.A.O.] ◀

1–16 **Frequency of Breast-Feeding and Serum Bilirubin Concentration.** Fairly rigid feeding schedules are still routine in many hospitals, but infrequent feedings may reduce the intake of breast-fed infants and delay removal of meconium from the gastrointestinal tract. Manoel De Carvalho, Marshall H. Klaus, and Ruth E. Merkatz (Case Western Reserve Univ.) found that increased frequency of breast-feeding is associated with lower serum bilirubin concentrations. Fifty-five mother-infant pairs were studied over the first 3 days after delivery. All the women were primiparas and had had uncomplicated pregnancies and deliveries. The infants were normal at birth and appropriate for gestational age. Breast-feeding began within an hour after delivery. Mothers were encouraged to nurse their infants whenever they thought they were hungry. Water and dextrose supplements were not given.

Infants who suckled more than eight times per 24 hours in the first 3 days had significantly lower serum bilirubin concentrations than those who fed less frequently (table). Weight loss on day 3 was comparable in the two groups. In the overall group, serum bilirubin concentrations on day 3 correlated negatively with the mean frequency of feedings in the first 3 days (Fig 1–7).

Feedings in young infants often are followed by passage of feces. An increase in the gastrocolic reflex after frequent breast-feedings may stimulate gut motility and reduce intestinal reabsorption of bilirubin. Policies that limit or reduce the number of feedings in the first days may interfere with normal mechanisms that help eliminate bilirubin from newborn infants. It is probably the frequency of breast-feeding, rather than the length or volume of feeds, that results in lower serum bilirubin concentrations. Water supplementation in breast-fed infants does not reduce the serum bilirubin concentration.

▶ [I've kept citing Dr. M. Jeffrey Maisels, Professor of Pediatrics, and Chief, Division of Newborn Medicine, Milton S. Hershey Medical Center of Pennsylvania State University. Now, let Jeff speak for himself:

RESULTS OF STUDY

	Group 1, ≤ 8 Feedings/24 hr	Group 2, > 8 Feedings/24 hr
No. of subjects	29	26
Feeding frequency/24 hr	6.8 ± 0.8* (5.3-8)	10.1 ± 1.6† (8.3-15.3)
Serum bilirubin, mg/dL	9.3 ± 3.5 (3.5-15.5)	6.5 ± 4.0‡ (1.5-12.5)
Length of feeding, min	14.3 ± 4	13.3 ± 3.7§
Weight loss, g	219 ± 86	216 ± 59§
Hematocrit, %	54 ± 6.5	55 ± 7.8§

*Mean ± SD (range).
†$P < .0001$
‡$P < .01$.
§Not significant.
(Courtesy of De Carvalho, M., et al.: Am. J. Dis. Child. 136:737–738, August 1982; copyright 1982, American Medical Association.)

(1–16) Am. J. Dis. Child. 136:737–738, August 1982.

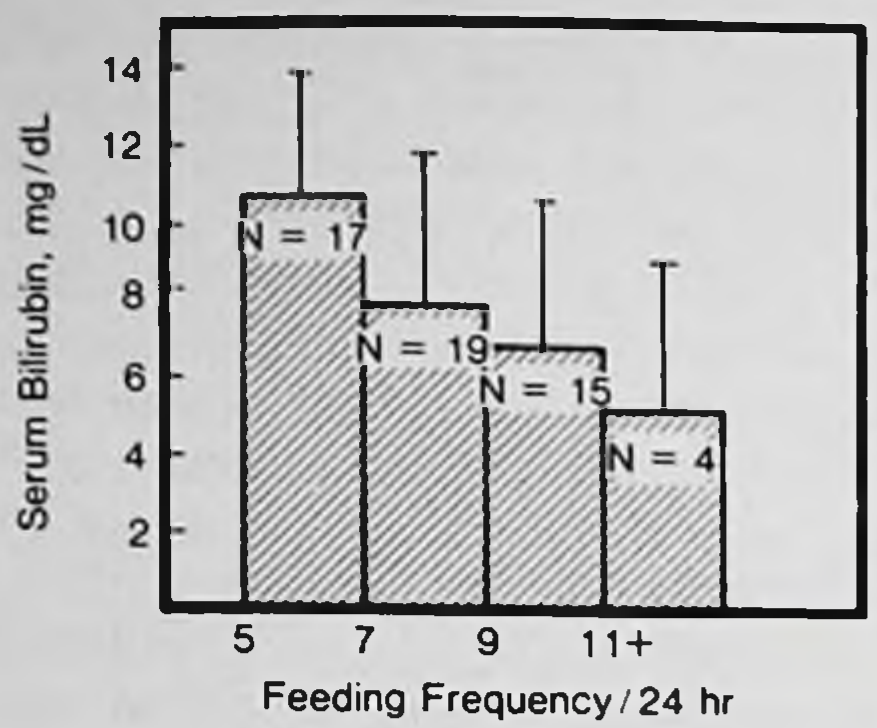


Fig 1–7.—Relation of mean frequency of feedings during first 3 days and serum bilirubin concentrations ($r = -.361$, $P < .01$). Vertical bars represent SDs. (Courtesy of De Carvalho, M., et al.: Am. J. Dis. Child. 136:737–738, August 1982; copyright 1982, American Medical Association.)

"Doctor De Carvalho and his colleagues continue to evaluate aspects of breast-feeding that are of importance to the pediatrician (see 1983 YEAR BOOK, p. 25). In this case, they have established an association between the frequency of breast-feeding and the serum bilirubin concentration in the first 3 days of life. The authors suggest that the increased frequency of feedings increases gut motility and decreases the intestinal reabsorption of bilirubin, although they did not measure fecal bilirubin content. Such measurements are necessary to substantiate their thesis, although other studies (cited by the authors) support this possibility. Designing a study of this nature is not easy because it is probably not possible to assign mothers (randomly) to nurse their babies frequently or infrequently. Nevertheless, it is difficult to know exactly what determined the frequency of nursing. Presumably some babies exhibited signs of hunger more frequently or certain mothers were more enthusiastic than others about feeding their babies. What effect either of these maternal or neonatal factors might have on the infants' serum bilirubin levels is unknown, but it is possible that something quite unrelated to enterohepatic circulation is involved.

"Whatever the mechanism, frequent nursing for the first few days of life should be encouraged because it makes eminent good sense—milk production and flow are established, engorgement is prevented, babies are less jaundiced and, one hopes, the temptation to thrust water on them (which produces no benefit and some potential harm) is diminished. As a result of this work and other studies, we may yet live to see the disappearance of the prepackaged bottle of sterile water from our nurseries!"] ◀

1–17 **Use or Abuse of Phototherapy for Physiologic Jaundice of Newborn Infants.** Helen M. Lewis, Richard H. A. Campbell, and

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DATA FROM HYPERBILIRUBINEMIC INFANTS IN EARLY AND LATE TREATMENT GROUPS*

	Early	Late	p
Birthweight (kg)	3·19±0·26	3·21±0·26	NS†
Age at entry (days)	3·5 (*2·5–7·5*)	3·5 (*2·5–4·5*)	NS‡
Serum bilirubin at entry (μmol/l)	262·5 (*250–370*)	265 (*255–325*)	NS‡
Maximum serum bilirubin (μmol/l)	265 (*250–370*)	280 (*255–350*)	NS‡
Time from entry to serum bilirubin <250 μmol/l (h)	18 (*12–84*)	54 (*12–180*)	<0·01
Age when serum bilirubin fell <250 μmol/l (days)	5 (*3–8*)	6·5 (*4–10·5*)	<0·05

*Mean ± SD birth weight; all other values are medians with ranges in parentheses.

†Not significant ($P > .05$) by Student's t test.

‡Not significant ($P > .05$) by Mann-Whitney test.

(Courtesy of Lewis, H. M., et al.: Lancet 2:408–410, Aug. 21, 1982.)

(1–17) Lancet 2:408–410, Aug. 21, 1982.

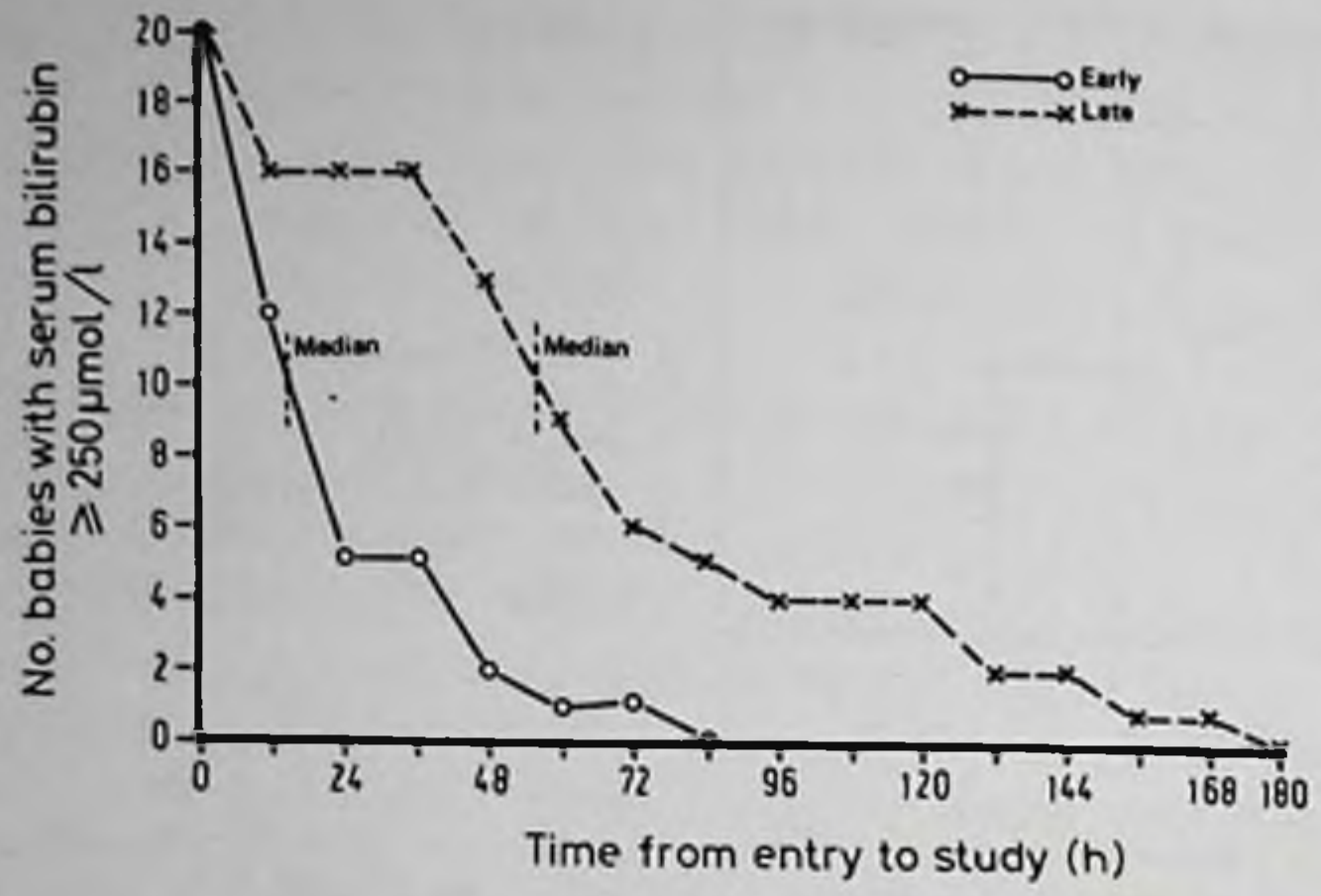

Fig 1–8.—Time for serum bilirubin to fall below 250 µmole/L. (Courtesy of Lewis, H. M., et al.: Lancet 2:408–410, Aug. 21, 1982.)

Garry Hambleton (Park Hosp., Manchester, England) report that to investigate the need for and effects of phototherapy in full-term, otherwise healthy babies with physiologic jaundice, 40 consecutive babies with serum bilirubin levels of 250 µmole/L or more were assigned randomly to two treatment groups. Phototherapy was started in the early treatment group when serum bilirubin was 250 µmole/L (14.5 mg%) and in the late treatment group when serum bilirubin reached 320 µmole/L (18.5 mg%) (which occured in only 3 of 20 patients in this group).

Phototherapy prevented a further rise in bilirubin in almost all treated babies, but the difference in peak bilirubin level between early and late treatment groups was not significant (table). Early phototherapy produced a more rapid decline in bilirubin (Fig 1–8); levels fell to below 250 µmole/L in a median of 18 hours with early treatment and 54 hours with late treatment. In each group, the ratio of boys to girls was 2:1 and boys remained jaundiced significantly longer.

Thus, phototherapy curtailed the rise and duration of hyperbilirubinemia, but the effect was small. Jaundice subsided spontaneously in most of these mature infants, especially the girls.

Phototherapy can separate mother from baby and is physiologically stressful. Treatment may be safely withheld until serum bilirubin exceeds 320 µmole/L (18.5 mg%).

1–18 **Chemoprevention of Neonatal Jaundice: Potency of Tin-Protoporphyrin in an Animal Model.** Bilirubin is a potential central nervous system toxin for infants immediately after birth when the blood-brain barrier is permeable to many substances. High plasma levels of bilirubin may occur with development of neonatal jaundice. George S. Drummond and Attallah Kappas (Rockefeller Univ. Hosp., New York), in a new approach to prevention of neonatal hyperbilirubinemia, used the principle of competitive enzyme inhibition to block

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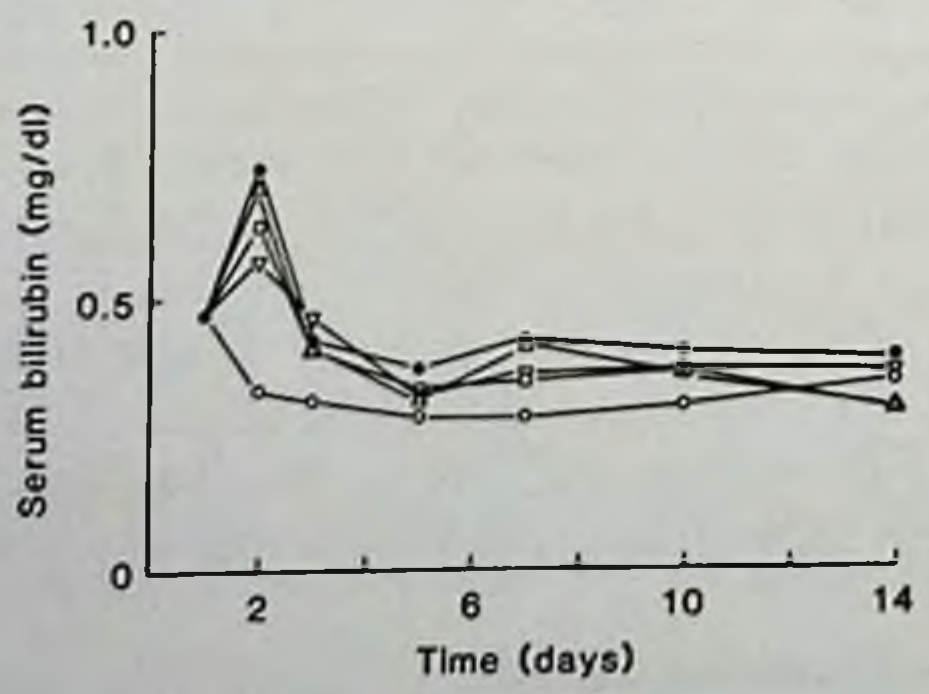
(1–18) Science 217:1250–1252, Sept. 24, 1982.

the degradation of heme to bile pigment by heme oxygenase. Tin-protoporphyrin, a synthetic metalloporphyrin that does not bind molecular oxygen and is not degraded by the enzyme, was used. With its use, bile pigment formation is diminished and serum bilirubin levels drop promptly. Other synthetic metalloporphyrins can inhibit heme oxidation competitively in vitro, but whole animal studies are essential to establish whether a synthetic metalloporphyrin that inhibits heme oxygenase in vitro also will prevent hyperbilirubinemia in the neonate.

When tin-protoporphyrin was administered to newborn rats at 10 μmole/kg, hepatic heme oxygenase activity promptly decreased and low levels of enzyme activity were maintained. This dosage of tin-protoporphyrin proved to be the lowest single dose effective in preventing hyperbilirubinemia. In contrast, even multiple administrations of zinc-protoporphyrin (5 doses each of 100 μmole/kg) during the 72 hours immediately after birth failed to prevent postnatal rise in hepatic heme oxygenase. At day 7 this hepatic enzyme activity decreased significantly in treated animals compared to controls, but only at a total dose of 500 μmole/kg. A comparable late decline in renal heme oxygenase activity was observed with an equally late inhibition apparent in the spleen. Zinc-protoporphyrin administration also failed to prevent the prompt postnatal rise in plasma bilirubin that occurs in neonates (Fig 1–9).

The apparent Michaelis constant (K_m) for human splenic heme oxygenase was determined from 6 different samples to yield a mean ± standard deviation of 19.04 ± 0.08 μmole (table). This value is similar to that previously reported for the human spleen enzyme, but is 3–4 times greater than that reported for rat spleen microsomal heme oxygenase and nearly 20 times greater than that for the heme oxygenase system reconstituted with its purified enzymic components. These and other findings indicate that the degradation of heme to bile

Fig 1–9.—Effects of tin-protoporphyrin and zinc-protoporphyrin on serum bilirubin levels in neonate rats. Each time point represents the average of a minimum of 3 litters (approximately 10 animals per litter). Bilirubin was estimated by a fluorometric method. Metalloporphyrins were administered subcutaneously: tin-protoporphyrin, 10 μmole/kg *(open circles)*; zinc-protoporphyrin, 20 μmole/kg *(open triangles)* or 100 μmole/kg at birth *(open squares)*, or 100 μmole/kg at birth and again 12, 24, 48, and 72 hours later *(inverted open triangles)*; control animals receiving equivalent volumes of saline *(closed circles)*. (Courtesy of Drummond, G. S., and Kappas, A.: Science 217:1250–1252, Sept. 24, 1982. Copyright 1982 by the American Association for the Advancement of Science.)



THE K_M OF HUMAN SPLEEN HEME OXYGENASE AND THE K_I OF TIN-PROTOPORPHYRIN FOR SIX DIFFERENT SAMPLES

Heme oxygenase K_m (μM)	Tin-protoporphyrin K_i (μM)
20.00	0.013
22.22	0.018
15.63	0.019
16.12	0.018
21.05	0.019
19.23	0.020
Mean:	Mean:
19.04 ± 0.08	0.018 ± 0.001

(Courtesy of Drummond, G. S., and Kappas, A.: Science 217:1250–1252, Sept. 24, 1982. Copyright 1982 by the American Association for the Advancement of Science.)

pigment in human spleen is several times more sensitive to blockade by tin-protoporphyrin administration than is the comparable tissue in the rat.

In neonatal rats, multiple administrations of tin-protoporphyrin in amounts totaling 500 μmole/kg have produced no evident toxicities, and treated animals have matured and reproduced normally. The biologic properties of tin-protoporphyrin and related metalloporphyrins should be explored, because similar control mechanisms may be of therapeutic value in human beings.

▶ [This approach to retarding heme breakdown has particular appeal to control hyperbilirubinemia and avoid the need for repetitive exchange transfusions in the management of babies with severe forms of hemolytic disease.

First a new theoretical approach to the management of hyperbilirubinemia and now a new theory of how bilirubin may produce its toxic effects: L. Morphis and associates (*Science* 218:156, 1982) have reported that bilirubin inhibits protein phosphorylation in cerebral cell-free preparations from neonatal rabbits. It has long been known that bilirubin inhibits oxidative processes in isolated mitochondria. This finding suggested that bilirubin exerted its cytotoxic effect by decreasing local adenosine triphosphate (ATP) concentration and eventually limiting energy-dependent cerebral metabolism. If synaptic protein phosphorylation is inhibited by bilirubin, it would be consistent with the clinical observation that moderate hyperbilirubinemia produces usually reversible manifestations such as sleepiness, sluggishness, and disturbances of respiratory and cardiac function. The long-lasting damage may be a consequence of impairment of phosphorylation on nuclear histones in the brain cell. We still don't know how much bilirubin is toxic and the mechanism of its toxicity. Maybe we are getting closer (and maybe the moon is made of cheese).—F.A.O.] ◀

1–19 **The Bronze Baby Syndrome** is an infrequent complication of phototherapy. Only 5 cases have been reported. K. L. Tan and E. Jacob (Natl. Univ. of Singapore) report 14 cases of bronze baby syndrome, diagnosed when definite bronzing of the skin was seen during or at the end of phototherapy, with spectroscopic evidence of increased absorbance at 416 nm. Phototherapy was continued until the

(1–19) Acta Pediatr. Scand. 71:409–414, May 1982.

indirect bilirubin concentration was below 11 mg/dl, despite the presence of bronzing.

In 13 infants bronzing was associated with phototherapy that used daylight or blue lamps; in the other case "thermotherapy" with an incandescent bulb, emitting mainly light ineffective for phototherapy, caused bronzing in an infant with respiratory failure. In all cases, some underlying condition had contributed to hyperbilirubinemia. The plasma appeared brownish gray or brownish black. Hepatic dysfunction, present in all infants, usually was most marked after the end of phototherapy. Plasma spectroscopy yielded abnormal results in all 8 infants studied for over a year, whereas the urine showed no pigment within 4 weeks of the onset of bronzing. The infants generally were well after improvement of their underlying conditions. Mental and physical progress was subsequently normal, except in an infant with congenital rubella.

The bronze baby syndrome develops during phototherapy only when jaundice and hepatic dysfunction are present. The presence of bronze pigment(s) appears to be harmless. Liver dysfunction has been maximal after the cessation of phototherapy. The wavelength responsible for the syndrome has not been clearly defined. The syndrome appears to be a response to phototherapy or thermotherapy, or both, when liver dysfunction is present. Its presence does not influence the natural disease process.

▶ [Doctor Arthur Kopelman, who first described the syndrome and currently is Director of Neonatology at the East Carolina University School of Medicine, comments as follows:

"We can agree that the bronze baby syndrome develops when phototherapy is used to treat infants with impaired hepatic excretion and elevated conjugated bilirubin values. But the origin of the circulating brown pigments isn't at all clear. It has been suggested that they may result when "unknown pigments" produced during phototherapy polymerize to bilifuscin-like substances (Onishi, S., et al.: *Pediatrics* 69:273–276, March 1982), from the bilirubin-sensitized photodegradation of copper porphyrins (Jori, G., et al.: *Lancet* 1:1072, May 1982; and Rubaltelli, F. F., et al.: *Pediatr. Res.* 17:327–330, 1983), when the geometric photoisomers (Z and E lumirubins) of bilirubin produced during phototherapy turn brown over time (McDonagh, A. F.: ibid., p. 326A [abstract]), or by as yet unknown mechanisms. It follows that we still don't know if the retained pigments are toxic, but they have been shown to persist in the serum for as long as a year (Onishi et al., cited above). There is even disagreement on whether the pigment does (McDonagh, cited above; Kopelman, A. E., et al.: *J. Pediatr.* 81:466, 1972; and Clark, C. F., et al.: ibid. 88:464–468, 1976) or doesn't (Tan and Jacob) bind to albumin and increase the risk of kernicterus.

"Fortunately, this lack of understanding of basic mechanisms needn't present much of a problem for clinicians. Conjugated bilirubin isn't considered toxic to the central nervous system. Therefore most neonates with conjugated hyperbilirubinemia, those at risk of developing bronze baby syndrome, don't require treatment for hyperbilirubinemia. In the very few who do require treatment, I would perform an exchange transfusion rather than use phototherapy."] ◀

1–20 **Developmental and Neurologic Progress of Preterm Infants With Intraventricular Hemorrhage and Ventricular Dilatation.** Penelope Palmer, Lilly M. S. Dubowitz, M. I. Levene, and V. Dubowitz (Hammersmith Hosp., London) performed a prospective neurologic and developmental assessment on 39 preterm infants of less

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(1–20) Arch. Dis. Child. 57:748–753, 1982.

than 34 weeks' gestation. Infants were assessed at ages 6, 9, and 12 months. In the newborn period, each infant had an assessment of gestation and sequential neurologic and ultrasound examinations and was placed in one of three groups: intraventricular hemorrhage (IVH, 14 infants), IVH followed by ventricular dilatation (11), and control infants with no evidence of IVH (14).

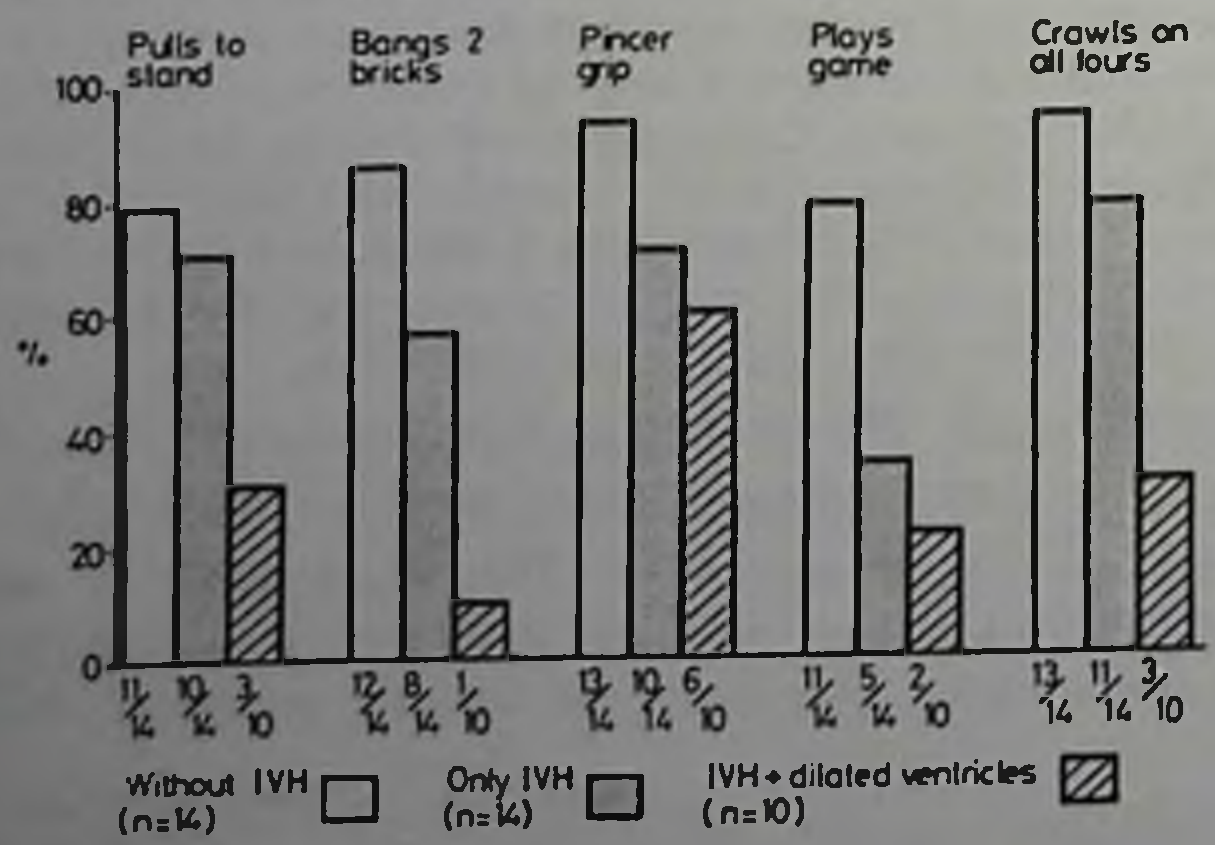
When corrected for prematurity, the Griffiths' developmental quotients (DQs) were normal at 6, 9, and 12 months for every infant except 1 aged 12 months; however, the distribution of the infants within each group was extremely different. The uncorrected DQs at 12 months were under 80 in only 1 infant without hemorrhage, as compared with 2 of those with IVH and 7 of 9 followed with IVH and dilatation.

There was also a higher incidence of neurologic abnormality at each follow-up age in infants with IVH and ventricular dilatation as compared with those in either of the other groups. Similar differences were also demonstrated in five milestones reflecting gross motor, fine motor, and social or verbal development in the groups at 6, 9, and 12 months (Fig 1–10).

At 1 year, there were no infants with major handicaps in the non-IVH or IVH groups, whereas 6 of 10 surviving infants with IVH plus ventricular dilatation had major handicaps at 1 year. These included developmental delay, profound sensorineural deafness, visual impairment, hemiplegia, and pronounced fine motor incoordination. The neurologic and developmental deficits seemed to relate more closely to the presence of posthemorrhagic ventricular dilatation than to the size of the initial hemorrhage.

The study shows that infants with ventricular dilatation after IVH have a high incidence of neurologic handicap, whereas the early development of infants with IVH but without dilatation is not very different from that of babies of similar gestation without hemorrhage, despite more frequent minor neurologic abnormalities. The results may have important implications for therapeutic intervention in the management of newborn infants with IVH and ventricular dilatation.

Fig 1–10.—Proportion of infants achieving various milestones at age 12 months. (Courtesy of Palmer, P., et al.: Arch. Dis. Child. 57:748–753, 1982.)



Use of uncorrected DQs rather than corrected DQs, is recommended as a better screen for persisting deficit in preterm infants.

1–21 **Assessment of Neurologic Outcome in Asphyxiated Term Infants by Use of Serial CK-BB Isoenzyme Measurement.** Peter Walsh, Roy Jedeikin, Graham Ellis, Robert Primhak, and Sinikka K. Makela (Hosp. for Sick Children, Toronto) report that the brain-type isoenzyme of creatine kinase (CK-BB) was measured serially in 45 healthy and 22 severely asphyxiated term infants. The enzyme was measured in cord blood and in venous, capillary, or arterial blood at 6–8 hours, 24–30 hours, and 72–80 hours after birth.

In healthy infants, a brief rise of CK-BB occurred at 6–8 hours. The CK-BB activities were greater than 2.5 log-transformed standard deviations above the mean of control values in 10 asphyxiated infants but in no control babies (1 infant, who was normal at last follow-up, was excluded from the control group because the CK-BB activity in cord blood was >20 times the mean). The means of the control and study groups diverged most in the cord blood and 6-hour to 8-hour samples (table).

Normal CK-BB activity was a predictor of good neurologic outcome, and elevated CK-BB was a predictor of subsequent neurologic abnormality in 17 of 22 cases (77%) and in 11 of the 12 survivors (92%) who had neonatal asphyxia (Fig 1–11). Four infants who died or were neurologically abnormal at follow-up had false negative results. One asphyxiated infant who was normal at follow-up had a result regarded as false positive. Eight of the 12 surviving infants had neonatal seizures, and outcome was predictable from CK-BB activity in all cases.

Serum CK-BB activity, especially when measured in cord blood and at 6–12 hours of life, correlates with neurologic outcome after severe asphyxia; long-term follow-up is required to confirm this observation. Serial CK-BB measurements compare favorably with radionuclide and computerized tomographic (CT) scanning as a method of predicting neurologic outcome after asphyxia. The absolute value of CK-BB was more related closely to clinical outcome than was total CK or the percentage of CK-BB in total CK. The good correlation between

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MEAN VALUES AND RANGES FOR CK-BB CONTROL INFANTS AND ASPHYXIATED INFANTS

	Control infants		*Asphyxiated infants*	
Sample	*Mean (U/L)*	*Range (U/L)*	*Mean (U/L)*	*Range (U/L)*
Cord blood	8.4	0-40	32.0	0-102
6-10 hr	43.7	16-93	123.6	0-466
24-30 hr	24.2	6-72	49.4	0-413
72-80 hr	24.6	6-82	15.3	0-97

(Courtesy of Walsh, P., et al.: J. Pediatr. 101:988–992, December 1982.)

(1–21) J. Pediatr. 101:988–992, December 1982.

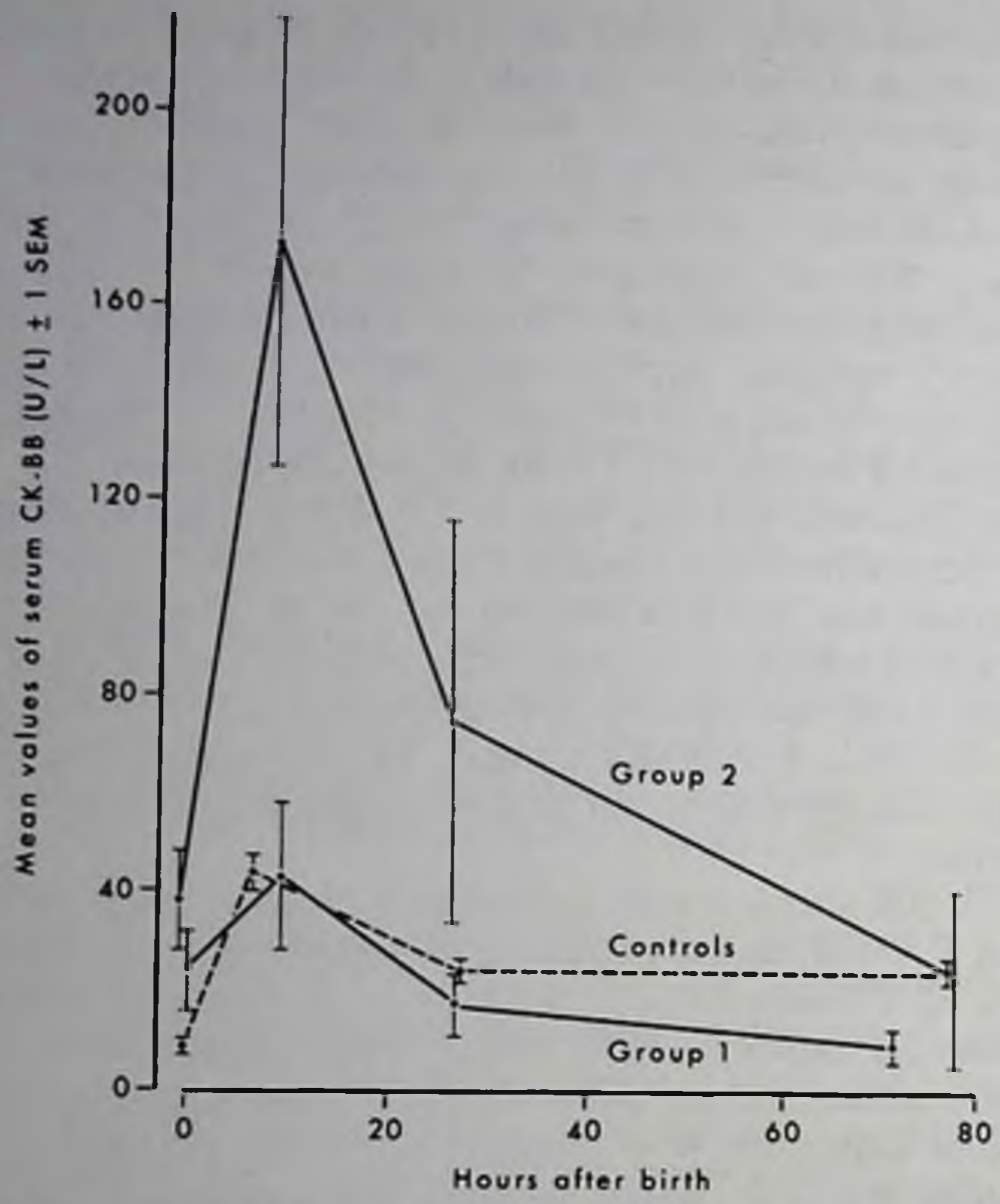

Fig 1–11.—Mean serum CK-BB activity for healthy term infants *(controls)*, asphyxiated infants who were normal at follow-up *(Group 1)*, and those who died or were neurologically abnormal at follow-up *(Group 2)*. (Courtesy of Walsh, P., et al.: J. Pediatr. 101:988–992, December 1982.)

serum CK-BB and neurologic outcome suggests that the blood-brain barrier is permeable to CK-BB in infants after asphyxia, as most asphyxiated infants did not have evidence of cerebral trauma on computed tomography scan or at postmortem examination.

1–22 **Head Growth and Developmental Outcome in Very Low Birth Weight Infants.** Steven J. Gross, Jerri M. Oehler, and Carol O. Eckerman (Duke Univ., Durham, N.C.) evaluated the predictive role of early head growth for subsequent outcome in 85 infants with very low birth weight (VLBW; <1,500 gm). On the basis of head circumference at birth and head growth between birth and age 6 weeks, infants were divided into four groups: microcephalic at birth with less (<3.5 cm) postnatal head growth (9 infants); microcephalic at birth with more (≥3.5 cm) postnatal head growth (12); normocephalic at birth with less head growth (32); and normocephalic at birth with more head growth (32).

At both 6 and 15 months of age, the two groups of VLBW infants with less postnatal head growth had an increased incidence of growth failure as compared with full-term infants, whereas the two groups with more postnatal head growth had a low incidence, similar to that for a matched full-term group. Major neurologic defects occurred sig-

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(1–22) Pediatrics 71:70–75, January 1983.

nificantly more frequently among infants who were microcephalic with less postnatal head growth; two-thirds showed evidence of blindness, hydrocephalus, or spastic diplegia. This group also performed more poorly on the Bayley Scales than the other groups. Infants with microcephaly and less postnatal growth had a 100% incidence of handicap at 6 and 15 months of age. Normocephalic infants with greater head growth were free of neurologic defects and had Bayley scores that did not differ from those of healthy full-term infants.

Infants with only poor intrauterine head growth or less postnatal head growth had intermediate scores at age 6 months. At age 15 months, those with normocephaly and less postnatal head growth continued to have intermediate scores. However, those with microcephaly and greater postnatal head growth showed developmental catch-up; their scores did not differ from those of infants who were normocephalic with greater head growth or the full-term group. Less postnatal head growth was associated with an increased incidence of need for mechanical ventilation, patent ductus arteriosus, sepsis, delayed tolerance of feeding, and slower weight gain.

The data suggest that early postnatal head growth may summarize the adverse effects of many perinatal risk factors and that head circumference at birth and head growth by 6 weeks are strong predictors of early developmental outcome in VLBW infants. The head circumference classifications alone accurately separated VLBW infants with developmental handicap from those without such handicap in 61% of the infants at age 6 months and in 76% of the infants at age 15 months. Only one additional variable—number of days to reach adequate enteral intake—added significantly to this predictive power, increasing the predictability to 75% at age 6 months and 84% at age 15 months.

▶ [As can be seen from this and the two preceding articles, we are still looking for accurate means of predicting eventual neurologic outcome in low birth weight infants. These three articles provide you with some options—ventricular dilatation, serial measurements of the serum concentration creatinine kinase–brain-type isoenzyme, or the measurement of head circumference at birth and again at age 6 weeks. I know that this is an oversimplification of a complex problem, but it seems that you can predict as much from the tape measure as you can from the fancier techniques. The tape measure won't tell you much about the cause of the problem, but it certainly tells you about its consequences.

These same authors previously reported that infants who were microcephalic at birth had poorer growth, increased neurologic defects, and poorer intellectual performance at age 5 years than did low birth weight infants who were normocephalic at birth (*Am. J. Dis. Child.* 132:753, 1978). Now it would appear that the combination of head circumference at birth coupled with the rate of head growth during the first 6 weeks of life is an even more valuable piece of information. All this sounds too good to be true, but remember, "Everyone has a scheme that will not work."—F.A.O.] ◀

1–23 **Pulmonary Microthrombi Syndrome in Newborn Infants With Unresponsive Persistent Pulmonary Hypertension.** Daniel L. Levin, Arthur G. Weinberg, and Ronald M. Perkin (Univ. of Texas Health Science Center, Dallas) recently encountered neonates who had diffuse pulmonary microthrombi and persistent pulmonary hy-

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(1–23) J. Pediatr. 102:299–303, February 1983.

PULMONARY MICROTHROMBI AND PPHN (MEANS ± 1 SD)

Group	n	Thrombi/cm² lung surface	Platelet count (μl)	ΔPaO₂* (mm Hg)
A	8	15.2 ± 18.1 (P<0.004)	51,750 ± 39,500 (P<0.01)	14.8 ± 14.1 (P<0.05)
B	15	0.2 ± 0.3	128,000 ± 79,000	83.6 ± 85.4

*ΔPa_{O_2}: increase in Pa_{O_2} in blood sampled from same site within 15 min of test dose of 1 mg of tolazoline per kg given intravenously.

(Courtesy of Levin, D. L., et al.: J. Pediatr. 102:299–303, February 1983.)

pertension of the newborn (PPHN) and who failed to respond favorably to vasodilator therapy with tolazoline. A clinical diagnosis of pulmonary hypertension had been made in 23 of 94 infants on whom autopsy had been performed, and all of them had received a test dose of 1 mg tolazoline per kg with measurements of Pa_{O_2}. More than one thrombus per square centimeter was found in 8 (group A) and fewer thrombi in 15 (group B).

Four of the 8 group A infants had pneumonia-sepsis, 3 had meconium inhalation syndrome, and 1 had primary PPHN. Four of the 15 group B infants had pneumonia-sepsis, 4 had meconium inhalation syndrome, 4 had primary PPHN, 2 had hyaline membrane disease, and 1 had congenital diaphragmatic hernia. Thrombi were found most often in small arteries with diameters of 100 to 250 μ, and they consisted of platelets or fibrin. In many cases they exhibited early endothelialization and organization. The only significant differences between the two groups were a lower platelet count and a smaller Pa_{O_2} response to tolazoline in group A (table). There were no significant group differences in gestational age, Apgar scores, time on mechanical ventilation, lowest Pa_{O_2} or arterial pH value, or use of umbilical arterial or venous or central venous catheters.

Some infants with PPHN of either the primary or the secondary form fail to respond to vasodilator therapy with a rise in arterial blood oxygen tension and have diffuse microthrombi in the pulmonary vasculature at autopsy. Pulmonary microthrombi may explain why some infants fail to respond to vasodilator therapy for PPHN. Thrombocytopenia may suggest the diagnosis. Amniotic fluid inhalation and platelet clumping may produce a pathophysiologic state similar to adult respiratory distress syndrome in these infants. If a test dose of tolazoline is ineffective, treatment might be directed to support, as is used in adult respiratory distress syndrome.

1–24 **Isolation of Human Surfactant From Amniotic Fluid and a Pilot Study of Its Efficacy in Respiratory Distress Syndrome.** Promising results have been obtained from the use of homologous natural surfactant to treat premature animals. Mikko Hallman, T. Allen Merritt, Howard Schneider, Benita L. Epstein, Frank Mannino, David K. Edwards, and Louis Gluck (Univ. of California, San Diego) have now isolated human surfactant and examined its efficacy in in-

(1–24) Pediatrics 71:473–482, April 1983.

fants with respiratory distress syndrome (RDS). Amniotic fluid was collected from term gestations at elective cesarean section, and surfactants were isolated within hours of sample collection in a sterile manner. Reference surfactant was isolated from lung lavages of adult rabbits by differential and density gradient centrifugation. The composition of human surfactant is shown in Table 1, and recovery of surfactant from amniotic fluids in Table 2.

Surfactant suspension was given intratracheally in saline in a bolus of 60 mg/kg to infants weighing less than 1,250 gm with a diagnosis of RDS who required an inspired oxygen fraction (FI_{O_2}) of 0.8 or greater. Surfactant was administered a mean of 6 hours after birth. The immediate effects of surfactant are shown in Table 3, in which

TABLE 1.—COMPOSITION OF HUMAN SURFACTANT FROM TERM AMNIOTIC FLUID
(N = 6)

	%	% of Dry Weight
Phospholipids	100.0	80.7 ± 4.2 (83.2 ± 5.0)*
Lecithin	77.6 ± 4.0†	62.8 ± 3.9‡
Disaturated lecithin	51.2 ± 2.9	40.0 ± 2.7
Phosphatidylglycerol	7.6 ± 1.7	6.1 ± 1.6
Phosphatidylinositol	6.4 ± 0.7	5.6 ± 0.7
Phosphatidylethanolamine	5.0 ± 0.4	3.8 ± 0.4
Sphingomyelin	1.6 ± 0.5	1.2 ± 0.4
Bis(monoacylglycerol) phosphate	0.8 ± 0.4	0.6 ± 0.3
Phosphatidylserine	0.4 ± 0.4	0.3 ± 0.3
Lysolecithin	0.6 ± 0.2	0.3 ± 0.1
"Neutral lipids"	100.0	9.4 ± 2.4
Cholesterol	59.9 ± 5.2	5.6 ± 1.1
Free fatty acids	16.8 ± 4.0	1.6 ± 0.8
Diglycerides	12.4 ± 5.9	1.2 ± 1.1
Triglycerides	6.1 ± 1.2	0.6 ± 0.2
Monoglycerides	2.2 ± 1.1	0.2 ± 0.2
Cholesterol esters	2.6 ± 0.3	0.2 ± 0.1
Protein	100.0	5.4 ± 2.0
Recovery		95.5 ± 7.8 (98.0 ± 8.0)*

*Value in parentheses is based on recovery of total lipid-phosphorus (mol wt 750).
†Molar distribution of phospholipids.
‡Weight estimate is based on assumption that lipids contain palmitate (disaturated lecithin) or 50% palmitate and 50% oleate.
(Courtesy of Hallman, M., et al.: Pediatrics 71:473–482, April 1983. Copyright American Academy of Pediatrics 1983.)

TABLE 2.—RECOVERY OF SURFACTANT FROM AMNIOTIC FLUID

	Total	Rejected	Total – Rejected
No. of amniotic fluids*	47 (54)	9	38
Total volume (L)	16.0	2.0	14.0
Recovery			
Total phospholipid (μmol)	860	100	760
Phospholipid/L of amniotic fluid (μmol/L)	54 (15–238)	50 (7–120)	54 (15–238)

*Amniotic fluids were rejected as follows: 7 before isolation (6, blood contamination; 1, meconium contamination); 5 due to insufficient surface activity; 1 due to insufficient activity and bacterial contamination (1 colony of *Staphylococcus aureus*, 1 colony of *S. epidermidis*); and 3 due to bacterial contamination (2 colonies of S. *epidermidis*, 1 colony of *S. aureus*).
(Courtesy of Hallman, M., et al.: Pediatrics 71:473–482, April 1983. Copyright American Academy of Pediatrics 1983.)

TABLE 3.—IMMEDIATE EFFECTS OF SURFACTANT SUPPLEMENTATION

	A Immediately Before Surfactant	B 5 Min After Surfactant	C 1 Hr After Surfactant
Pa_{O_2} (mm Hg)	69 ± 11	239 ± 19*	73 ± 13
Pa_{CO_2}	50 ± 3	48 ± 1	44 ± 2†
pH	7.26 ± 0.04	7.26 ± 0.03	7.32 ± 0.02
Fi_{O_2}	0.94 ± 0.03	0.95 ± 0.03	0.49 ± 0.03*
MAP (cm H_2O)	10.3 ± 1.1	10.2 ± 1.2	9.5 ± 0.7‡

*$P < .001$ compared with A.
†$P < .025$ compared with A.
‡$P < .05$ compared with A.

(Courtesy of Hallman, M., et al.: Pediatrics 71:473–482, April 1983. Copyright American Academy of Pediatrics 1983.)

MAP stands for mean airway pressure. Beneficial effects persisted for 8 to 15 hours in 4 infants before their respiratory state deteriorated somewhat, although their RDS was less severe than before treatment and there were no pulmonary complications. A fifth infant improved strikingly for a few hours and then became markedly worse and developed bronchopulmonary dysplasia and intraventricular hemorrhage. No side effects from surfactant administration was observed. The 5 infants given surfactant generally seemed to have less lung injury than did 5 control infants with RDS. Protease activity in lung effluent was lower in the first week of life in treated infants.

Human surfactant had variable but generally beneficial effects in infants with RDS in this study, and its administration appeared to be safe. Further clinical trials of exogenous human surfactant are warranted, but a substantial reduction in life-threatening complications of RDS and a decrease in lung injury must be demonstrated before this therapy can be recommended.

1–25 **Extracorporeal Membrane Oxygenation for Newborn Respiratory Failure: Forty-Five Cases.** Supportive treatment for newborn respiratory failure (oxygen and positive airway pressure) can damage the lung, and newborn respiratory failure remains a major cause of morbidity and death in infants. Extracorporeal membrane oxygenation (ECMO) involves the use of a modified heart-lung machine to support gas exchange for days or weeks until the lung has recovered. Robert H. Bartlett, Alice F. Andrews, John M. Toomasian, Nick J. Haidue, and Alan B. Gazzaniga used ECMO in 45 moribund newborn infants who were unresponsive to maximal therapy and had less than 10% chance of survival.

In these cases, venoarterial cardiopulmonary bypass was established by cannulating the right atrium via the right internal jugular vein and the aortic arch via the right common carotid artery under local anesthesia (Fig 1–12). Heparin was infused continuously to maintain whole blood activated clotting time at 250 to 300 seconds.

(1–25) Surgery 92:425–433, August 1982.

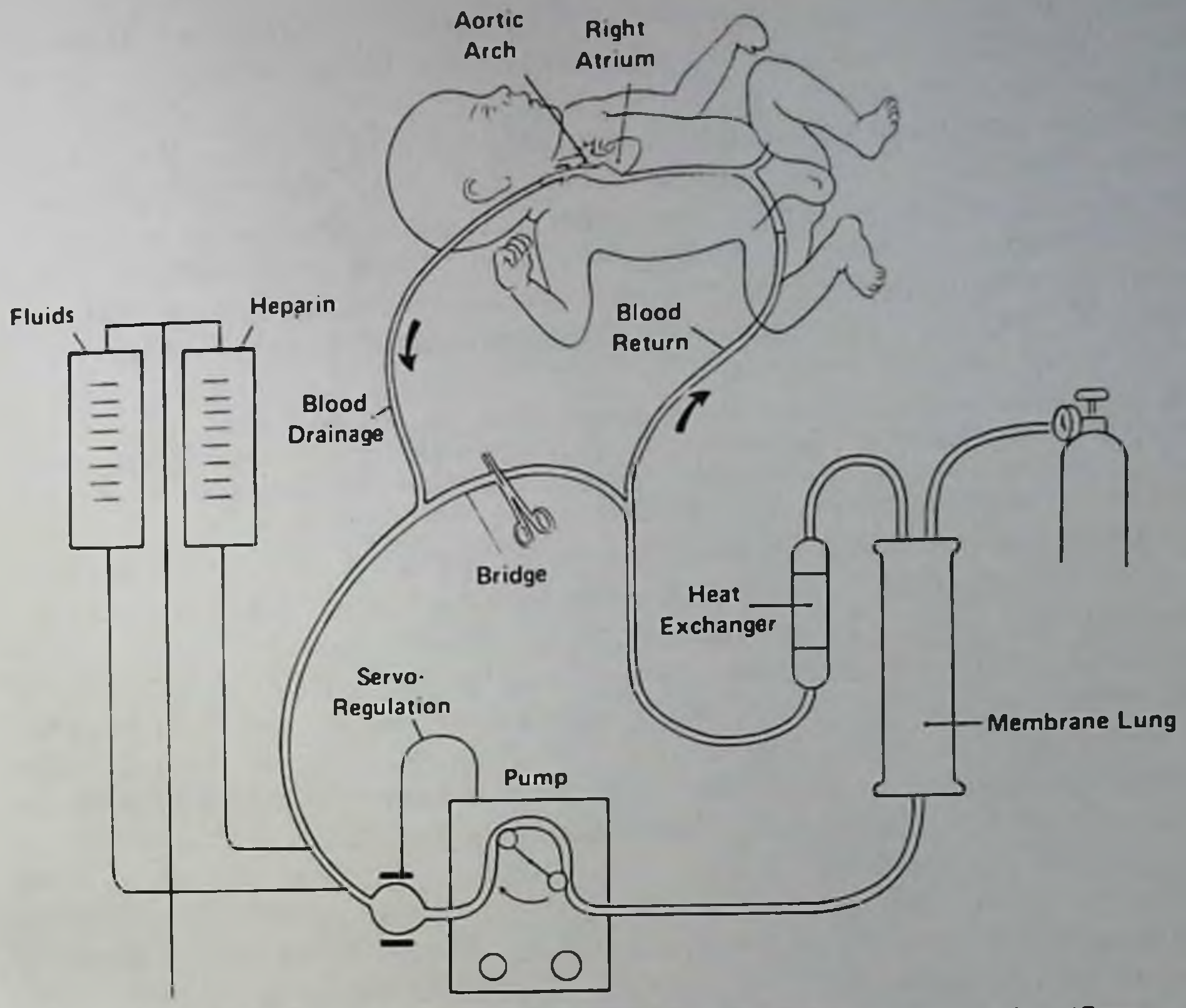

Fig 1–12.—Circuit diagram for venoarterial extracorporeal membrane oxygenation. (Courtesy of Bartlett, R. H., et al.: Surgery 92:425–433, August 1982.)

Airway oxygenation and pressure were reduced to low levels. Full-calorie parenteral nutrition and antibiotics were given. As lung function improved and systemic oxygen tension rose at low ventilator settings, ECMO flow was proportionately decreased, allowing more blood to flow through the lungs.

After the patient underwent bypass and ventilator pressure was decreased, air leaks due to prior barotrauma sealed promptly. Twenty-five infants survived. Of 14 patients with hyaline membrane disease, 6 survived; of 22 with meconium aspiration, 15 survived; of 5 with persistent fetal circulation including diaphragmatic hernia, 3 survived; and of 4 with sepsis, 1 survived. The survivors received ECMO for an average of 90 hours. Growth, development, and brain and lung function are normal in 20 survivors.

The major complication and the most common cause of death was intracranial hemorrhage, which occurred in 16 patients; 15 died. Other major bleeding episodes were observed in 2 patients. Hemodialysis was used in 5 patients; all died. Of 17 patients who had major seizures, 9 died. No episodes of local, pulmonary, or systemic infection were recognized (except in those with primary sepsis). Nine major mechanical complications occurred. While technical repairs were

being made, patients were returned to maximal ventilatory support without ECMO, and 4 suffered cardiac arrest, brain damage, or intracranial hemorrhage.

When compared with data for similar groups of patients, the results from this phase I trial suggest that ECMO and "lung rest" decrease mortality, intracranial hemorrhage, and bronchopulmonary dysplasia. Further evidence can only be secured from a randomized trial, which is currently under way. Results of the phase I study suggest that ECMO may be effective in older patients if used before irreversible lung damage occurs.

▶ [If you review the 1979 YEAR BOOK, pages 28–30, you will find a description of this technique by Robert H. Bartlett and his co-workers. He has persisted and perfected the technique, which admittedly is a last-ditch maneuver to salvage babies who are judged to be unsalvagable by more conventional methods.—F.A.O.] ◀

1–26 **Physiologic Fetal Defecation in Midpregnancy.** Disaccharidase and fetal intestinal alkaline phosphatase values are high in midpregnancy but virtually absent at term. Since disaccharidases occur chiefly in fetal jejunal mucosa and the alkaline phosphatase is specific to fetal gut, their mode of entry into the amniotic fluid may be fetal defecation. David R. Abramovich and Elizabeth S. Gray (Univ. of Aberdeen) examined meconium patterns in fetuses delivered by spontaneous and prostaglandin-induced abortion and at hysterotomy at 14–27 weeks' gestation. Twenty spontaneously aborted fetuses, 9 from prostaglandin terminations, and 2 hysterotomy specimens were examined. Seven fetuses were of gestational age 16 weeks or less, 14 were at 17–20 weeks, and 10 were at over 20 weeks' gestation.

Older fetuses generally showed more meconium that had descended through the intestinal tract. This finding was most evident at 16–21 weeks' gestation. All fetuses aged 16 weeks or less with meconium present had anal meconium, indicative of recent defecation. Two of 6 fetuses aged 17–18 weeks and 3 of 8 aged 19–20 weeks showed evidence of having defecated, as did 1 of the 10 aged 20–27 weeks. The reduction in incidence of apparent defecation after 20 weeks' gestation was significant. Prostaglandin-induced abortion was not associated with any particular pattern.

The findings indicate that the fetus routinely defecates in utero until 16 weeks' gestation and stops defecating by 18–20 weeks' gestation. The significance of this is unclear, but the finding may aid the diagnosis of congenital gut diseases such as cystic fibrosis.

▶ [The fetus never ceases to amaze me. In early pregnancy he (or she) swallows amniotic fluid, voids into the amniotic fluid, and, we learn now, apparently defecates as well. If ontogeny recapitulates phylogeny, it also recapitulates social mores, because the authors suggest that the fetus stops defecating indiscriminately around his home after 20 weeks' gestation. This early spontaneous defecation is not to be confused with the much less common occurrence of meconium staining of amniotic fluid, under conditions of fetal distress, in the immature infant (Ostrea, E. M., Jr., et al.: *Acta Obstet. Gynecol. Scand.* 61:275, 1982).—F.A.O.] ◀

1–27 **Naloxone Reverses Neonatal Depression Caused by Fetal Asphyxia.** Endogenous opiates appear to have a role in the ventilatory

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(1–26) Obstet. Gynecol. 60:294–296, September 1982.
(1–27) Science 216:1252–1253, June 11, 1982.

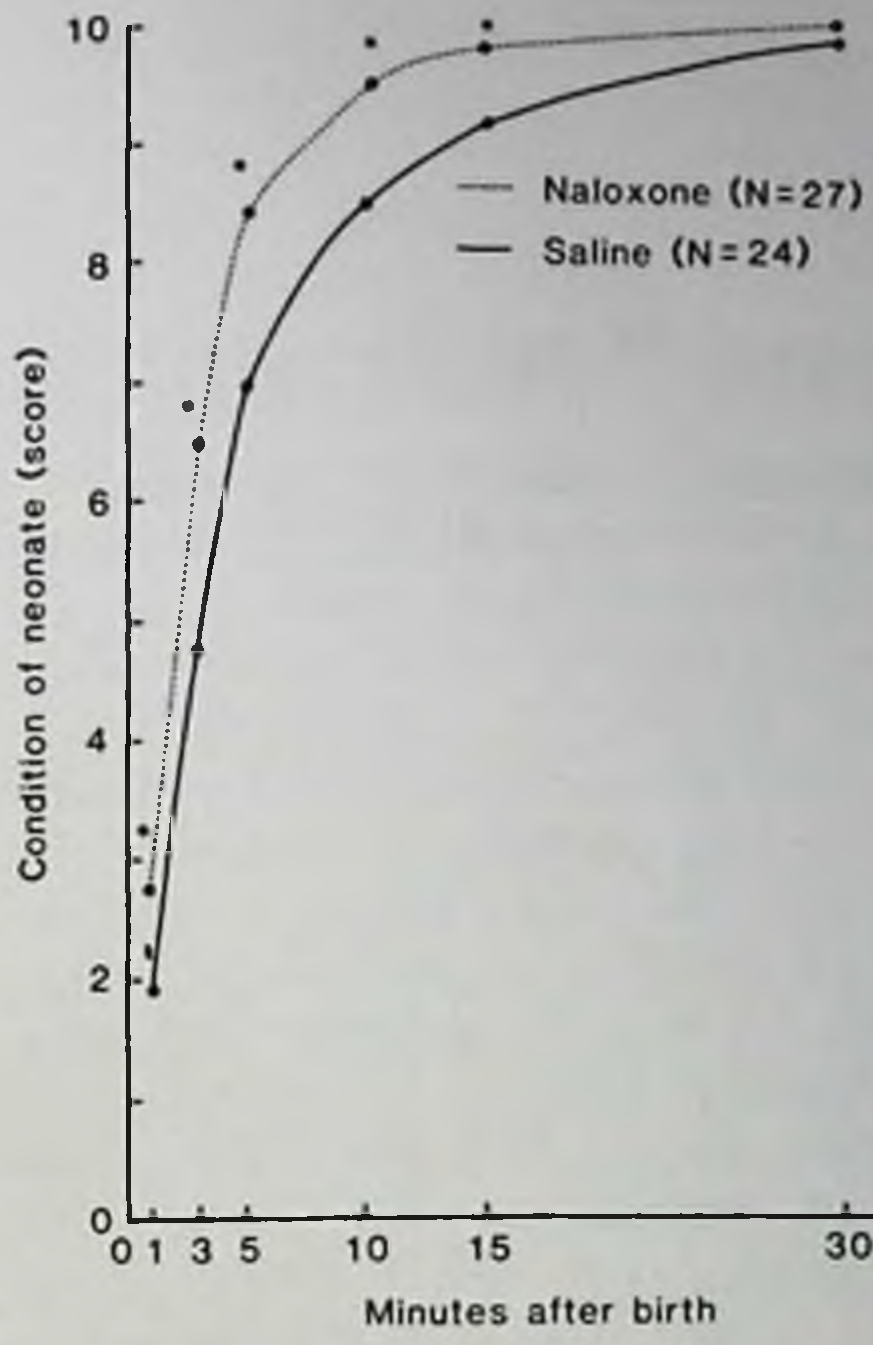

Fig 1–13.—Mean postnatal scores for pups of mothers treated with naloxone or saline and asphyxiated in utero. Asterisks indicate significant differences ($P < .05$, Spearman's rank correlation test). All pups survived to 30 minutes. (Courtesy of Chernick, V., and Craig, R. J.: Science 216:1252–1253, June 11, 1982. Copyright 1982 by the American Association for the Advancement of Science.)

response of neonates to asphyxia or hypoxia. Many of the features of the asphyxic neonate mimic the effects of exogenous opiates. Victor Chernick and Randy J. Craig (Univ. of Manitoba, Winnipeg) postulated that endogenous opiates may be implicated in the neonatal depression following intrauterine asphyxia. Pregnant near-term rabbits were given either naloxone, 1 mg/kg, or saline intravenously before being asphyxiated, and the fetuses were delivered by cesarean section and observed for up to 30 minutes. Postnatal scores are shown in Figure 1–13. Pups of naloxone-treated mothers had significantly higher scores at most intervals than those of saline-treated mothers.

The poor condition of neonates asphyxiated in utero may be due at least partly to the release of endogenous opiates, and naloxone may be effective in resuscitating neonates that have suffered asphyxia during delivery. Naloxone, however, may be a less selective antagonist of endogenous opiates than previously thought. It should not be used clinically until a controlled trial has been done to examine both beneficial and potential adverse effects of naloxone in the depressed newborn infant.

▶ [Naloxone was synthesized about 25 years ago—long before we knew anything about the endogenous synthesis of endorphins. Naloxone was used successfully to antagonize the respiratory depression produced in the newborn by the administration of oplates to the mother during labor. We know that the fetus produces endorphins and that the stress of labor produces increases in the cord blood concentration of β-endorphins (Bridgens, N. K.: *J. Am. Osteopath. Assoc.* 82:198, 1982). It only seems reasonable to believe that naloxone might correct the depression seen in infants born after a stressful delivery. The work in rabbits looks promising and is included here in hopes that it will stimulate further trials—not in rabbits, but in human beings. For more on naloxone, a drug with great promise in the treatment of all forms of shock, see the 1982 YEAR BOOK, pages 427–430.—F.A.O.] ◀

2. Infectious Disease and Immunity

2–1 **Observation Scales to Identify Serious Illness in Febrile Children.** Young children with fever and serious illness may not manifest classic findings suggestive of the illness, and pediatricians rely on clues gained before physical examination, sometimes referred to as "toxicity." Paul L. McCarthy, Michael R. Sharpe, Sydney Z. Spiesel, Thomas F. Dolan, Brian W. Forsyth, Thomas G. DeWitt, Howard D. Fink, Michael A. Baron, and Domenic V. Cicchetti (Yale Univ.) undertook to define valid, reliable observational data for making such judgments by using information from two previous studies to construct three-point scales of 14 observed items that correlated with serious illness. The scaled items then were scored by attending physicians, residents, and nurses, before history-taking and examination, for 312 consecutive children aged 2 years and younger who had a temperature of 101 F or above. Thirty-seven of the children were found to have serious illness.

An analysis based on patients seen by at least 1 attending physi-

TABLE 1.—Agreement Data for 11 Observation Items Scored in 68 Children Seen by Same 2 Attending Physicians in Primary Care Center

Observation Item	κw	Observed Agreement (%)	Change Expected Agreement (%)
Playing with object	.85	95	67
Movement	.79	94	72
Reaction to parent stimulation	.73*	92	69
Response to social overtures	.73*	90	64
Respirations	.58	82	56
Quality of cry	.56*	89	74
Color	.55*	97	93
Appearance of eyes	.50	80	59
State variation	.47*	95	91
Response to visual stimulation	.37	91	85
Hydration	.10†	88	87

*Item included in predictive model, $P \leq .0001$.
†Item included in predictive model, $P \leq .05$.
(Courtesy of McCarthy, P. L., et al.: Pediatrics 70:802–809, November 1982. Copyright American Academy of Pediatrics 1982.)

(2–1) Pediatrics 70:802–809, November 1982.

cian at a primary care center revealed six items that were significant independent predictors of serious illness. The items were quality of cry, reaction to parents, state change, color, state of hydration, and response to social overtures. Agreement between 2 attending physicians in scoring these items ranged from 88% to 97% (Table 1). The

TABLE 2.—PREDICTIVE MODEL: SIX OBSERVATION ITEMS AND THEIR SCALES

Observation Item	1 Normal	3 Moderate Impairment	5 Severe Impairment
Quality of cry	Strong with normal tone OR Content and not crying	Whimpering OR Sobbing	Weak OR Moaning OR High pitched
Reaction to parent stimulation	Cries briefly then stops OR Content and not crying	Cries off and on	Continual cry OR Hardly responds
State variation	If awake → stays awake OR If asleep and stimulated → wakes up quickly	Eyes close briefly → awake OR Awakes with prolonged stimulation	Falls to sleep OR Will not rouse
Color	Pink	Pale extremities OR Acrocyanosis	Pale OR Cyanotic OR Mottled OR Ashen
Hydration	Skin normal, eyes normal AND Mucous membranes moist	Skin, eyes-normal AND Mouth slightly dry	Skin doughy OR Tented AND Dry mucous membranes AND/OR Sunken eyes
Response (talk, smile) to social overtures	Smiles OR Alerts (≤2 mo)	Brief smile OR Alerts briefly (≤2 mo)	No smile Face anxious, dull, expressionless OR No alerting (≤2 mo)

(Courtesy of McCarthy, P. L., et al.: Pediatrics 70:802–809, November 1982. Copyright American Academy of Pediatrics 1982.)

items, used together, were 88% specific and 77% sensitive in identifying serious illness. The scale points for the items are shown in Table 2. Serious illness was present in 92.3% of patients with a score of 16 and over and in 2.7% of those with scores of 10 and under. The sensitivity of the six-item model for detecting serious illness, when combined with the history and physical findings, was 92%.

A reliable predictive model has been found to detect serious illness in febrile children. It is most sensitive when combined with the history and physical findings. Patient observation is a useful initial hypothesis-generating measure in evaluating febrile children, establishing the prior probability of serious disease being present. Where the observational findings are equivocal, further clues must be sought in the history and physicial examination and, frequently, in screening laboratory tests.

► [As long as there are children, there will be febrile children; as long as there are febrile children, there will be febrile children without an apparent cause for their fever. Fever without a focus remains a frustrating problem for the physician but, gradually, as a result of the work of McCarthy and others, the clinical signs of serious illness in infants and children are being identified and rational management plans devised.

This article and the next four all deal with some aspect of the problem of the febrile patient. For more of the same, see the 1983 YEAR BOOK (pp. 83–85), 1982 YEAR BOOK (pp. 67–76), and 1981 YEAR BOOK (pp. 93–94). Better still, read the book *The Febrile Child: Clinical Management of Fever and Other Types of Pyrexia*, by Martin I. Lorin (published by John Wiley & Sons). It won't be much of a movie, but it is a wonderful little book.—F.A.O.] ◄

2–2 **Febrile Infants: Predictors of Bacteremia.** Ellen F. Crain and Steven P. Shelov (Albert Einstein College of Medicine, New York) studied 175 infants younger than age 8 weeks presenting to an emergency room with rectal temperature ≥38 C (100.4 F). House officers recorded their impressions of the infants on a number of variables prior to performing a lumbar puncture and obtaining laboratory data and cultures. Impression of sepsis was a global judgment, which a subsequent sample of house staff indicated was based primarily on five factors: the infant's level of activity, feeding pattern, irritability, responsiveness, and ability to be consoled.

All infants were admitted for parenteral antibiotic therapy pending culture results. A major goal was to determine whether there were any early predictors of bacteremia in 134 infants who had no visible source for their fever during the first examination.

Culture-positive bacterial infections occurred in 6.3% (table); the incidence of bacteremia was 3.4%. Nearly all cases of aseptic meningitis presented in the summer, whereas pneumonia was much more common in the winter. Infants younger than age 2 weeks or with fever greater than 39.8 C were rare, but such infants nearly always had a source for the fever and were likely to have bacteremia.

The individual variables of white blood cell count ≥15,000/cu mm, band count ≥500/cu mm, temperature, impression of irritability, tone, cry, and activity level were not related to the presence of bacteremia. An erythrocyte sedimentation rate (ESR) ≥30 and the ex-

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(2–2) J. Pediatr. 101:686–689, November 1982.

INFANTS WITH POSITIVE BACTERIAL CULTURES

Patient	*Age*	*Month*	*Highest temperature (°C)*	*ER diagnosis (prior to LP)*	*Impression of sepsis*	*WBC/mm³*	*ESR*	*Culture*	*Source*	*Discharge diagnosis*
3	5 wk	May	38.4	GE/r/o sepsis	Ambivalent	10.4	52	Salmonella	B, S	GE with bacteremia
14	5 wk	April	38.8	Otitis media	Negative	16.1	52	Pneumococcus	B	Otitis media
30	13 days	July	39	r/o sepsis	Strong	3.2	2	Group B streptococcus	B, CSF	Meningitis
36	7 wk	Dec.	40	r/o sepsis	Strong	4.3	40	*H. influenzae*	B, CSF	Meningitis
37	8 wk	Sept.	40	r/o sepsis	Ambivalent	15.9	150	Pneumococcus	B	Osteomyelitis
42	7 wk	Sept.	38.6	r/o sepsis	Ambivalent	7.4	35	Salmonella	B, S	GE with bacteremia
24	8 wk	May	38.9	GE/r/o sepsis	Negative	12.6	—	Salmonella	S	GE
41	6 wk	Nov.	39.9	r/o sepsis	Ambivalent	6.3	18	Salmonella	S	GE
43	3 wk	Aug.	38.4	Otitis media	Negative	9.7	—	Shigella	S	Otitis media, GE
44	8 wk	May	38.8	r/o sepsis	Ambivalent	6.3	6	Salmonella	S	GE
49	5 wk	Dec.	38.4	UTI	Negative	9.8	8	*E. coli*	U	UTI

ER, emergency room; LP, lumbar puncture; UTI, urinary tract infection; r/o, rule out; B, blood; S, stool; U, urine; CSF, cerebrospinal fluid; GE, gastroenteritis.

(Courtesy of Crain, E. F., and Shelov, S.P.: J. Pediatr. 101:686–689, November 1982.)

amination's impression of sepsis were significantly associated with bacteremia but did not correctly identify all cases. However, the combination of impression of sepsis, count ≥15,000/cu mm, and ESR ≥30 identified all infants with bacteremia and excluded 82% of those eventually shown not to have bacteremia.

▶ [The "impression of sepsis" based on the infant's level of activity, feeding pattern, irritability, responsiveness, and ability to be consoled are extremely similar to the six factors described by McCarthy and associates (see the preceding article) as being the most useful predictors of significant illness. McCarthy found that the quality of the cry, reaction to parents, state variation, color, state of hydration, and response to social overtures were the most useful.

From all that is written on this subject, one may conclude that somewhere between 5% and 10% of infants and young children with a fever of 40 C (104 F) will have no apparent focus for their illness. The incidence of occult bacteremia in this group of patients will range from 3.5% to 10%. If you add one additional criterion such as blood cell count, erythrocyte sedimentation rate, zeta sedimentation rate, C-reactive protein, etc., to the fever criterion, you can increase the probability of any given patient with a fever of 40 C being bacteremic from 5%–10% to 20%–30%. The treatment options are: treat nobody until culture results are known, treat everybody until culture results are known, and treat selective patients until culture results are known. It would seem that selective treatment is the preferred option, and we are just struggling with the selection criteria. The clinical features identified in this study and those of McCarthy et al. certainly should be included in these selection criteria.—F.A.O.] ◀

2–3 **Evaluation and Treatment of the Febrile Infant.** Febrile infants are thought to be at increased risk of developing life-threatening infections, and at many pediatric centers all such infants are hospitalized for systemic antibiotic therapy. William B. Caspe, Oscar

TABLE 1.—DISCHARGE DIAGNOSES IN 305 INFANTS LESS THAN AGE 60 DAYS WITH TEMPERATURES OF AT LEAST 100.4 F

	No.	% of Total
Presumed viral illness		
Upper respiratory tract infection	115	37.7
Nonspecific viral illness	84	27.5
Gastroenteritis	41	14.3
Aseptic meningitis	15	4.9
Bronchiolitis	1	0.3
Total	256	83.8
Bacterial illness		
Sepsis/meningitis	11	3.6
Urinary tract infection	7	2.3
Gastroenteritis	8	2.6
Omphalitis	3	1.0
Pustulosis	3	1.0
Total	32	10.5
Bacterial or viral illness		
Otitis media	8	2.6
Pneumonia	4	1.3
Total	12	3.9
Other illness		
Narcotic withdrawal	3	1.0
Diphtheria-pertussis-tetanus toxoid	1	0.3
Necrotic hemangioma	1	0.3
Total	5	1.6

(Courtesy of Caspe, W. B., et al.: Pediatr. Infect. Dis. 2:131–135, Mar.–Apr. 1983.)

(2–3) Pediatr. Infect. Dis. 2:131–135, Mar.–Apr. 1983.

TABLE 2.—INFANTS WITH POSITIVE BLOOD CULTURES

Patient	Age (Days)	Temperature (°C)	Appearance*	WBC (× 10³)	Band Count	Culture	Source†
V. E.	56	38.8	+	6.6	396	*E. coli*	B
M. M.	17	38.9	+	14.0	0	*E. coli*	B, U
A. V.	51	38.9	+	16.0	2,400	*E. coli*	B, U
G. M.	17	39.2	−	16.2	1,134	GBS	B
S. J.	5	38.9	+	10.2	0	GBS	B, CSF
T. T.	19	38.9	+	9.2	184	GBS	B, J
D. S.	23	38.6	+	8.1	0	GBS	B
R. A.	56	39.7	+	38.5	23,485	*S. pneumoniae*	B, CSF
J. R.	50	40.0	+	22.8	912	*S. pneumoniae*	B
R. Q.	16	38.9	+	23.9	2,868	Salmonella Group B	B
D. P.	10	39.4	+	9.7	485	*Staph. aureus*	B, J

*+, Appeared ill; −, appeared well.
†B, blood; U, urine, J, joint, CSF, cerebrospinal fluid.
(Courtesy of Caspe, W. B., et al.: Pediatr. Infect. Dis. 2:131–135, Mar.–Apr. 1983.)

Chamudes, and Beth Louie (Bronx-Lebanon Hosp. Center, New York) reviewed the findings in 305 infants aged 2 months or younger who had a rectal temperature of 100.4 F or above and were evaluated for sepsis in a 5½-year period. The largest number of febrile infants was seen in July through September.

TABLE 3.—COMPARATIVE FEATURES OF FEBRILE INFANTS LESS THAN AGE 60 DAYS WITH AND WITHOUT BACTEREMIA

	No. of Patients	Mean Age (Days)	Mean Temperature (°F)	% of Infants with WBC ≥15,000
Bacteremia	11	29.1	102[a]	45
No bacteremia	256	37	101[a]	15
P		NS*	<0.01	<0.05

*Not significant.

(Courtesy of Caspe, W. B., et al.: Pediatr. Infect. Dis. 2:131–135, Mar.–Apr. 1983.)

TABLE 4.—INCIDENCE OF BACTEREMIA IN FEBRILE INFANTS ACCORDING TO AGE AND PERIPHERAL WHITE BLOOD CELL COUNT

	% of Patients with Bacteremia	
	<30 days (107)*	>30 days (198)
Overall incidence	6.5	2
WBC ≥ 15,000	6.5	10.7
WBC < 15,000	7.2	0.5

*Numbers in parentheses denote numbers of patients.

(Courtesy of Caspe, W. B., et al.: Pediatr. Infect. Dis. 2:131–135, Mar.–Apr. 1983.)

Discharge diagnoses are listed in Table 1. Significant disease was present in one fifth of the infants, although only 3.6% had bacteremia. Neither age nor degree of fever helped identify infants with bacteremia, but a white blood cell count greater than 15,000/cu mm was helpful in infants older than age 1 month (Table 2). The differential white blood cell count was not helpful in identifying bacteremic infants. The appearance of the infant was the most important predictor of bacteremia. Features of the infants with and those without bacteremia are compared in Tables 3 and 4. The 96 ill-appearing infants included all but 1 of the bacteremic patients, 12 of the 15 with aseptic meningitis, and all 3 with pneumonia. An infant aged 1 to 2 months who appeared to be ill and had a white blood cell count of 15,000/cu mm or above had a 27% chance of having bacteremia.

Bacteremia is relatively infrequent in febrile infants younger than age 2 months, but serious infection is likely in infants who are bacteremic. The clinical appearance and laboratory findings are helpful in identifying bacteremic infants, but they are not sensitive enough to detect all such infants, especially those younger than age 1 month. The authors believe it is wise to hospitalize all febrile infants younger than age 2 months and perform a complete sepsis evaluation. Those younger than age 30 days receive parenteral antibiotics pending the

culture results, even if the clinical and laboratory findings are normal. Well-appearing infants older than age 30 days who have normal cerebrospinal fluid and urine studies and a peripheral white blood cell count of less than 15,000/cu mm can be observed without receiving antibiotics.

▶ [This study nicely depicts the problem. Shannon's Law states, "Nothing is simple." Remember, there is no problem a good miracle can't solve. And in the *Talmud* we are told, "Where there is no solution, there is no problem."—F.A.O.] ◀

2–4 **Occult Bacteremia in Toxic-Appearing, Febrile Infants: A Prospective Clinical Study in an Office Setting.** Richard H. Schwartz and Raoul L. Wientzen, Jr. (Georgetown Univ., Washington, D.C.) evaluated the prevalence of occult bacteremia prospectively in two groups of infants aged 2–36 months: those with a toxic appearance and temperature greater than 38.8 C (102 F) and those with similar fever but without a toxic appearance. Patients were diagnosed by 1 physician in a suburban, middle-class, private ambulatory pediatric practice.

Toxicity scores were based on results of history and physical examination (Table 1); febrile infants with a toxicity rating of 2+ or 3+ were considered "toxic-appearing." Blood cultures and white blood cell (WBC) counts were obtained for each child.

An infectious source, commonly otitis media, was found in 26 (50%) of 52 toxic children; 18 (35%) of the toxic-appearing patients had WBC counts greater than 15,000/cu mm. Bacteremia was documented in 6 toxic patients (12%), due to *Streptococcus pneumoniae* in 5 and to group-C *Streptococcus* organisms in 1. In 5 of these bacteremic infants, no overt focus of infection could be identified. None of 31 febrile children without a toxic appearance had bacteremia; 23% had WBC counts ≥15,000/cu mm.

Associations statistically significant for bacteremia included WBC count ≥15,000/cu mm, diagnosis of acute fever of unknown origin (FUO) plus a toxic appearance, diagnosis of FUO plus leukocytosis, and the combination of a diagnosis of acute FUO, toxic appearance, and leukocytosis (Table 2). Five patients with bacteremia were treated with penicillin derivatives on an ambulatory basis after WBC counts and blood cultures were obtained. All 5 were afebrile and well, with sterile blood cultures, 48 hours later. The 1 patient not treated with an antibiotic at the initial assessment was still febrile and toxic 24 hours later and had to be hospitalized.

It is concluded that the risk for occult bacteremia may be high in the moderately toxic febrile child with no focus of infection. Toxic appearance, as determined by an experienced pediatrician, may be the most significant clinical correlate to bacteremia in a child with high fever. Toxicity diagnosed on the basis of clinical findings in a febrile infant warrants obtaining a WBC count and a blood culture. Study of larger numbers of nontoxic febrile children is needed to delineate the risk of bacteremia in this group.

(2–4) Clin. Pediatr. (Phila.) 21:659–663, November 1982.

TABLE 1.—Toxicity Score Criteria

Patient Group	Toxicity Score*	Clinical Presentation
Hospitalize	4+	Child looks seriously ill: severe lethargy, inactivity, inattentiveness, anorexia, apathy, weak cry
Study	3+	Child looks moderately ill during entire period of observation: moderate lethargy or irritability, poor eye-to-eye contact, diminished activity and playfulness, decreased appetite, attenuated cry, diminished resistance to performance of painful parts of physical examination
	2+	Child looks somewhat ill: some discernible and persistent lethargy and irritability, diminished activity and playfulness, decreased appetite
Control	1+	Child looks mildly ill at times but has intermittent periods of alertness, playfulness, interest in other people, and enough strength to resist otoscopic and intraoral examination
	0	Child generally alert, active, playful, interested in other people; good appetite at least for liquids; actively resists otoscopic and intraoral examination

*All scores assigned by 1 physician.
(Courtesy of Schwartz, R. H., and Wientzen, R. L., Jr.: Clin. Pediatr. (Phila.) 21:659–663, November 1982.)

▼ [M. A. Baron and H. D. Fink (*Pediatrics* 66:171, 1980; and 1982 Year Book, pp. 68–71), in a suburban pediatric office setting, found that 8 of 76 (10.5%) infants, aged 3–24 months, with a temperature of 39.5 C or more without apparent focus were bacteremic. The addition of a white blood cell count and differential assisted in identifying a subgroup of infants who were at greatest risk.

TABLE 2.—Clinical and Laboratory Correlates of Bacteremia

Patient Characteristic	Prevalence of Bacteremic	Significance*
Toxicity		
≥2+	6/52 (12%)	p > 0.1
<2+	0/31 (0%)	
Diagnosis		
FUO	5/45 (11%)	p > 0.1
non-FUO	1/38 (3%)	
WBC count		
≥15,000	5/26 (19%)	p < 0.05
<15,000	1/57 (2%)	
Toxicity and FUO		
toxicity and FUO	5/26 (19%)	p < 0.05
toxicity only, FUO only, or neither	1/57 (2%)	
Toxicity and WBC count		
toxicity and WBC ≥15,000	5/19 (26%)	p < 0.01
toxicity only, WBC ≥15,000 only, or neither	1/64 (2%)	
FUO and WBC		
FUO and WBC ≥15,000	4/14 (29%)	p < 0.01
FUO only, WBC ≥15,000 only, or neither	2/69 (3%)	
Toxicity, FUO, WBC		
toxicity + FUO + WBC ≥15,000	4/9 (44%)	p < 0.01
Lacking 1, 2 or all 3 characteristics	2/74 (3%)	

*By χ^2 analyses.

(Courtesy of Schwartz, R. H., and Wientzen, R. L., Jr.: Clin. Pediatr. (Phila.) 21:659–663, November 1982.)

Toxic appearance, as judged by an experienced pediatrician, may be as useful as any screening laboratory procedure in identifying the infants at highest risk.

How common a problem is this for the pediatrician in practice? R. Hoekelman (*Am. J. Dis. Child.* 133:1017, 1979) calculated that every 4.6 days a practicing pediatrician would see 1 febrile child, aged 1–24 months, without localizing findings, and every 36.7 days would see 1 such patient with a temperature of 40 C or more. Baron and Fink calculated that a pediatrician would encounter such a situation once every 15 days.—F.A.O.] ◄

2-5 **Unsuspected Meningococcemia** is discussed by Barry Dashefsky, David W. Teele, and Jerome O. Klein (Boston Univ.). Of 536 episodes of bacteremia caused by *Streptococcus pneumoniae, Hemophilus influenzae,* or *Neisseria meningitidis* during 1971 to 1981, 26 (5%) were caused by *N. meningitidis.* Most cases of meningococcemia occurred in clusters and during the winter or spring. Of the 25

(2–5) J. Pediatr. 102:69–72, January 1983.

cases of meningococcemia for which records were available, 13 (52%) were in children sufficiently ill for prompt hospitalization and initiation of empiric parenteral antibiotic therapy and 12 (48%) were in children sufficiently well not to raise concern for serious, invasive disease.

The 12 children with "unsuspected meningococcemia" were aged 3 to 20 months (median, 8 months). All were febrile but without rash or signs of shock. White blood cell counts were greater than 15,000/cu mm in only 2 of 9 children, and lumbar puncture studies were normal in 2 of 2. Of these 12 children, 8 were given oral antimicrobial therapy and 4 were not.

At recall 4 hours to 3 days (median, 1 day) after presentation, 4 of 8 initially given oral antibiotics were improved and 4 were not (table). Of these 8 children, 7 were given appropriate antibiotic therapy parenterally and 1 completed a course of oral antibiotics; all recovered without complications. The 4 children with unsuspected meningococcemia not initially treated with oral antibiotics were unimproved when reevaluated. Of these, 2 responded to antibiotic therapy and 2 deteriorated over 4 to 8 hours and died. Both deaths were in children with neutropenia at the time of initial evaluation.

An adverse outcome (meningitis or death) occurred more often ($P = 0.005$) with unsuspected meningococcemia (4 of 12 patients; 33%) than with unsuspected bacteremia caused by *S. pneumoniae* (4 cases of meningitis and no deaths in 97 patients; 4%) or *H. influenzae* (3 cases of meningitis and no deaths in 42 patients; 7%).

▶ [Meningococcemia in this population was a relatively uncommon event, representing only 5% of episodes of bacteremia. Unfortunately, almost one-half (12 of 25) were unsuspected. N. Quoc and associates (in press) have found that approximately 15% of children presenting with fever and petechiae will be bacteremic and about 50% of this group will have meningococcemia.

OUTCOME AT FOLLOW-UP EVALUATION OF CHILDREN WITH UNSUSPECTED MENINGOCOCCEMIA

	Treated with oral antimicrobials at initial evaluation	*Not treated with oral antimicrobials at initial evaluation*
Improved*	4	0
Persistent bacteremia†	0/4	0
Unimproved	4	4
Persistent bacteremia†	1/4	1/4
Meningitis	2	1
Death	0	2

*Afebrile without a new focus of infection.

†Number with positive blood cultures/number from whom blood culture obtained.

(Courtesy of Dashefsky, B., et al.: J. Pediatr. 102:69–72, January 1983.)

M. Robinow and associates (*Am. J. Dis. Child.* 137:279, 1983) describe a 30-month old girl who was found to have partial destruction of the right humeral and right femoral head 2 years after recovery from meningococcal septicemia and disseminated intravascular coagulation. Seven other cases previously have been described, and these skeletal lesions appear to be a characteristic sequelae of infantile meningococcemia complicated by disseminated intravascular coagulation.

For more on the complications and sequelae of meningococcal infections in children, see the 1983 YEAR BOOK (pp. 71–73) by M. S. Edwards and C. Baker.—F.A.O.] ◀

2–6 **End-of-Treatment Spinal Tap in Bacterial Meningitis: Is It Worthwhile?** Many physicians still routinely perform a lumbar puncture at the end of treatment of bacterial meningitis to confirm that the patient is cured, but the grounds for such "test-of-cure" procedures are questionable. David T. Durack and Alan Spanos (Duke Univ.) reviewed the findings in 275 cases of bacterial meningitis treated in 1969–1980, including 163 cases in which cured patients had posttreatment spinal taps. Posttreatment taps were done in 165 of the 243 surviving patients, mostly on the first or second day after discontinuation of antimicrobial therapy. Most patients were discharged within 2 days after the posttreatment lumbar puncture.

In posttreatment taps, the ranges of glucose levels and polymorphonuclear leukocytes per cu mm compatible with cure were wide. Cerebrospinal fluid (CSF) protein levels were above 45 mg/dl in 38% of cases, and were above 100 mg/dl in 8% of cases. High protein levels were not associated with unusually low glucose levels, and neither was associated with unusually high cell counts in the same samples. The posttreatment tap directly affected treatment in only 8% of cases. All these patients were clinically well, and none had a relapse or later complications. Only 2 patients in the overall series had complications after the initial course of antimicrobial therapy.

No patient in this series was benefited by the performance of a lumbar puncture after completion of treatment of bacterial meningitis. Unwarranted concern about "abnormal" findings led to postponement of discharge and further unnecessary taps in some cases. The burden of proving the value of the posttreatment lumbar puncture lies with those who continue to use it.

▶ [Yes, you are right, these conclusions already have been reached by others (Jacob, J., et al.: *Am. J. Dis. Child.* 131:46, 1977; Chartrand, S. A., et al.: *J. Pediatr.* 88:424, 1976; Schaad, U. B., et al.: *Pediatrics* 67:188, 1981; and Rutman, D. L., et al.: *Clin. Pediatr.* (Phila.) 20:192, 1981). I hope you are convinced.—F.A.O.] ◀

2–7 **Conjunctivitis-Otitis Syndrome.** Frank Franjo Bodor (Fairview Hosp. Physicians' Center, Cleveland) studied purulent conjunctivitis associated with otitis media (PCOM) in 113 patients over a 1-year period.

Of 132 patients seen with purulent conjunctivitis (PC), 96 (73%) concurrently had otitis media (OM). Of patients with PCOM, 50% were younger than age 2 years (Fig 2–1); among patients with OM, only 30% were younger than age 2 years. In 28 (49%) of 57 families

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(2–6) JAMA 248:75–78, July 2, 1982.
(2–7) Pediatrics 69:695–698, June 1982.

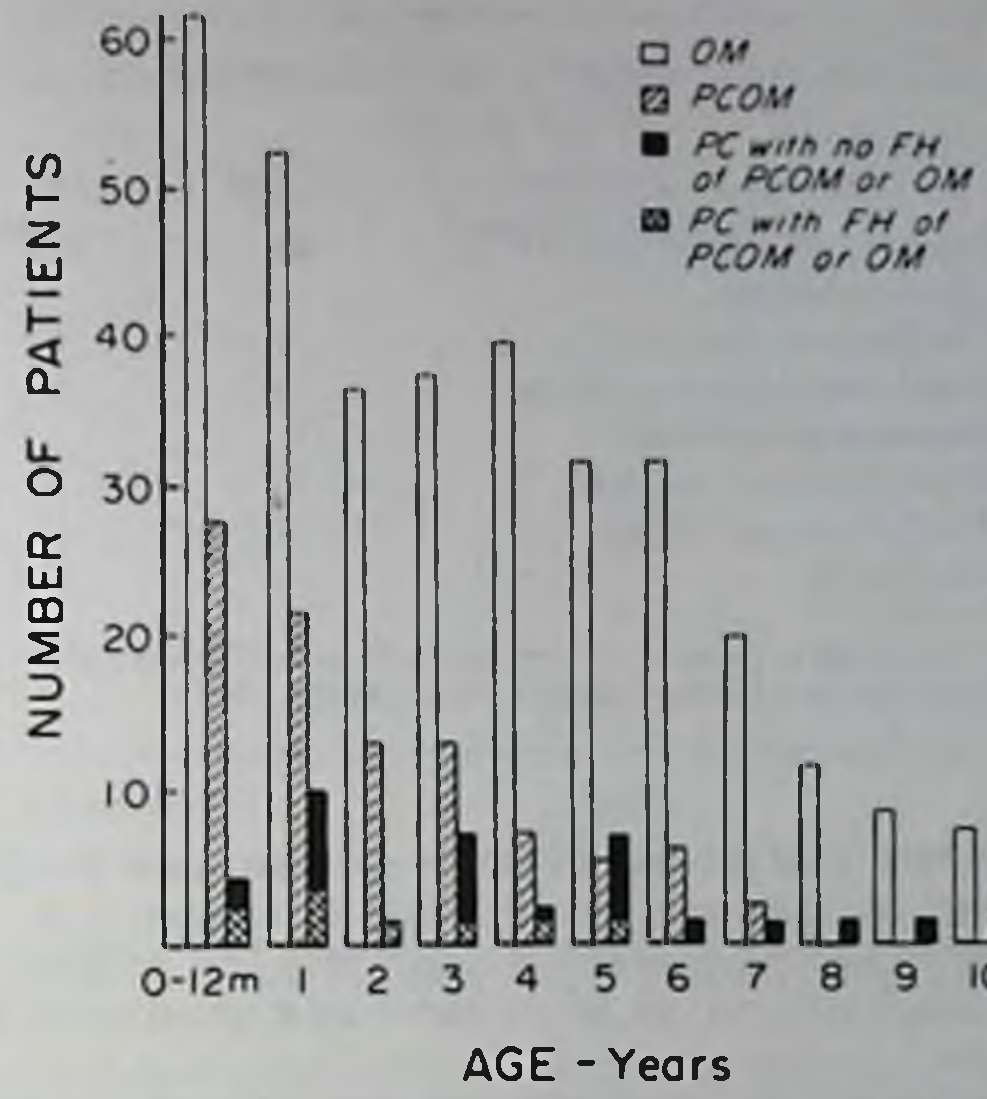

Fig 2–1.—Distribution by age of 96 patients with PCOM, 346 with OM, and 36 with PC. FH = family history. (Courtesy of Bodor, F. F.: Pediatrics 69:695–698, June 1982. Copyright American Academy of Pediatrics 1982.)

with more than 1 child, siblings of the index cases had PC or OM, or both, simultaneously or within 1 month. Four mothers had PC simultaneously with PCOM in their children.

The illness usually started with fever, mucopurulent rhinorrhea, and cough. Pain in the eye with purulent discharge usually began 3 or 4 days later. The conjunctivae were injected and tearing occurred. Earache usually started on the same day as the eye symptoms or 1 to 3 days later. There were great variations between cold and warm seasons in numbers of patients with OM, but this was not the case with occurrence of PCOM.

Haemophilus influenzae was isolated from 55 (73%) of the conjunctival cultures done on patients with PCOM (table). Of 18 cultures that were typed, 6 were type B. Of 31 patients who had nasal cultures taken simultaneously with conjunctival cultures, 27 (87%) had identical microorganisms.

▶ [I was very impressed by this paper because of its practical nature and the fact that it was conducted in a private office setting. I asked Dr. Ellen R. Wald, Associate Professor of Pediatrics, University of Pittsburgh School of Medicine, and "Doctor Sinus" to me, to comment. Doctor Wald writes:

"Conjunctivitis is a common clinical problem in neonates as well as toddlers and school-age children. Neonatal conjunctivitis may be caused by a variety of agents—the etiology is most likely surmised according to the time of onset. Chemical conjunctivitis, a nearly universal accompaniment of silver nitrate prophylaxis, is seen in the first few days of life. At age 3–5 days, the presence of purulent conjunctivitis should prompt the consideration of gonococcal ophthalmia. By age 5–14 days, *Chlamydia trachomatis* is the most common etiologic agent of ophthalmia neonatorum. *Chlamydia trachomatis* conjunctivitis may be prevented by the treatment of the maternal cervical infection with orally administered erythromycin (McMillan: *Pediatr. Res.* 17:277A, 1983); alternatively, erythromycin ophthalmic preparation may be used as a prophylactic agent for the infant at delivery (*JAMA* 244:2291, 1980). Infection with *C. trachomatis* may be treated with either topical or systemic erythromycin therapy.

CONJUNCTIVAL CULTURES OF 75 PATIENTS WITH PCOM AND PC

Bacterial Agent	PCOM	PC
Haemophilus influenzae (nontypable)	49	14
H influenzae type B	6	1
Streptococcus pneumoniae	3	2
Neisseria catarrhalis	1	
Staphylococcus aureus	1}	
Staphylococcus albus	11	1
No growth	4	8

(Courtesy of Bodor, F. F.: Pediatrics 69:695–698, June 1982. Copyright the American Academy of Pediatrics 1982.)

Although both adequately treat the eye findings, only systemic therapy has the potential to eradicate nasopharyngeal colonization with C. *trachomatis* (*Am. J. Dis. Child.* 136:817, 1982). Coagulase-positive staphylococci may, on occasion, cause purulent conjunctivitis in the newborn and, as such, serve as a source for Ritter's disease or scalded skin syndrome.

"The etiology of conjunctivitis in infants and children was recently investigated by Gigliotti and colleagues (see 1982 YEAR BOOK, p. 356). In a prospective study, *Hemophilus influenzae, Streptococcus pneumoniae* and adenovirus were shown to be the common agents causing this infection. These investigators made an important clinical observation: when patients with purulent conjunctivitis had concurrent otitis media, *H. influenzae* was recovered from eye cultures 75% of the time. On the other hand, the presence of conjunctivitis and pharyngitis was predictive of adenoviral disease in two thirds of the patients.

The current study extends these observations of the frequent concurrence of otitis media and purulent conjunctivitis and underscores two facts: (1) there is a great likelihood of transmission of this syndrome or its clinical components within households or among playmates, and (2) one third of the organisms recovered from the conjunctival cultures are *H. influenzae* type b.

The therapy of bacterial conjunctivitis is another area of interest. A recent abstract (Gigliotti: *Pediatr. Res.* 17:271A, 1983) reported the efficacy of topical ophthalmic therapy in 80 children between ages 1 month and 18 years. The youngsters were entered into a randomized double-blind trial designed to determine whether topical antibiotic therapy was beneficial. The bacterial etiology of the conjunctivitis was confirmed in 44 patients: 28 with *H. influenzae* and 16 with *S. pneumoniae*. Patients were treated 4 times a day for 7 days with drug (ophthalmic ointment containing polymyxin and bacitracin) or placebo (the ointment vehicle). Clinical response at 3–5 days and bacteriologic cure at 10 days were both statistically significantly better in the drug-treated than in the placebo-treated patients. Although I would not have chosen the particular ophthalmic preparation used here, it appears as though it is satisfactory for accomplishing a more rapid clinical and bacteriologic cure. Treatment of the index case may result in reduced transmission of *H. influenzae* and fewer secondary cases."] ◄

2–8 **Treatment of *Staphylococcus Aureus* Infections in Children in Office Practice.** *Staphylococcus aureus* infections continue to be a troublesome problem in clinical practice. Frank A. Disney and Michael E. Pichichero (Rochester, N. Y.) reviewed experience with 105 *S. aureus* infections occurring in 79 children in a private office practice in 1977–1980. Various antibiotics were prescribed in courses of 7–10 days and usually given on an 8-hour schedule. Some infections were treated only by topical emulsion cleansing and bacitracin oint-

(2–8) Am. J. Dis. Child. 137:361–364, April 1983.

TABLE 1.—COMPARISON OF ANTIBIOTIC DISK SUSCEPTIBILITY INTERPRETATION

Antibiotic	% Sensitive*	
	Hospital Laboratory	Office Laboratory
Ampicillin	10	15
Cefaclor	ND	100
Cephalotnin	100	ND
Clindamycin	97	95
Cloxacillin	ND	95
Erythromycin	95	92
Oxacillin	97	ND
Penicillin	10	15
Sulfamethoxazole-trimethoprim	100	ND
Vancomycin	97	ND

*Percentage of isolates sensitive to designated antibiotic. *ND*, not done.
(Courtesy of Disney, F. A., and Pichichero, M. E.: Am. J. Dis. Child. 137:361–364, April 1983; copyright 1983, American Medical Association.)

ment application. Office and hospital disk susceptibility tests are compared in Table 1.

A total of 132 treatment episodes were evaluated (Table 2). Nearly half the episodes were vesicular pyoderma. Topical therapy plus an oral antibiotic eradicated infection in 86% of 71 pyoderma infections. Nine of 16 episodes of pyoderma were successfully managed by topical therapy only. Oral antibiotics almost always were successful in treating furunculosis. Empirical treatment was effective in children having carbuncles surgically drained. Of 3 children with suppurative otitis media that led to spontaneous tympanic membrane rupture, only 1 responded to initial treatment with amoxicillin. Twenty-three patients required a second therapeutic approach. Susceptibility testing correctly predicted clinical failure or success in 21 patients (Table 3).

Comparable results have been obtained in children with *S. aureus* infections using erythromycin estolate, erythromycin ethylsuccinate, clindamycin, cephalexin, cefaclor, and dicloxacillin. Selection among these agents may be based on cost, patient acceptance, and toxic effects. The authors favor initial treatment with erythromycin once the diagnosis is established. Failure may occur with any regimen, however, and in vitro antibiotic susceptibility testing can be of considerable value in these cases. Drugs active against both staphylococci and streptococci should be used in patients with vesicular pyoderma.

2–9 **Generalized Pustular Rash Associated With Primary Atypical Pneumonia.** *Mycoplasma pneumoniae* infection has been associated with many skin diseases. Motoo Matsubara, Keiichi Ueda, Saburo Kishimoto, Hirokazu Yasuno, Jungi Ikada, Sachiko Sakagami, and Yoshihito Morioka report the case of girl, aged 4, with a skin eruption associated with *M. pneumoniae* infection.

(2–9) J. Dermatol. 9:197–202, June 1982.

TABLE 2.—ANTIMICROBIAL THERAPY FOR *STAPHYLOCOCCUS AUREUS* INFECTIONS*

Infection	Total	Antimicrobial Agent							
		Erythromycin Estolate	Erythromycin Ethylsuccinate	Clindamycin Hydrochloride	Cephalexin/ Cefaclor	Cloxacillin Sodium/ Dicloxacillin Sodium	Amoxicillin/ Penicillin V Potassium	Topical Bacitracin Only	Other
Vesicular pyoderma†	52/63	19/20	17/19	...	4/5	3/3	1/3	8/13	...
Bullous pyoderma	5/7	3/3	2/2	...	...	0/1	...	0/1	...
Secondary pyoderma	14/17	6/7	1/2	4/4	1/1	...	...	1/2	1/1‡
Furunculosis	14/18	3/3	4/4	1/1	...	5/6	1/1	0/3	...
Carbunculosis	12/16	2/3	3/4	4/4	...	1/2	...	...	2/3§
Cellulitis	3/4	2/2	...	1/1	...	0/1	...	...	...
Suppurative otitis media	3/5	1/1	...	...	...	...	1/3	...	1/1‖
Paronychia	2/2	2/2	...	...	...	...	...	...	...

*Episodes of infection successfully treated/total number of episodes.
†In only 3 episodes was a concomitant group A β-hemolytic Streptococcus involved.
‡A case of adolescent acne secondarily infected was successfully treated with tetracycline.
§Carbunculosis was treated by incision and drainage without concomitant antibiotics.
‖A case of suppurative otitis media was treated successfully with sulfamethoxazole-trimethoprim.
(Courtesy of Disney, F. A., and Pichichero, M. E.: Am. J. Dis. Child. 137:361–364, April 1983; copyright 1983, American Medical Association.)

Girl, 4, had been febrile for 6 days and developed a cough 3 days later. A chest x-ray film taken on admission to Matsushita Hospital, Osaka, Japan, showed a shadow in the right lower lobe. Pustules with erythema developed over the hands (Fig 2–2) forearms, legs, and thighs within a day of admission and there was a papulovesicular rash on the trunk. Noninvolvement of the

TABLE 3.—TREATMENT FAILURES*

Unsuccessful Therapy (No. of Failures)	Successful Therapy (No. of Failures)
Erythromycin estolate/erythromycin ethylsuccinate (5)	Erythromycin estolate/erythromycin ethylsuccinate (2), cephalexin/cefaclor (2), and clindamycin hydrochloride (1)
Penicillin V potassium/amoxicillin (4)	Erythromycin estolate/erythromycin ethylsuccinate (2), cefaclor (1), sulfamethoxazole-trimethoprim (1)
Cloxacillin sodium (3)	Erythromycin estolate/erythromycin ethylsuccinate (2), clindamycin hydrochloride (1)
Topical bacitracin (8)	Erythromycin estolate/erythromycin ethylsuccinate (7), cloxacillin sodium (1)
Incision and drainage (1)	Erythromycin estolate/erythromycin ethylsuccinate (1)

*All antibiotics given orally except bacitracin.

(Courtesy of Disney, F. A., and Pichichero, M. E.: Am. J. Dis. Child. 137:361–364, April 1983; copyright 1983, American Medical Association.)

muco-ocular area was noted. Skin biopsy showed subcorneal pustules containing neutrophils and eosinophils with underlying perivascular infiltration of lymphocytes, histiocytes, and neutrophils. Administration of erythromycin cleared up the rash in 17 days. Because drugs had been administered prior to admission, it was difficult to determine whether or not the pustular eruption occurred secondary to *M. pneumoniae*.

The association of *M. pneumoniae* with Stevens-Johnson (S-J) syndrome or erythema multiforme manifesting vesiculobullous

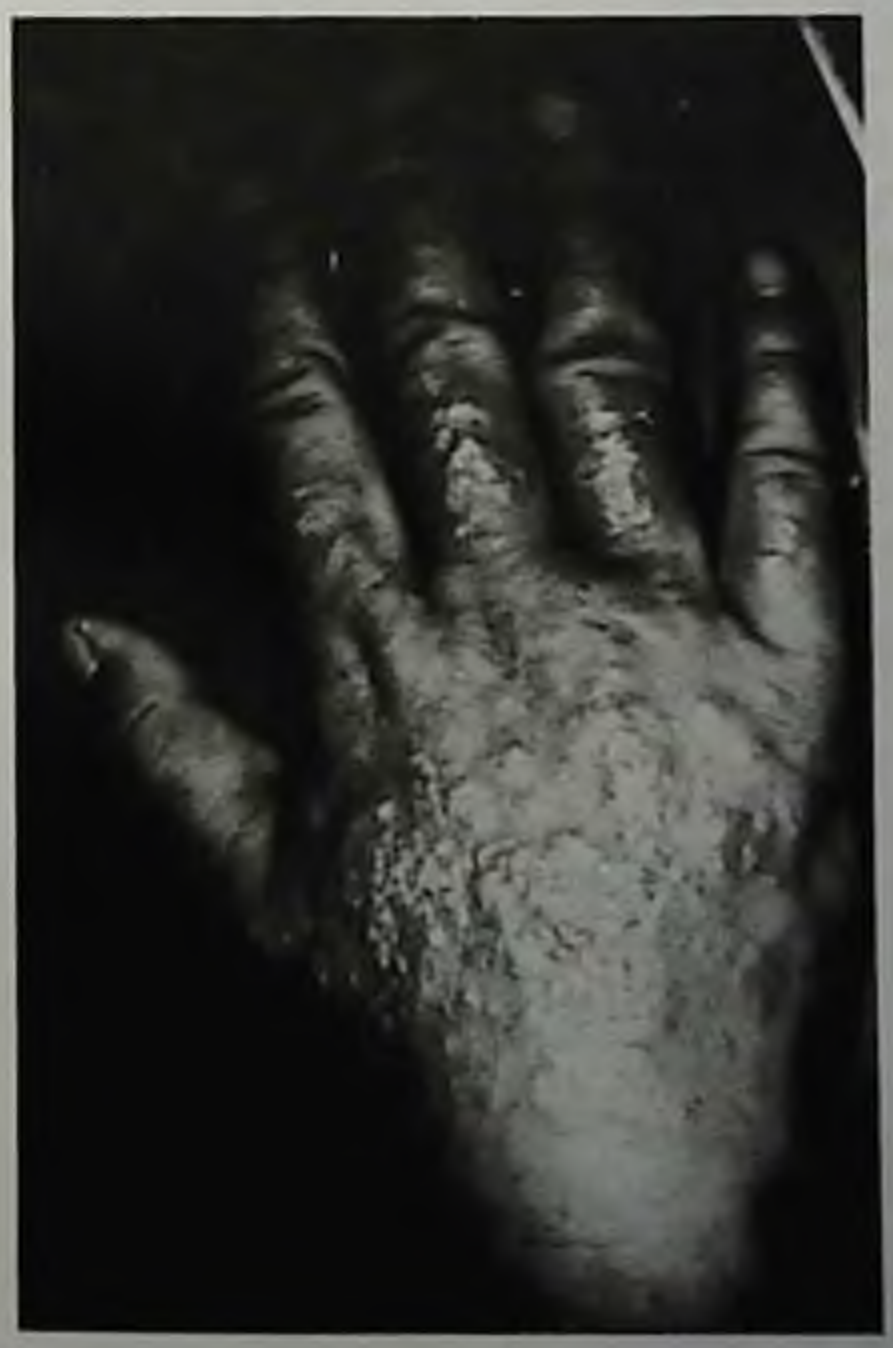

Fig 2–2.—Discrete pustules on the dorsal aspect of the hand. (Courtesy of Matsubara, M., et al.: J. Dermatol. 9:197–202, 1982.)

eruptions is well known; because of the absence of lesions in the muco-ocular region, this case was not diagnosed as S-J syndrome. Rather, the clinical findings were similar to acute generalized pustular bacterid reported by Tan or vesiculopustular eruption with *Mycoplasma* infection described by Teisch. Serologic examinations, including complement fixation test, cold agglutination test, and passive hemagglutination test, confirmed the *M. pneumoniae* infection.

Streptococcal or *M. pneumoniae* infection should be suspected whenever generalized pustular eruptions occur.

2–10 **Immunologic and Epidemiologic Aspects of Varicella Infection Acquired During Infancy and Early Childhood.** Koichi Baba, Hyakuji Yabuuchi, Michiaki Takahashi (Osaka Univ., Osaka, Japan), and Pearay L. Ogra (Children's Hosp. of Buffalo) studied the development of varicella-zoster virus (VZV) infection in infants younger than age 1 year during three varicella outbreaks in a semiclosed domiciliary institution for infants in Japan. Over a 4-year period, many residents ranging in age from 27 days to 32 months were tested for cutaneous reactivity to VZV antigen and VZV-specific antibody activity before, during, and after each varicella outbreak.

Eighty-five subjects developed clinical varicella, with an overall attack rate of 100% for those who were susceptible. All infants younger than age 2 months were infected after exposure, despite the presence of preexisting maternal antibody. The degree of cutaneous involvement appeared to be milder (<20 vesicles) in infants younger than age 2 months, and severe cutaneous disease (>400 eruptions or confluent rash) occurred more often in subjects aged 2 to 11 months (Table 1).

Preexisting levels of VZV antibody in the serum of patients infected with VZV were, in general, low (<1:32). Although lack of detectable preexisting antibody was correlated with the development of moderate or severe skin eruption, the presence of low levels of preexisting antibody (1:4 to 1:16) did not provide significant protection against the appearance of severe cutaneous eruption (Table 2).

TABLE 1.—Relationship of Age of Infants at Time of Onset of Varicella and Degree of Subsequent Cutaneous Involvement

Age (mo)	*Total No.*	*Extent of cutaneous eruption (No. [%] subjects)*		
		Mild	*Moderate*	*Severe*
< 2	5	5(100.0)	0	0
2-5	22	7 (31.8)	5(22.7)	10(45.5)
6-11	26	6 (23.1)	10(38.5)	10(38.5)
12-32	32	14(43.8)	15(46.9)	3(9.4)

(Courtesy of Baba, K., et al.: J. Pediatr. 100:881–885, June 1982.)

(2–10) J. Pediatr. 100:881–885, June 1982.

TABLE 2.—EFFECT OF PREEXISTING MATERNAL ANTIBODY ON OUTCOME OF NATURAL VARICELLA AND DEGREE OF SUBSEQUENT CUTANEOUS INVOLVEMENT*

Titer pre-existing antibody (FAMA)	*Total No.*	*Extent of cutaneous eruption (No. subjects)*		
		Mild	*Moderate*	*Severe*
< 4	7	0	3	4
4	5	3	1	1
8	4	2	1	1
16	2	1	1	0

*All subjects had no skin reactivity (< 1 mm) to VZV antigen prior to exposure to natural varicella.

(Courtesy of Baba, K., et al.: J. Pediatr. 100:881–885, June 1982.)

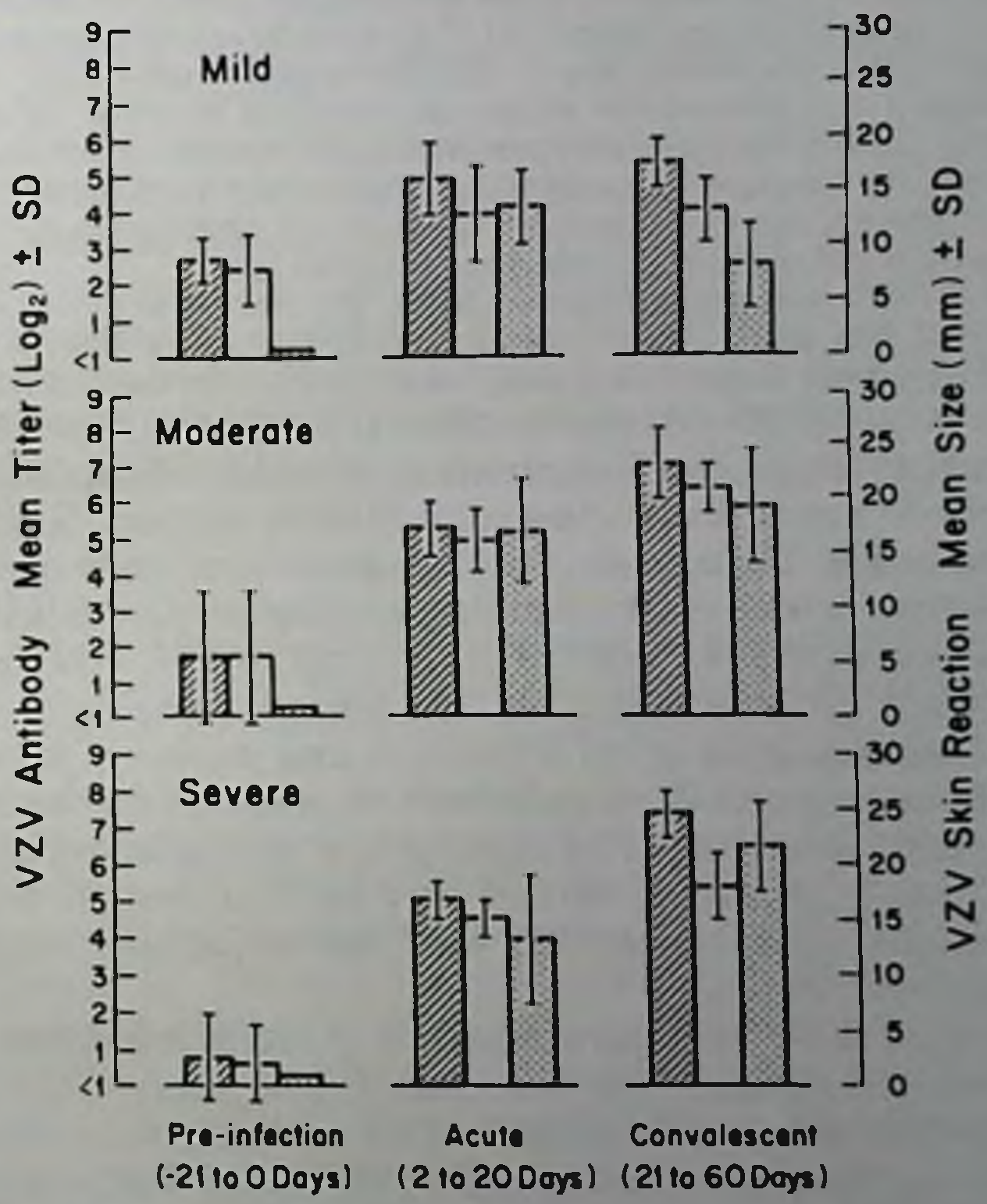

Fig 2–3.—Relationship of extent of cutaneous involvement and preexisting transplacentally acquired antibody to development of antibody and cutaneous reactivity response to VZV after natural varicella infection. *Clear bars*, antibody detected by neutralization; *hatched bars*, antibody detected by fluorescent antibody staining of membrane antigen; and *dotted bars*, cutaneous reaction to intradermal inoculation of VZV antigen. (Courtesy of Baba, K., et al.: J. Pediatr. 100:881–885, June 1982.)

All patients developed significant VZV antibody after infection. However, peak titers of antibody were higher in subjects without prior antibody activity than in those whose serum contained antibody at the time of infection. All subjects manifested positive cutaneous responses

to VZV antigen after onset of varicella (Fig 2–3). The size of skin reactions in children aged 2 to 8 months was 3 to 4 times larger than that of infants younger than age 2 months. Subjects with mild disease had lower antibody response and skin reactivity during convalescence (21 to 60 days) than those with moderate or severe cutaneous involvement.

▶ [Doctor Philip A. Brunell, Professor of Pediatrics and Division Head, Pediatric Infectious Diseases, the University of Texas Health Science Center at San Antonio, and a lifelong student of varicella, writes:

"The authors once more document the conundrum that is immunity to varicella. They restate the well-known observation that chickenpox tends to occur more frequently than other childhood diseases during the early months of life. This is not because fewer mothers have had chickenpox. As they demonstrate, chickenpox is a very contagious disease; a 100% attack rate was observed in their study. Nor can one explain the susceptibility of young infants to the failure of maternal antibody to cross the placenta. The antibody measured in infant's serum does not, at least by itself, prevent chickenpox. This raises additional questions about what we are measuring. It is not clear that some of the antibody we are measuring may not inactivate virus in vitro in the conventional neutralization test. This is not to say that this antibody might not participate with white blood cells in host response to varicella-zoster virus. It is known, moreover, that some white blood cell functions may not be fully matured during infancy. This raises some very practical questions about the value of giving varicella-zoster immunoglobulin to young infants and might explain some of the failures observed when it has been used in this age group. Unfortunately, the protective role of antibody in the newborn period is not resolved fully.

"The varicella skin test antigen appears to be less reactive in the very young, as it is in the very old. The value of this material for determining immunity is still unclear. As is true of skin tests in general, it may be difficult to standardize. Unfortunately, there are too few published data on susceptible adults to judge its value."] ◀

2–11 **Viral Infections of the Respiratory Tract in Hospitalized Children: Study From Oslo During a 90-Month Period.** K.-H. Carlsen, I. Ørstavik, and K. Halvorsen (Oslo) undertook a study of viral infections of the respiratory tract occurring in hospitalized children during 90 months between 1972 and 1979. A total of 979 viral respiratory infections were diagnosed during this period. Respiratory syncytial virus (RSV) caused 58% of all infections and occurred in winter epidemics. Influenza A and B virus infections occurred in the late winter and spring and rhinovirus infections in the spring and autumn. Adenoviruses types 1, 2, and 5 showed no distinct seasonal distribution. Twenty patients, 19 of whom had RSV infection, had concurrent infection with two viruses.

Patients with RSV and parainfluenza 3 virus infections were the youngest, whereas those with influenza B and adenovirus type 7 infections were the oldest. Nearly half of all patients were younger than age 1 year. The diagnoses are given in the table. Respiratory syncytial virus chiefly was associated with bronchiolitis and adenovirus type 7 chiefly was associated with pneumonia. Rhinovirus infection occurred most often in children with episodes of acute bronchial asthma. Influenza and adenovirus infections often occurred with extrarespiratory tract symptoms, including febrile seizures. Otitis media occurred in a minority of patients in all viral groups. Asthma occurred in 13% of all patients and febrile convulsions in 13%. Upper respiratory tract infection alone was most frequent in patients with

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(2–11) Acta Paediatr. Scand. 72:53–58, January 1983.

DISTRIBUTION BY DIAGNOSIS AMONG MOST FREQUENTLY OCCURRING VIRUS INFECTIONS*

	RSV	Rhinovirus	Influenza A and B	Para-influenza 3	Adenovirus 1, 2, 5	Adenovirus 7
URTI only	46 (8)	32 (52)	31 (48)	17 (45)	56 (62)	9 (38)
Laryngitis	3 (1)	2 (3)	1 (1)	4 (10)	1 (1)	1 (4)
Bronchitis	14 (3)	1 (2)	0	0	3 (3)	0
Bronchiolitis	344 (62)	12 (19)	2 (3)	9 (24)	5 (6)	0
Pneumonia	120 (22)	10 (16)	11 (17)	8 (21)	16 (18)	12 (50)
Influenza-like illness	24 (4)	5 (8)	20 (31)	0	9 (10)	2 (8)
Total	551 (100)	62 (100)	65 (100)	38 (100)	90 (100)	24 (100)
Otitis media	109 (20)	5 (8)	14 (22)	4 (10)	15 (17)	4 (17)
Bronchial asthma	75 (14)	29 (47)	6 (9)	2 (5)	5 (6)	0
Febrile convulsions	23 (4)	5 (8)	30 (46)	6 (16)	36 (40)	3 (13)

*Numbers represent numbers of patients, with percent within each viral group in parentheses.
(Courtesy of Carlsen, K.-H., et al.: Acta Paediatr. Scand. 72:53–58, January 1983.)

endemic adenovirus infections. Influenza-like illness, or hyperpyrexia without obvious respiratory symptoms, was most frequent in patients infected by influenza virus.

Children in this series who were admitted primarily because of acute respiratory tract infection tended to be young and to be infected by RSV and parainfluenza virus 3. Older children with severe respiratory tract symptoms had adenovirus 7 infection. Children infected by influenza virus or an endemic adenovirus often had extrarespiratory tract symptoms such as febrile convulsions. Secondary pulmonary manifestations such as attacks of acute asthma were chiefly associated with rhinovirus infections, and also with RSV infection in older children.

▶ [Respiratory syncytial virus (RSV) is a worldwide problem. The encouraging news is that an effective treatment appears to be available. C. C. Hall and associates (*N. Engl. J. Med.* 308:443, 1983) used aerosolized ribavirin, a new antiviral agent, for the treatment of infants with lower respiratory tract infections from RSV and contrasted their course with a group of placebo-treated controls. Infants receiving ribavirin got better faster, as judged by clinical criteria and blood gas determinations, and had shorter periods of virus shedding. No side effects or toxicity were observed. For more on RSV infections in children with congenital heart disease, see this edition of the YEAR BOOK, Chapter 8, "The Heart and Blood Vessels."—F.A.O.] ◀

2–12 **Spectrum of Amebiasis in Children.** Russell J. Merritt, Edward Coughlin, Daniel W. Thomas, Leena Jariwala, Virginia Swanson, and Frank R. Sinatra (Univ. of Southern California, Los Angeles) reviewed findings in 11 children with amebiasis seen in Los Angeles between 1977 and 1980. All but 1 were Hispanic, and the exceptional patient was exposed to a person recently returned from Central America. Findings included hematochezia alone in 4 children, dysentery in 2, dysentery and appendicitis in 1, exacerbation of ulcerative colitis in 2, and hepatomegaly, fever, and diarrhea in 2. The clinical course is outlined in Table 1. Amebiasis was diagnosed by recognizing colitis and finding cysts and trophozoites of *Entamoeba histolytica* in fresh fecal smears in most instances. Rectal biopsies showed edema of the lamina propria and focal infiltration of the surface epithelium

(2–12) Am. J. Dis. Child. 136:785–789, September 1982.

TABLE 1.—CLINICAL COURSE OF PATIENTS WITH AMEBIASIS

Patient/Sex/Age	Initial Complaint	Diagnosis at Referral	Therapy Before Diagnosis	Therapy for Amebiasis	Outcome
1/M/5 mo	Dysentery	Intractable diarrhea, combined cow's milk-soy protein intolerance	Antibiotics, hyperalimentation, elemental formula	Metronidazole	Resolved
2/M/3 yr 9 mo	Dysentery	Anal fissure	None	None	Resolved
3/M/5 yr 9 mo	Hematochezia, abdominal pain	Anal fissure	None	Metronidazole	Resolved
4/F/5 yr 10 mo	Hematochezia, abdominal pain	Anal fissure	Stool softeners	Metronidazole	Resolved
5/M/2 yr 6 mo	Hematochezia	Colitis	None	Metronidazole	Resolved
6/M/1 yr 7 mo	Hematochezia	Parasites	Mebendazole	Metronidazole	Resolved
7/F/4 yr 6 mo	Flare of ulcerative colitis	Chronic ulcerative colitis	Prednisone, sulfasalazine	Colectomy, metronidazole, iodoquinol (diiodohydroxyquin)	Ileostomy, resolved
8/M/13 yr 8 mo	Flare of ulcerative colitis	Chronic ulcerative colitis	Prednisone, sulfasalazine	Colectomy, metronidazole, antibiotics	Ileostomy, resolved
9/M/3 yr 2 mo	Appendicitis, dysentery, fever	Appendiceal abscess	Antidiarrheal agent, antibiotics	Colectomy, metronidazole, antibiotics	Ileostomy, resolved
10/M/11 mo	Fever, diarrhea, abdominal distention, hepatomegaly	Intussusception	Antibiotics	Antibiotics, surgical drainage	Died
11/M/2 yr	Fever, anorexia, abdominal pain, hepatomegaly	Liver abscess	Antibiotics	Antibiotics, metronidazole, surgical drainage	Resolved

(Courtesy of Merritt, R. J., et al.: Am. J. Dis. Child. 136:785–789, September 1982; copyright 1982, American Medical Association.)

by neutrophils. Extension of the process resulted in superficial microulcers of the epithelium.

Amebiasis should be considered in Latin patients with hematochezia. Any infant with hepatic abscess of uncertain origin should be treated, because delayed treatment of extraintestinal amebiasis may be fatal. Amebic colitis can complicate preexisting inflammatory bowel disease. Proctoscopy was informative in all patients examined. Serologic titers are not always elevated in amebic colitis. Three of the present patients required colectomy, and 1 child died. Current recommendations for drug therapy are summarized in Tables 2 and 3. Metronidazole has been used as the primary amebicide. Emetine and other drugs cause significant potential side effects. It is important to screen household contacts of symptomatic patients for symptomatic and asymptomatic infection. Clusters of infected patients are not uncommon. Diloxanide furoate appears to be effective in clearing amebic cysts from the stool.

2–13 **Age-Specific Presentation of *Campylobacter* Enteritis in Children** is described by Shehla H. Naqvi, Lisa M. Dunkle, and Monica A. Clapper (St. Louis Univ.). During a 28-month period, *Campylobacter* species were isolated from 39 (1.15%) of 3,393 stool specimens; isolation rates for *Salmonella* and *Shigella* were 4.6% and 0.85%, respectively. *Campylobacter* isolation rates were highest in the summer.

Of the 39 patients from whom *Campylobacter* species were isolated, 27 had medical records available for review. These 27 patients were aged 3 weeks to 15 years (mean, 48 months), and only 29% were hospitalized. The frequency of bloody diarrhea did not differ among the various age groups, but other findings were more common in specific age groups (Fig 2–4). A temperature above 101 F was present in 15%

(2–13) Clin. Pediatr. (Phila.) 22:98–100, February 1983.

TABLE 2.—Recommendations for Drug Therapy for Amebiasis From the Centers for Disease Control (CDC), Atlanta

Treatment	Drug	Dosage	
		Adult	Pediatric
Asymptomatic infection			
Preferred drug	Diloxanide furoate*	500 mg 3 times daily for 10 days	20 mg/kg/day in 3 doses for 10 days
Alternative 1	Iodoquinol (diiodohydroxyquin)	650 mg 3 times daily for 20 days	30-40 mg/kg/day in 3 doses for 20 days (maximum, 2 g/day)
Alternative 2	Metronidazole	750 mg 3 times daily for 5-10 days	35-50 mg/kg/day in 3 doses for 10 days
Mild to moderate intestinal disease			
Preferred drug	Metronidazole	750 mg 3 times daily for 5-10 days	35-50 mg/kg/day in 3 doses for 10 days
Alternative 1	A tetracycline	500 mg 4 times daily for 10 days	10 mg/kg 4 times daily for 10 days (maximum, 2 g/day)
	Iodoquinol	650 mg 3 times daily for 20 days	30-40 mg/kg/day in 3 doses for 20 days (maximum, 2 g/day)
Alternative 2	Paromomycin sulfate	25-30 mg/kg/day in 3 doses for 5-10 days	Same as adult dosage
	Iodoquinol	650 mg 3 times daily for 20 days	30-40 mg/kg/day in 3 doses for 20 days (maximum, 2 g/day)
Severe intestinal disease			
Preferred drug	Metronidazole	750 mg 3 times daily for 5-20 days	35-50 mg/kg/day in 3 doses for 10 days
Alternative 1	A tetracycline	500 mg 4 times daily for 10 days	10 mg/kg 4 times daily for 10 days (maximum, 2 g/day)
	Iodoquinol	650 mg 3 times daily for 20 days	30-40 mg/kg/day in 3 doses for 20 days (maximum, 2 g/day)
Alternative 2	Emetine hydrochloride	1 mg/kg/day (maximum, 60 mg/day) for up to 6 days	0.5 mg/kg/day 2 times daily (maximum, 60 mg/day) for up to 5 days
	Iodoquinol	650 mg 3 times daily for 20 days	30-40 mg/kg/day in 3 doses for 20 days (maximum, 2 g/day)
Alternative 3	Dehydroemetine dihydrochloride	1.0-1.5 mg/kg/day (maximum, 90 mg/day) for up to 5 days	Same as adult dosage
	Iodoquinol	650 mg 3 times daily for 20 days	30-40 mg/kg/day in 3 doses for 20 days (maximum, 2 g/day)
Hepatic abscess			
Preferred drug	Metronidazole	750 mg 3 times daily for 5-10 days	35-50 mg/kg/day in 3 doses for 10 days
Alternative 1	Dehydroemetine	1.0-1.5 mg/kg/day (maximum, 90 mg/day) for up to 5 days	Same as adult dosage
	Chloroquine phosphate	1 g (600-mg base) daily for 2 wk then 500 mg (300-mg base) daily for 2-3 wk	10 mg (base) kg/day for 21 days (maximum, 600 mg/day)
Alternative 2	Emetine	1 mg/kg/day (maximum, 60 mg/day) for up to 6 days	0.5 mg/kg 2 times daily (maximum, 60 mg/day) for up to 5 days
	Chloroquine	Same as described in alternative 1	Same as described in alternative 1

*Diloxanide furoate, available from the CDC, is an outstanding oral amebicide for the treatment of asymptomatic patients who pass cysts; it is a luminal amebicide. Other recommendations are based on the relative value of the drugs as systemic or luminal amebicides.

(Courtesy of Merritt, R. J., et al.: Am. J. Dis. Child. 136:785–789, September 1982; copyright 1982, American Medical Association.)

TABLE 3.—Recommendations for Drug Therapy for Amebiasis From the American Academy of Pediatrics, Evanston, Illinois*

Asymptomatic infection
  Diloxanide furoate
    (available from Centers for Disease Control)
Mild to moderate intestinal disease
  Metronidazole, 35-50 mg/kg for 10 days in 3 doses (maximum, 800 mg)
Severe intestinal disease
  Metronidazole, 35-50 mg/kg for 10 days in 3 doses (maximum, 800 mg)
Hepatic abscess
  Metronidazole, 35-50 mg/kg for 10 days in 3 doses (maximum, 800 mg)

*These recommendations for pediatric dosage are from the 1982 report of the Committee of Infectious Diseases, American Academy of Pediatrics.

(Courtesy of Merritt, R. J., et al.: Am. J. Dis. Child. 136:785–789, September 1982; copyright 1982, American Medical Association.)

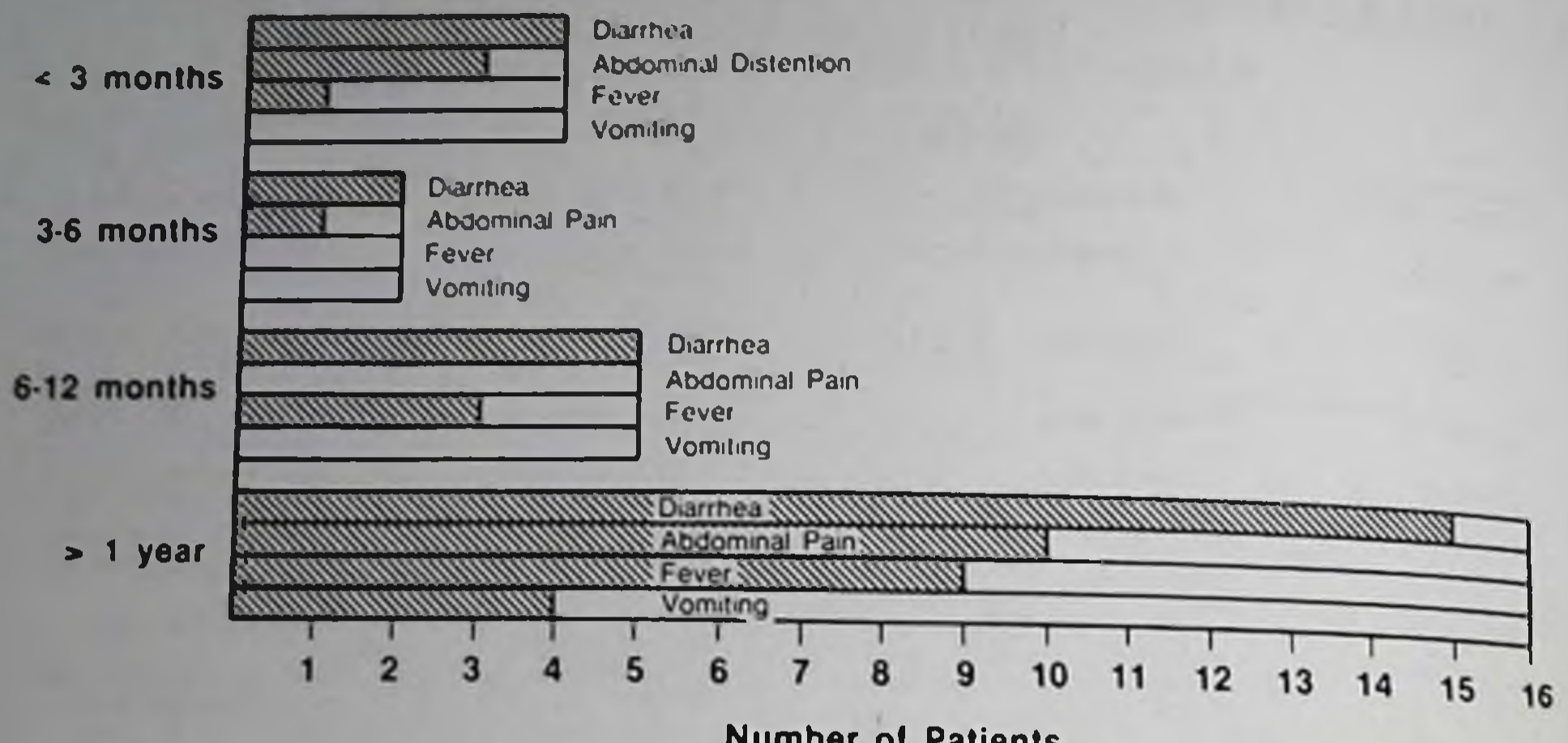

Fig 2–4.—Age-specific presentation of *Campylobacter* enteritis. Hatched bars indicate number of patients with the sign or symptom, and open bars denote number of patients with the sign or symptom. (Courtesy of Naqvi, S. H., et al.: Clin. Pediatr. (Phila.) 22:98–100, February 1983.)

of infants younger than age 6 months but in 61% of older patients. Abdominal distention was common in infants younger than age 3 months. Abdominal pain was common in children older than 1 year. All 3 infants younger than age 1 month had absolute monocytosis (range, 1,092 to 5,168 monocytes per cu mm; mean, 2,634), whereas older patients had monocyte counts of less than 900/cu mm. Twelve patients were treated orally with erythromycin, but lack of follow-up prevented assessment of its efficacy.

Campylobacter enteritis is usually a self-limited illness (diarrhea lasting 7 to 12 days in untreated patients) requiring no more than one clinic visit, but many young infants require brief hospitalization for rehydration. Early treatment may be justified in some patients with a severe clinical course so as to shorten the duration of illness and prevent intrafamilial spread.

► [For more on *Campylobacter*, please move on to the following article and its commentary by Dr. John D. Nelson or move back to the 1983 YEAR BOOK, pages 91–93.—F.A.O.] ◄

2–14 ***Campylobacter* Enteritis: Early Diagnosis With Gram Stain.** *Campylobacter jejuni* has become an important cause of infectious diarrhea in both adults and infants in the United States. Bloody diarrhea or profound dehydration may complicate the disease, making prompt diagnosis and specific antimicrobial therapy important. Stool cultures often require 2–5 days. David D. Ho, Mark J. Ault, Mary A. Ault, and Glen H. Murata (Cedars-Sinai Med. Center, Univ. of California, Los Angeles) evaluated the stool Gram stain for making an early presumptive diagnosis of *Campylobacter* enteritis at a large community teaching hospital. Standard Gram stain studies were done on stool specimens from 400 patients with diarrhea in a 6-month period in mid-1981. The appearance of *C. jejuni* is shown in Figure 2–5.

Twenty-three patients (5.8%) were found to have *C. jejuni*. *Shigella*

(2–14) Arch. Intern. Med. 142:1858–1860, October 1982.

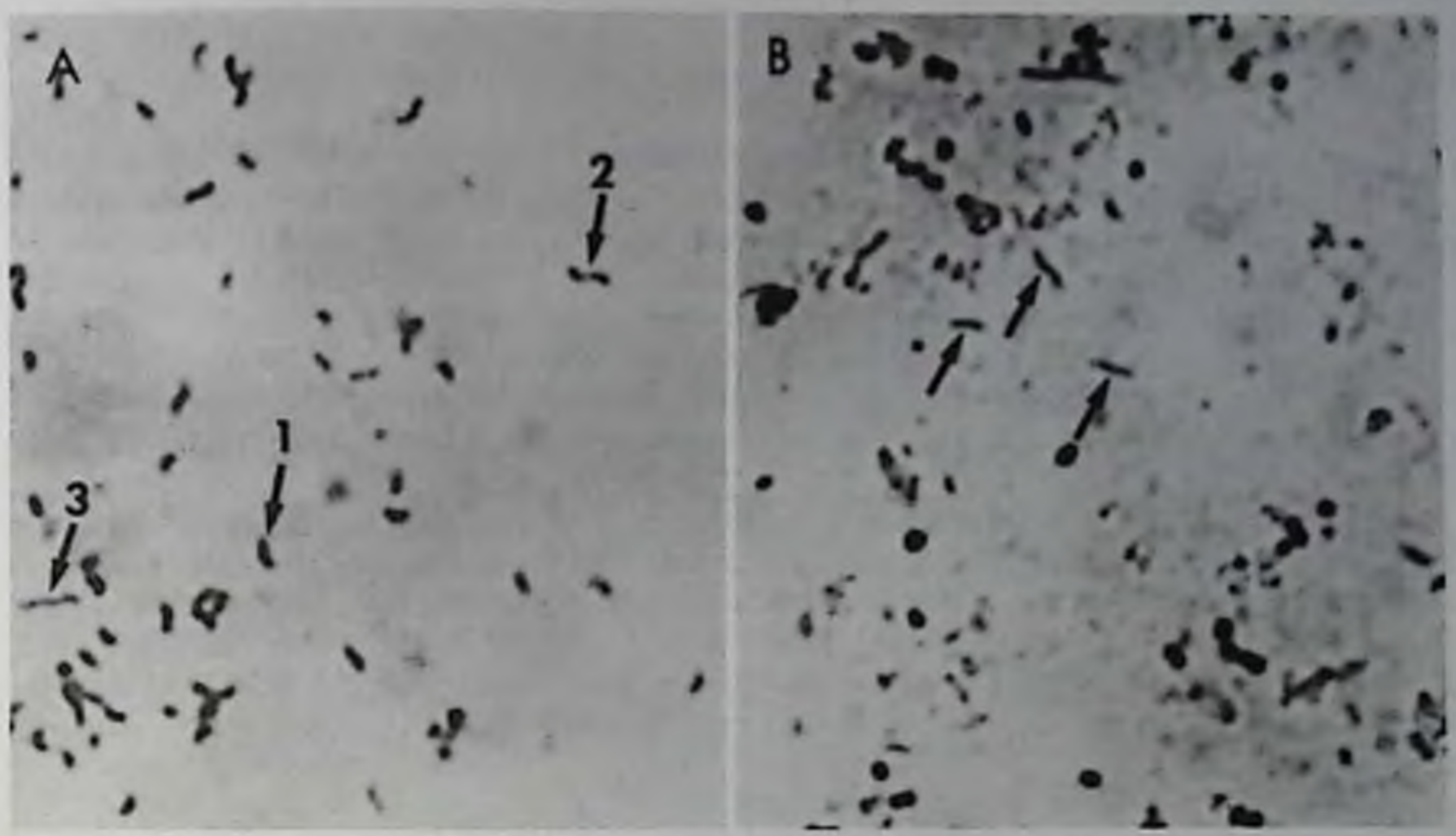

Fig 2–5.—A, standard Gram stain of pure culture of *Campylobacter jejuni*, showing different structures: *1*, simple curve; *2*, "equivalent sign"; *3*, "seagull" form. **B,** standard Gram stain of fecal specimen from patient with *Campylobacter* enteritis, showing typical vibrio organisms *(arrows);* reduced from ×2,000. (Courtesy of Ho, D. D., et al.: Arch. Intern. Med. 142:1858–1860, October 1982; copyright 1982, American Medical Association.)

was found in 3.3% of cases, *Salmonella* in 2.0%, and *Clostridium difficile* in 1.5%. The patients with *Campylobacter* enteritis were aged 1–75 years. All had diarrhea, and most had fever and abdominal pain. Bloody diarrhea was present in 12 of the 23 patients. On blind evaluation of 200 unknown slides, Gram staining for diagnosis of *Campylobacter* enteritis had a sensitivity of 43.5%, a specificity of 99.4%, and an accuracy of 93%. Calculated positive and negative predictive values exceeded 80% for incidence rates of 5%–20%. No significant differences were noted between patients with gram-positive and those with gram-negative *Campylobacter* enteritis. No pathogen was isolated from the 1 patient with a false-positive Gram stain.

Only about half of patients with *C. jejuni* infection will be detected by Gram staining of the stool, but the test is so specific that a positive result warrants temporary erythromycin therapy in patients ill enough to require treatment. Early, appropriate antibiotic therapy may lead to symptomatic improvement, and reduces the carrier rate. Unnecessary hospitalizations and diagnostic procedures may be avoided in some cases.

▶ [I always can count on Dr. John D. Nelson, Professor of Pediatrics, the University of Texas Health Science Center at Dallas, for an erudite and comprehensive commentary. This year is no exception. Doctor Nelson writes:

"The organism we now know as *Campylobacter fetus ssp. jejuni* was first recognized as a distinct species by Elizabeth O. King (*J. Infect. Dis.* 101:119, 1957), who called it "related vibrio" because it resembled avian vibrios. I recall vividly the 1960 American Pediatric Society-Society for Pediatric Research meeting at which Warren Wheeler reported the first 3 cases of "vibrionic enteritis," as he called it, in which diarrhea was complicated by positive blood cultures. He was unable to cultivate the organisms from feces. Doctor Wheeler ended his presentation with the prophetic statement, "Once the clinical manifestations of vibrionic enteritis in infants are recognized, and practical ways to meet the unusual growth requirements of the orga-

nisms are known, pediatricians will be able to look for further instances of an infection which is undoubtedly more common than these few cases would indicate" (*Am. J. Dis. Child.* 100:677, 1960).

"It was 12 years before Dekeyser and colleagues in Brussels succeeded in cultivating the organism from feces (*J. Infect. Dis.* 125:390, 1972) and several more years before technical advances made it possible for routine diagnostic laboratories to identify *Campylobacter* in clinical specimens.

"Now we know from many surveys in various countries that Dr. Wheeler's prediction was too cautious. *Campylobacter* accounts for 5% to 10% of cases of acute diarrhea and is more common than *Shigella* and *Salmonella* in many areas. Identifying *Campylobacter* by culture in clinical specimens is difficult and usually requires 48 to 72 hours.

"Four controlled clinical trials of erythromycin therapy have shown effective eradication of the organisms from stools but have not demonstrated significant resolution of clinical signs (Pitkanen, T., et al.: ibid. 145:128, 1982; Anders, B. J., et al.: *Lancet* 1:131, 1982; Robins-Browne, R. M., et al.: *Am. J. Dis. Child.* 137:282, 1983; and Pai, C. H., et al.: ibid., p. 286). However, all studies were flawed by the fact that therapy was started late in the course of illness and, anecdotally, many individual patients with severe disease or the few cases treated early in the course of illness have seemed to show clinical responses.

"Several attempts at early laboratory recognition have been made. Wet mounts of fecal specimens examined by phase-contrast microscopy reveal spirillar organisms with characteristic corkscrewing motion darting about the field. But that method is not practical for the routine laboratory. Nothing could be simpler than a Gram stain and, in the report by Ho et al., the characteristic appearance of *Campylobacter* was recognized in 10 Gram-stained specimens from 23 patients with *Campylobacter* by culture.

"*Campylobacter* take up the safranine stain rather poorly. Richard H. Schwartz and colleagues found that 1% aqueous basic fuchsin caused more intense staining than Gram staining (*Pediatr. Infect. Dis.* 2:298, 1983) Fuchsin-stained stool specimens were called "definitely positive" in 8 and "probably positive" in 2 of 12 culture-confirmed cases, for a sensitivity of 83%, or almost twice the sensitivity reported by the Gram stain method. Of 103 specimens negative by culture, they read 5 as "probably positive" by direct staining, for a false positive rate of 4.8%.

"Simple screening with Gram or basic fuchsin stains of stool specimens apparently can detect 50% or more of cases of *Campylobacter* enteritis with a low rate of false positivity. This method is easily adaptable to the private office, clinic, or emergency room. The 1% aqueous basic fuchsin stain is stable for months. The procedure requires only a 15-second stain of a dried, fixed thin smear of feces on a microscope slide. Stool from an infant is most easily obtained by reversing a disposable diaper so the stool collects on the slick surface.

"The procedure takes so little time that it could be done in all children with diarrhea. However, the highest yield would come from those with the typical symptoms of fever, abdominal pain, and bloody stool.

"I believe that the general experience of benefit from antibiotic therapy is sufficient to warrant its use until results of properly conducted studies are known. Most strains are susceptible to erythromycin, clindamycin, and tetracycline, and all are susceptible to furazolidone and chloramphenicol (Vanhoof, R., et al.: *Antimicrob. Agents Chemother.* 21:990, 1982). The greatest experience is with erythromycin, but furazolidone deserves a trial. Surprisingly, the "cephalowonder" drugs (cefoperazone, cefotaxime, moxalactam) are not effective, but thienamycin is (Ahoukhai, V. I., et al.: ibid. 20:850, 1981)."] ◄

2–15 **Gastroenteritis Associated with Enteric-Type Adenovirus in Hospitalized Infants.** Enteric types of adenovirus (ET Ad) recently have been identified as a causative agent of infantile gastroenteritis. Robert H. Yolken, Faye Lawrence, Flora Leister, Howard E. Takiff, and Stephen E. Strauss used enzyme immunoassay and tissue culture techniques to study prospectively the role of ET Ad in diarrhea occurring in hospitalized infants.

(2–15) J. Pediatr. 101:21–26, July 1982.

ASSOCIATIVE IDENTIFICATION OF ENTERIC PATHOGENS WITH GASTROENTERITIS

	No. (%) patients with diarrhea	*No. (%) patients without diarrhea*
Enteric type adenovirus	14 (51.9)	1 (1.5)
Adenovirus—all others	2 (7.4)	5 (6.9)
Salmonella enteriditis	2 (7.4)	0 (0)
No agent isolated*	9 (33.3)	66 (91.6)

*All stool specimens were negative for rotavirus and *E. coli* heat-labile enterotoxin. Stool specimens from children with diarrhea also were found to be negative for ECHO and coxsackieviruses and known bacterial pathogens.
(Courtesy of Yolken, R. H., et al.: J. Pediatr. 101:21–26, July 1982.)

Rectal swab specimens were collected twice weekly from 99 infants aged 4 weeks to 25 months, who were hospitalized between Oct. 15, 1980, and Jan. 5, 1981. Specimens were examined for rotavirus, *Escherichia coli* heat-labile enterotoxin, and the common hexon antigen of adenovirus by means of enzyme immunoassay. Specimens from children with diarrhea were examined also for coxsackie viruses A and B as well as bacterial pathogens. Specimens found to be positive for adenovirus antigen were further assayed for ET Ad. The presence or absence of diarrhea, respiratory infection, and other clinical findings was determined independently. The late autumn study was timed to coincide with frequent past episodes of diarrhea of indeterminate origin.

Twenty-seven (27%) children had an episode of diarrhea, and ET Ad was found in the stools of 14 (52%) of these children (table). Enteric-type adenovirus was found in only 1 of 72 children without diarrhea ($P < .001$). Two episodes of diarrhea were associated with adenoviruses other than ET Ad; however, such viruses were also found in the stools of 5 children without diarrhea. The association of types other than ET Ad with diarrhea was not significant. Although *Salmonella enteritidis* was the causative agent in 2 cases of diarrhea, no agent was identified in 9 patients with acute gastroenteritis. Children infected with ET Ad had diarrhea for a mean of 8 days, compared with a mean duration of 4.2 days for children whose gastroenteritis was not associated with ET Ad. Among the 14 children with ET Ad, 13 had respiratory symptoms such as cough, rhinorrhea, or wheezing, 6 had x-ray evidence of pneumonia, and 3 had bilateral conjunctivitis.

The pathogenic mechanism by which ET Ad infection is associated with gastrointestinal and respiratory symptoms is not known. Many strains of adenovirus can replicate in the respiratory tract, and ET Ad may be replicating simultaneously in intestinal and respiratory tracts of infected children.

▶ [Anyone who was trained more than 20 years ago was taught that diarrhea often accompanied parenteral infections, but nobody was taught that the same agent produced the cough, pneumonia, wheezing, runny nose, or conjunctivitis. It seems clear from this study that when you encounter diarrhea in association with signs of a respiratory tract infection or conjunctivitis, adenovirus should be your prime suspect. An adenovirus, adenovirus type 7, although usually associated with acute respiratory illness, pneumonia, or keratoconjunctivitis, also may produce encephalitis. K. S. Kim and R. S. Gohd (*Arch. Neurol.* 40:58, 1983) describe the course of acute encephalop-

athy in 13-month-old twins in whom adenovirus was recovered from a variety of sources but not the cerebrospinal fluid. The twins, who ran a parallel course, started out with a 1-week history of coughing and coryza and 3 days of conjunctivitis before they developed their central nervous system symptomatology. They recovered, although some reports have placed the mortality as high as 10% to 38% (*Acta Paediatr. Scand.* 59:310, 1970).—F.A.O.] ◄

2–16 **Incidence of Convulsions and Encephalopathy in Childhood *Shigella* Infections: Survey of 117 Hospitalized Patients.** Avraham Avital, Chani Maayan, and Kalman J. Goitein (Hadassah Univ. Hosp., Jerusalem) report that of 117 children ill enough to be hospitalized with *Shigella* gastroenteritis, 53% had neurologic symptoms, most during the onset of high fever; 11% had convulsions alone, 22% had encephalopathy alone, and 20% had convulsions and encephalopathy (table).

There was a significant male predominance, especially among patients with neurologic manifestations. No child older than age 6 years had convulsions. The neurologic manifestations preceded gastrointestinal symptoms in 24% of the patients, thus simulating primary CNS disease.

Bloody diarrhea was present in only 46% of the patients. Mild dehydration was present in 26% of patients; only 3% had severe dehydration.

Shigella sonnei was the predominant organism found in this study, especially in patients with neurologic symptoms; 87% of the bacteria isolated were sensitive to cotrimoxazole, ampicillin, and chloramphenicol. Only 5 cerebrospinal fluid samples (9%) were found to have more than 5 white blood cells/cu mm. Cerebrospinal fluid cultures were all sterile. The mean durations of diarrhea and of hospitalization were least in patients treated with trimethoprim-sulfamethoxazole, but they may have represented a group with milder infection.

Controversy exists as to the need for antibiotic treatment of *Shigella* gastroenteritis, because it is a self-limited disease and excretion of bacteria ceases after 1 week in about 60% of patients without antibiotic treatment. Only antibiotics producing significant tissue concentration eradicate *Shigella* organisms. Agents that suppress intestinal motility might be harmful.

► [R. Sandyk and M. J. W. Brennan (*Arch. Dis. Child.* 58:70, 1983) describe 3 patients with fatal fulminating encephalopathy associated with *Shigella flexneri* infections. The patients from South Africa were aged 9–11 years. In all 3 patients, areas of hemorrhage and necrosis were present in the brains at autopsy. The neurologic symptoms preceded the gastrointestinal in 1 of the 3 patients. A neurotoxin must be operative.

A change in behavior may be a manifestation of other gastrointestinal problems as well. A. Rachmel and associates describe 5 infants, aged 6–12 months, whose prominent complaints early in the course of their disease were apathy and listlessness. They all proved to have intussusception. Apathy and listlessness generally are regarded as late, and ominous, signs of intussusception rather than early presenting complaints.

What is the lesson from all of this? When you encounter an infant or child with an unexplained seizure or change in mental status, never overlook the gut as the cause of the problem. Your head hurts? Okay, let me do a rectal examination.—F.A.O.] ◄

(2–16) Clin. Pediatr. (Phila.) 21:645–648, November 1982.

PATIENT POPULATION ACCORDING TO CLINICAL PRESENTATION

	Patients Without Neurologic Symptoms		Patients with Convulsions Alone		Patients with Encephalopathy Alone		Patients with Convulsions and Encephalopathy		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total patients	55	47	13	11	26	22	23	20	117	100
Sex										
Male	31	56	9	69	19	73	15	65	74	63
Female	24	44	4	31	7	27	8	35	43	37
Age: Mean	4.5 years		2.4 years		5.2 years		2.6 years		3.0 years	
2–11 months	8	15	1	8	0	0	1	4	10	9
1–5 years	30	55	12	92	17	65	22	96	81	69
6–11 years	17	30	0	0	9	35	0	0	26	22
Fever										
<39 C	33	60	11	85	21	81	22	96	87	74
>39 C	22	40	2	15	5	19	1	4	30	26
Hyperperistalsis	46	84	11	85	24	92	19	83	100	85
Vomiting	39	71	7	54	20	77	10	43	76	65
Diarrhea										
Mucus	31	56	8	62	19	73	15	65	73	62
Bloody	25	45	6	46	12	46	11	48	54	46
Watery	22	40	3	23	7	27	6	26	38	32

(Courtesy of Avital, A., et al.: Clin. Pediatr. (Phila.) 21:645–648, November 1982.)

PREVIOUS EXPERIENCE RELATING BLOOD AMMONIA LEVELS TO PATIENT OUTCOME*

Investigators	No. of Patients	Ammonia Level			Comments
	Total (Survived/Died)	Upper Normal	Time	Frequency Obtained	
Huttenlocher	11 (8/3)	150 μg/100 ml	Initial	Every 12–24 hr	2/3 who died had NH_3 levels >5 × normal
Lovejoy et al	40 (23/17)	NG	Initial/serial	Every 24 hr	Only 1 patient with initial NH_3 >300 μg/100 ml survived
Roe et al	7 (4/3)	64 μg/100 ml	Initial	NG	3/3 who died had NH_3 levels >5 × normal
Lovejoy et al	16 (11/5)	50 μg/100 ml	Initial/peak	NG	5/5 who died had NH_3 levels >5 × normal
Mickell et al	9 (3/6)	150 μg/100 ml (2) 40 μg/100 ml (7)	Initial	NG	3/6 who died had NH_3 levels >5 × normal
Corey et al	248 (151/97)	48 μg/100 ml	Peak	NG	Mortality rose from 27% to 65% when ammonia level exceeded 6 × normal ($P <$ .001)
Shaywitz et al	29 (27/2)	NG	Peak	Every 8 hr	NH_3 >500 μg/100 ml correlates with more severe disease in terms of required doses of mannitol ($P < .001$)

*NG, not given.
(Courtesy of Fitzgerald, J. F., et al.: Pediatrics 70:997–1000, December 1982. Copyright American Academy of Pediatrics 1982.)

2–17 **Prognostic Significance of Peak Ammonia Levels in Reye's Syndrome.** Joseph F. Fitzgerald, Joseph H. Clark (Indiana Univ., Indianapolis), Anastasios G. Angelides (New Hyde Park, New York), and Robert Wyllie (Cleveland Clinic) examined the prognostic value

(2–17) Pediatrics 70:997–1000, December 1982.

of the peak plasma ammonia in 95 cases of Reye's syndrome seen in 1972–1981. The 53 female and 42 male patients were aged 4 months to 30 years. The diagnosis was based on a typical history with normal cerebrospinal fluid, hepatic dysfunction, and a serum bilirubin level below 3 mg/dl. Patients with a peak ammonia value less than 3 times normal were managed by fluid restriction and 10% dextrose administration. Others initially were managed by exchange transfusion or peritoneal dialysis and they received mannitol for increased intracranial pressure. Subsequently, controlled ventilation was instituted, and exchange transfusions and dexamethasone were abandoned. Intracranial pressure monitoring was carried out in patients with peak ammonia levels greater than 3 times normal. Barbiturate-induced coma now is used to augment osmotherapy in patients with peak ammonia levels greater than 5 times normal.

No patients with peak blood ammonia levels less than 5 times normal (groups 1 and 2) died, regardless of the neurologic status at admission. Peak ammonia levels occurred within 4 hours of admission in 88% of cases. Survival of patients with peak ammonia levels more than 5 times normal has increased progressively over the review period. All such patients seen in 1981 and 87% of those seen in 1980 survived.

An association between Reye's syndrome and blood ammonia has long been recognized (table). Peak ammonia levels are predictive of patient survival. Management of patients with ammonia levels 3–5 times normal has become progressively less invasive. Patients with ammonia levels more than 5 times normal may deteriorate rapidly if aggressive treatment is not instituted immediately. Recent advances in treatment have greatly improved the survival of these severely affected patients. Over 80% of such patients now survive with intracranial pressure monitoring and aggressive control of cerebral edema.

2–18 **National Surveillance for Reye's Syndrome: A 5-Year Review** is reported by Eugene S. Hurwitz, David B. Nelson, Cornelia Davis, David Morens, and Lawrence B. Schonberger (Centers for Disease Control, Atlanta). Over 2,000 cases of Reye's syndrome were reported during 5 years of national surveillance for Reye's syndrome in 1973–1974 and 1976–1980. The highest reported incidence was during years of primary influenza B and A (H1N1) activity (table), although the incidence was somewhat lower during one period of influenza A (H3N2) activity. The distribution of cases is shown in Figure 2–6. Regional outbreaks of Reye's syndrome were associated with influenza A (H1N1) and B, but not with influenza A (H3N2). Cases in whites tended to be evenly distributed by age, but a large percentage of cases in blacks were reported in young infants in recent years. In recent years, about two thirds of cases have been associated with antecedent respiratory illness and the rest with varicella and gastrointestinal illness.

The case-fatality ratio has declined in recent years. A fall from 41% in 1974 to 21% in 1980 is apparent. The total number of cases of Reye's syndrome reported annually since 1974 has not in-

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(2–18) Pediatrics 70:895–900, December 1982.

INCIDENCE OF REYE'S SYNDROME IN THE UNITED STATES, 1973–1974 AND 1976–1980

Year	Major Influenza Activity	No. of Cases	Incidence*	Death-Case Ratio	
				No. of Deaths/ Cases†	Ratio (%)
1973–1974	B	379	0.58	157/379	41
1976–1977	B	454	0.71	156/373	42
1977–1978	A (H3N2)	237	0.37	66/225	29
1978–1979	A (H1N1)	389	0.62	113/349	32
1979–1980	B	548	0.88	114/516	22

*Cases/100,000 population younger than age 18 years.
†With known outcome.
(Courtesy of Hurwitz, E. S., et al.: Pediatrics 70:895–900, December 1982. Copyright American Academy of Pediatrics 1982.)

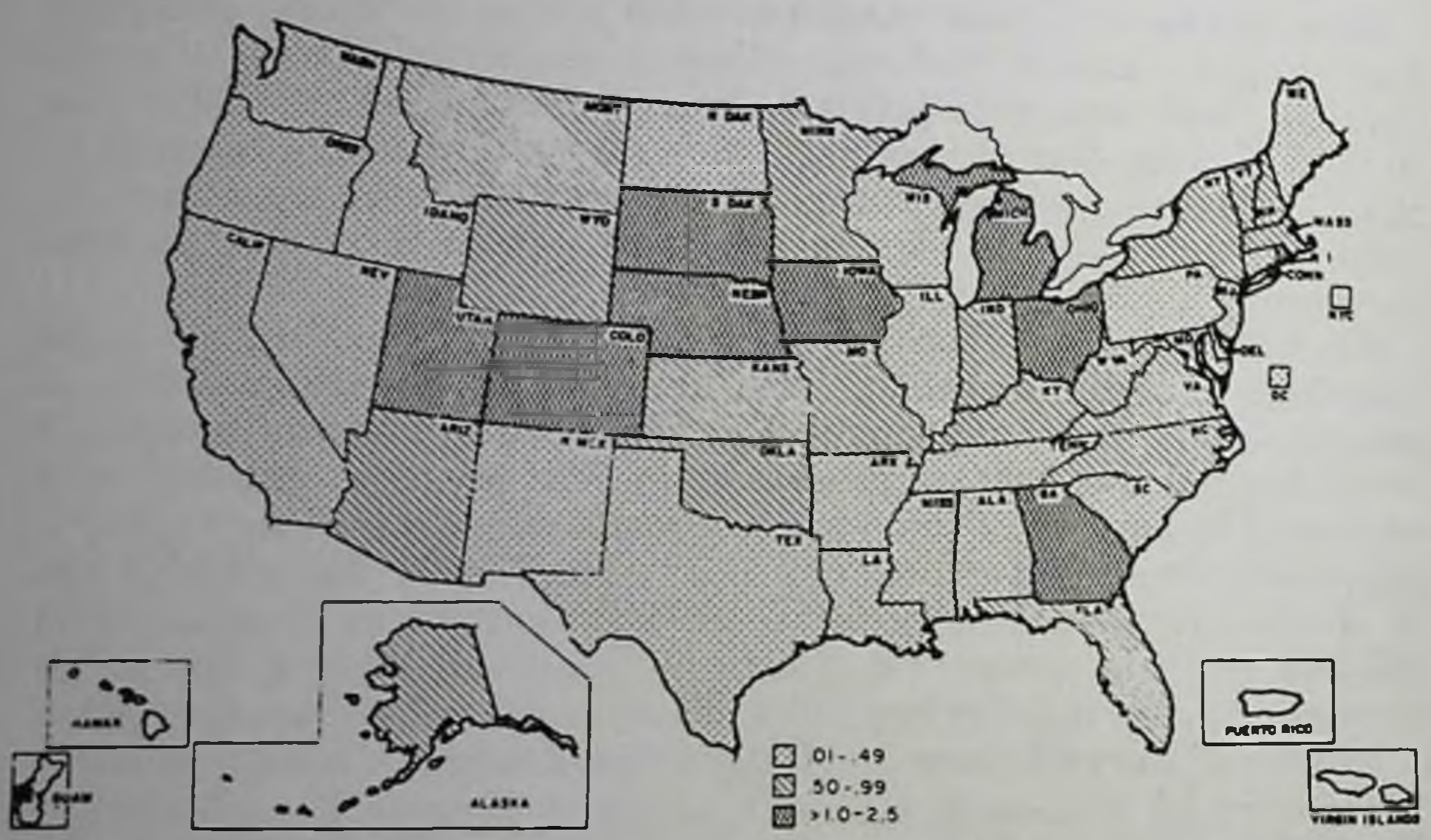

Fig 2–6.—Average annual incidence of Reye's syndrome (cases/100,000 population ≤18 years of age), by state, in the United States from 1977 to 1980. (Courtesy of Hurwitz, E. S., et al.: Pediatrics 70:895–900, December 1982. Copyright American Academy of Pediatrics 1982.)

creased, except in 1980, while the total number of deaths reported each year has fallen by about 30%. More patients now are admitted in earlier stages of disease and fewer in later stages. The percent of patients admitted in earlier stages who progressed to coma has declined in recent years.

Reye's syndrome appears to be a multifactorial disease, possibly the result of interactions between a number of different factors including viral infections and certain drugs. Further epidemiologic studies are needed, including population-based studies to define its demography and possible geographic differences in occurrence of the disease. More also needs to be learned of the association between Reye's syndrome and viral infections, as well as the role of such potential risk factors as salicylate ingestion.

▶ [These figures may require revision in light of the report of P. K. Lichtenstein

and associates, from Cincinnati, Ohio, where they describe the frequent occurrence of grade 1 Reye's syndrome (*N. Engl. J. Med.* 309:133, 1983). In a 1-year prospective study, they assessed the incidence of Reye's syndrome in children presenting with acute onset of vomiting after a prodromal upper respiratory tract infection or varicella, and with serum alanine or aspartate aminotransferase levels at least three times higher than normal, and with a paucity of neurologic findings. In 1 year, 25 patients met these criteria, 19 had liver biopsies and 14 of the 19 (74%) biopsies were diagnostic of Reye's syndrome. No signs of hepatitis were evident. Transitory transaminase elevations are very common with varicella (see *Pediatrics* 65:631, 1980, in 1981 YEAR BOOK, pp. 72–73; and *Arch. Dis. Child.* 57:317, 1982). Is this Reye's syndrome?

What about the aspirin connection? The debate continues (see Daniels, S. R., et al.: *JAMA* 249:1311, 1983; and Deshmukh, D. R., et al.: *Proc. Natl. Acad. Sci. USA* 79:7557, 1982). K. M. Starko and F. G. Mullick (*Lancet* 1:326, 1983) reviewed the histology of autopsy records of 13 children with accidental or therapeutically induced salicylate intoxication from the files of the Armed Forces Institute of Pathology. They concluded that the light microscopy hepatic findings and the gross cerebral findings, in most patients, were the same as those for children with Reye's syndrome. Kwan-Sa You (*Science* 221:163, 1983) reported that electron microscopic and spectrophotometric studies showed that salicylate causes gross swelling of mitochondria suspended in isotonic salt solutions and that the mitochondrial changes resemble those seen in Reye's syndrome. The mitochondria that were deformed by salicylate tended to return to their original condensed form when the drug was removed.

Now even the rheumatologists are claiming that the entity previously termed "rheumatic encephalopathy" may represent aspirin-induced Reye's syndrome (Riviello, J. J., et al.: *Pediatr. Res.* 17:367A, 1983).

Has all this given you a headache? The world is getting more complicated all the time. In 1980 we elected an actor to be President. Four years later, because of the complex turn of events, we need more than an actor, we better elect a song-and-dance man.—F.A.O.] ◀

2–19 **Consequences of Confirmed Maternal Rubella at Successive Stages of Pregnancy.** Between January 1976 and September 1978, all pregnant women with rubella confirmed by a public health laboratory in England and Wales were followed up prospectively. Elizabeth Miller, John E. Cradock-Watson, and Thomas M. Pollock (Central Public Health Lab., London) report that 95% of the 1,016 women in the study had a rash. Attacks peaked each year in spring and summer and the rate increased with age, probably because older women are generally of greater parity and more likely to be exposed to younger children with rubella. Of the 966 women for whom outcome of pregnancy was known, 523 (54%) had therapeutic abortions and 36 (4%) had spontaneous abortions. The proportion of women who continued their pregnancy rose from 6% among those infected during the first trimester to nearly 50% infected at 13–16 weeks. Among the 407 pregnancies that continued, there were 9 (2%) stillbirths and a further 5 infants (1%) died in the neonatal period.

Presence of IgM antibody soon after birth or persistence of IgG after the first year was taken as evidence of congenital infection. In all, 269 infants were tested (104 for IgM and IgG; 12 for IgM only). Every infant whose mother had symptomatic rubella between the first and 12th week of pregnancy was infected. The infection rate declined to 25% of infants whose mothers were infected at the end of the second trimester and rose again to a high figure in the last month. Follow-

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(2–19) Lancet 2:781–784, Oct. 9, 1982.

RUBELLA DEFECTS FOUND AT FOLLOW-UP IN INFANTS INFECTED AT SUCCESSIVE STAGES OF PREGNANCY

Stage of pregnancy (wk)	No. followed up	Seropositive infants: Heart and other defect	Seropositive infants: Deafness alone	Seropositive infants: % with defect	Overall risk* of rubella defect (%)
<11	9	5	4	100	90
11–12	4	0	2	50	33
13–14	12	0	2	17	11
15–16	14	0	7	50	24
17–18	10	0	0	..	..
>18	53	0	0	..	..
Total	102	5	15	20	..

Overall risk equals percent seropositive with defects times number of infants infected.

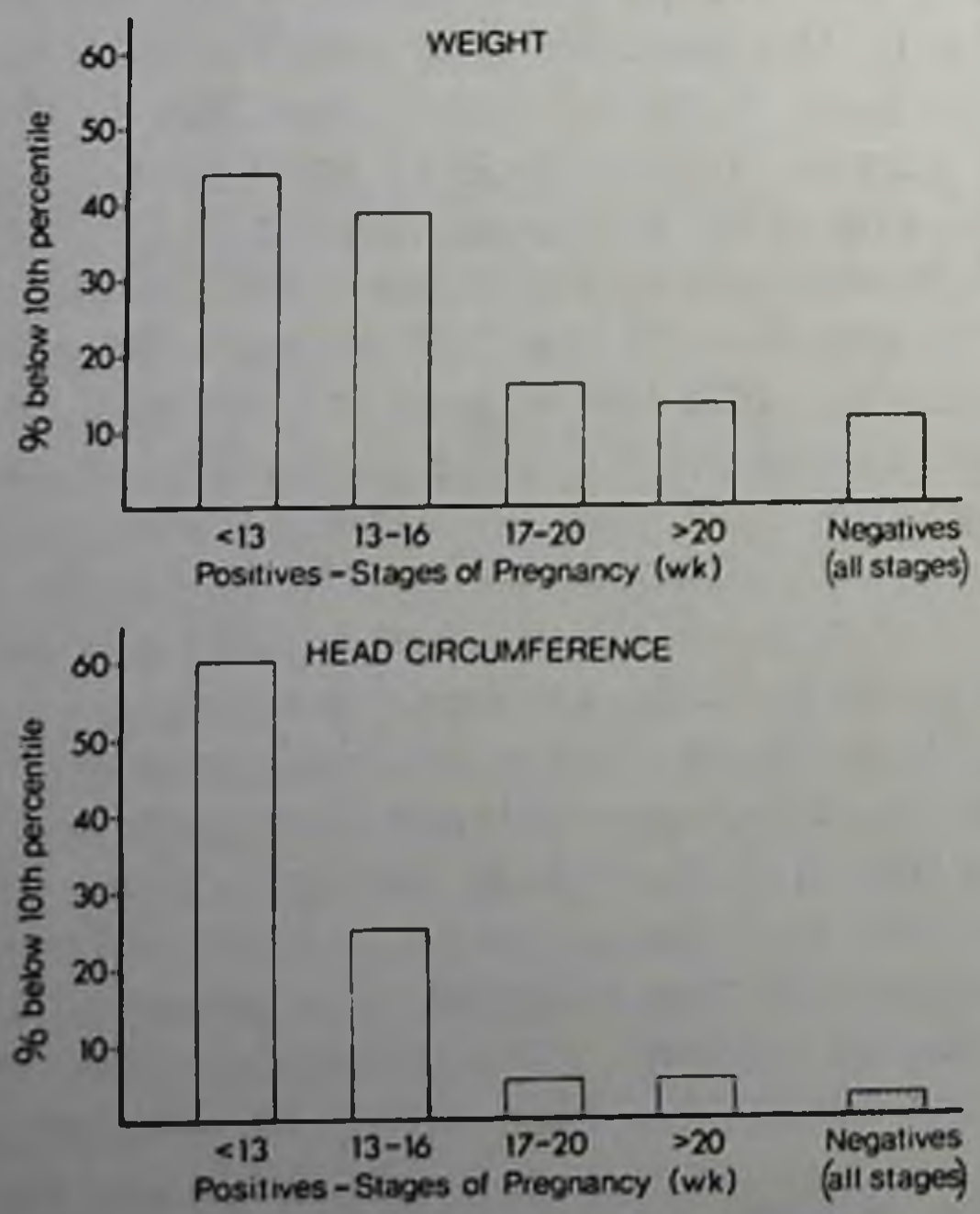
*Estimated from congenital infection rate after symptomatic rubella at different stages of pregnancy.

(Courtesy of Miller, E., et al.: Lancet 2:781–784, Oct. 9, 1982.)

up included 273 children at a mean age of 26 months. Defects consistent with congenital rubella were found in 20 children (table).

A significantly higher proportion of seropositive infants had birth weights below the 10th percentile—25% compared with 8% of the seronegative infants, the excess being most pronounced during the first trimester. No reduction in birth weight was apparent for infants infected during the latter half of the second trimester or those whose mother had rubella shortly before full term. Body weight and head

Fig 2–7.—Percentage of children whose weight and head circumference were below the 10th percentile at follow-up. (Courtesy of Miller, E., et al.: Lancet 2:781–784, Oct. 9, 1982.)



circumference of seropositive and seronegative children at follow-up are shown in Figure 2–7. Growth retardation was apparent at follow-up in children infected during the first 16 weeks of pregnancy.

In this study, the risk of abnormality after symptomatic rubella in the first 4 months of pregnancy appeared to be greater than has been shown previously. This may be explained by the fact that in previous studies the diagnosis of rubella in the mother had been made solely on clinical grounds. This is often incorrect, whereas the present study is based on the more precise serologic diagnosis.

2–20 **Intradermal Immunization With Human Diploid Cell Rabies Vaccine: Serologic and Clinical Responses of Persons With and Without Prior Vaccination With Duck Embryo Vaccine.** The new human diploid cell rabies vaccine (HDCV) provides safer protection against rabies than does the standard duck embryo vaccine (DEV). Michael J. Burridge, George M. Baer, John W. Sumner, and Oscar Sussman compared the clinical and serologic responses to administration of intradermal HDCV in persons with and without previous vaccination with DEV. Of 240 volunteers from a veterinary hospital, 165 were vaccinated previously with DEV. Two doses of HDCV were given to all unvaccinated persons and to some of those previously vaccinated with DEV. The doses were given intradermally 28 days apart.

Excellent serologic responses to intradermal HDCV were observed. All but 1 of 210 persons who completed the study produced rabies antibody titers of 0.5 IU/ml or greater. The safety of vaccination was good; only minor reactions occurred, and all resolved spontaneously. Only 3.4% of persons experienced possible systemic reactions to the first dose of HDCV and 2.9% to the second dose. Two individuals with a long history of multiple allergies had no adverse reactions to intradermal HDCV administration.

Two intradermal doses of HDCV given a month apart appear to constitute a safe, efficient, and economical regimen for immunizing high-risk groups against rabies, regardless of their previous DEV vaccination history. Studies of the decay of antibody titers and of serologic responses to booster injections of HDCV are needed to formulate a complete schedule for intradermal HDCV in rabies preexposure prophylaxis.

2–21 **Seizures Following Childhood Immunizations.** Deborah G. Hirtz, Karin B. Nelson, and Jonas H. Ellenberg (Natl. Inst. of Health) studied the incidence of seizures that followed immunizations and their neurologic consequences, using data from the National Collaborative Perinatal Project (NCPP), which covers about 54,000 pregnant women and their children observed to age 7 years.

Of the 2,766 children in the NCPP who experienced 1 or more seizures during the first 7 years, 39 (1.4%) experienced 40 convulsions within 2 weeks of an immunization. Most seizures followed a diphtheria-pertussis-tetanus (DPT) or a measles immunization (Table 1), and most occurred between ages 4 months and 4 years (Fig 2–8). Most

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(2–20) JAMA 248:1611–1614, Oct. 1, 1982.
(2–21) J. Pediatr. 102:14–18, January 1983.

TABLE 1.—Distribution of Time of Onset of Postimmunization Seizures by Type of Immunization

Immunization	Number of immunizations	Time (days) 1	2	3 to 6	7 to 10	11 to 14	Exact time unknown
DPT	7	4	2				1
DPT + polio	2	2					
DPT + smallpox	1			1			
Measles	10		2	1	6		1
Influenza	3	3					
Smallpox	5		1	1	3		
Tetanus booster	1	1					
Poliomyelitis	2	1			1		
Unknown vaccine	9	3		1	3		2
Total	40	14	5	4	13	0	4

(Courtesy of Hirtz, D. G., et al.: J. Pediatr. 102:14–18, January 1983.)

were generalized and tonic-clonic, single, and brief (Table 2). At the time of the seizure, all children but 1 were febrile; in at least 25 the temperature was 102 F or higher. Fourteen children had non-CNS infections at the time of the seizure, but none had encephalitis or meningitis.

Before the seizure, 2 children had definite and 2 had suspected neurologic abnormalities. Of the 39 children, 3 had prior febrile sei-

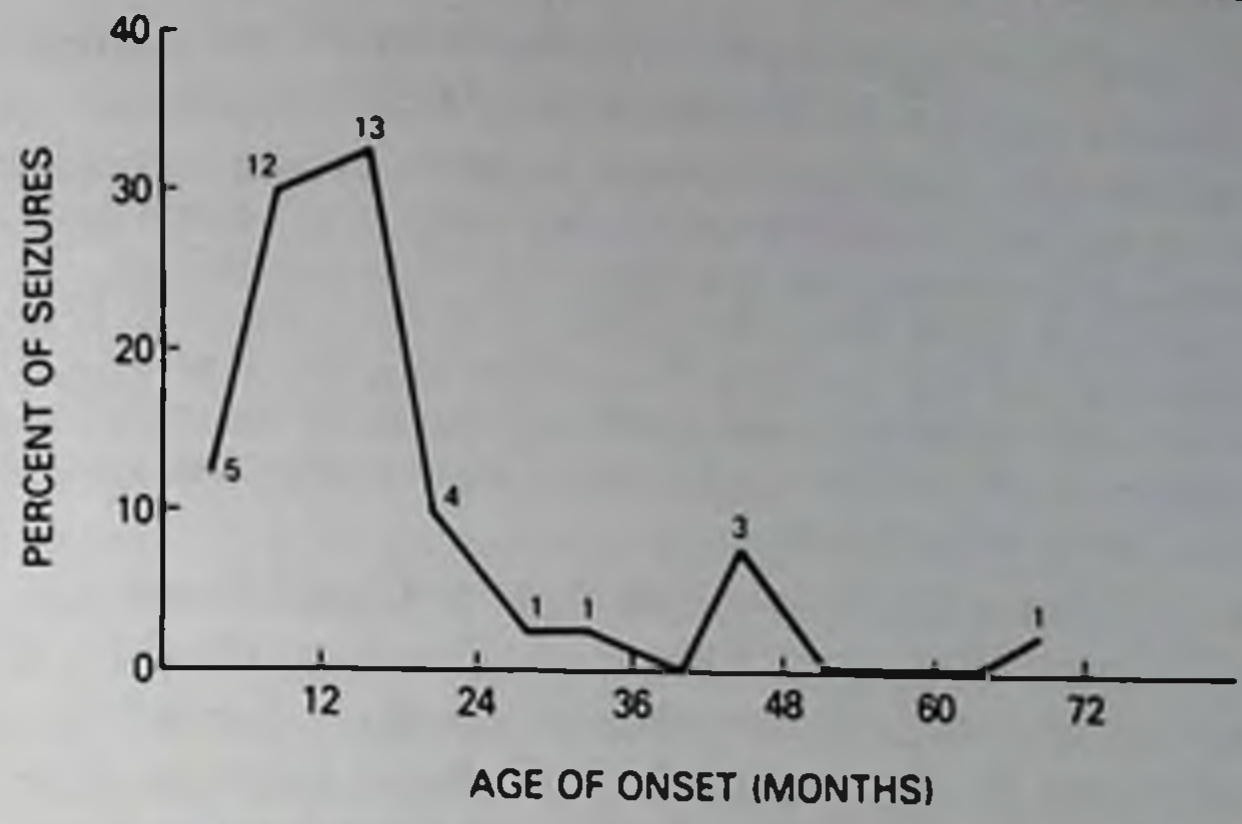


Fig 2–8.—Postimmunization seizures, showing numbers of cases. (Courtesy of Hirtz, D. G., et al.: J. Pediatr. 102:14–18, January 1983.)

zures and 14 had subsequent febrile seizures (1 child had both), for a total of 16 children (41%) experiencing at least 1 other febrile seizure before age 7 years. In comparison, 3.5%–4% of NCPP children had at least 1 febrile seizure, and a third of those had at least 1 other febrile seizure. A family history of febrile or nonfebrile seizures was recorded in 23% of the 39 children with immunization-associated seizures, in 14% of 1,706 NCPP children with febrile seizures, and in 7% of the rest of the NCPP population.

At follow-up (at age 7 years in 37 of the children), mean full-scale IQs were 108 for whites (range, 70–154) and 92 for nonwhites (range, 70–109). In only 1 child did a motor deficit have its onset within 2 weeks of an immunization, and that child, who had a long-term handicap of moderate severity, had had prolonged focal seizures after a DPT immunization.

Both in clinical presentation and generally benign outcome, immunization-related seizures closely resemble the febrile seizures that are common in early childhood. Because DPT immunization may

TABLE 2.—SEIZURE DURATION AND TYPE

Seizure duration and type	*Number*
Brief	
Generalized single	22
Generalized multiple	7
Focal single	2
Total	31
Lengthy (>30 min)	
Generalized single	1
Generalized multiple	1
Focal multiple	1
Total	3
Unknown	6
Total	40

(Courtesy of Hirtz, D. G., et al.: J. Pediatr. 102:14–18, January 1982.)

cause fever and hypoglycemia, administration of antipyretics and sweetened juices may be advisable after DPT injections.

▶ [For more on the nature and rates of adverse reactions associated with diphtheria-pertussis-tetanus and diphtheria-tetanus immunizations in infants and children, and for a commentary on this issue, see the 1983 YEAR BOOK (pp. 55–58).

For further evidence of the devastating effects of omitting early diphtheria-pertussis-tetanus immunization, see a description of two epidemics of whooping cough in Finland (Riita, H.: *Acta Paediatr. Scand.* [Suppl.] 298:5–9, 1982). M. H. Bellman and co-workers (*Lancet* 1:1031, 1983) could find no evidence to link infantile spasms to pertussis immunization.—F.A.O.] ◀

2–22 **Reversal of Enterocolitis-Associated Combined Immunodeficiency by Plasma Therapy.** Robert A. Cannon, Paul M. Blum, Marvin E. Ament, William J. Byrne, Margaret Soderberg-Warner, Robert C. Seeger, Andrew E. Saxon, and E. Richard Stiehm (Univ. of California, Los Angeles) report that 2 male infants, aged 6 months, with diarrhea, malabsorption, and hypoproteinemia, initially diagnosed as having primary combined immunodeficiency syndrome, recovered with intensive plasma therapy. Both patients had intractable diarrhea for more than a month and had received total parenteral nutrition through central venous catheters with full nutritional support for 4–6 weeks before plasma therapy was instituted.

CASE 1.—Male infant, aged 6 months, had normal serum protein and lymphocyte values prior to onset of diarrhea. Immunologic features of combined immunodeficiency included lymphopenia, diminished T and B cells, cutaneous anergy, low immunoglobulin levels, and poor lymphocyte proliferative responses in vitro. Prior to therapy, there were rectal ulcerations revealed by proctosigmoidoscopy, colitis by rectal biopsy, and moderate to severe intestinal villus abnormalities by small bowel biopsy; plasma cells were absent. A chest radiograph showed no thymic shadow. The child had generalized malabsorption of all nutrients.

The infant was given irradiated fresh-frozen plasma (FFP) for a total of 60 days, beginning at 20 ml/kg/day, then 20 ml/kg every other day, to replace intestinal protein losses. During this time, diarrhea slowed, biopsy morphology improved, and immunoglobulin levels and T cell function became normal. After discontinuance of plasma therapy, normal immune function and reversal of malabsorption continued. Antibody production was demonstrated by an increase in isohemagglutinin titer from 1:1 to 1:128.

CASE 2.—Male infant, aged 6 months, had a history and course similar to those of the first patient. However, there was a thymus shadow on the chest film, and there were plasma cells in rectal biopsy specimens. The B cells were present in normal or increased numbers. This patient received FFP infusions, 10 ml/kg/day for 15 days and then every other day for 2 more weeks. In vitro studies showed that at age 8.5 months (prior to FFP therapy), radiation-sensitive mononuclear cells from this patient were potent suppressors of normal B cell immunoglobulin synthesis (G, M, and A). Their presence correlated with a peripheral "monocytosis." These cells did not inhibit total protein synthesis.

Just before the patient's discharge at age 10½ months, the abnormal suppressor cell activity was no longer present. However, the patient's cells were unable to become immunoglobulin-producing cells with normal T helper cells. To some extent, this B cell deficiency was reflected by low serum IgM and IgA values.

(2–22) J. Pediatr. 101:711–717, November 1982.

The cause of the diarrhea in these patients is not clear. Recovery of immunologic functions indicates that these infants had a secondary immunodeficiency rather than a primary combined immunodeficiency. In Case 1, it is likely that the immunodeficiency was associated with immunoglobulin and lymphocyte loss through the gastrointestinal tract. Prior steroid therapy may have accounted for the absence of a thymus shadow on chest film and for the lymphopenia.

Patients with severe enterocolitis may lose sufficient immunoglobulin and lymphocytes so as to resemble those with primary combined immunodeficiency. Patients with severe enterocolitis may benefit from FFP therapy, which may help to distinguish a secondary combined immunodeficiency from primary combined immunodeficiency.

▶ [For once, my good friend, Dr. Michael Miller, Professor and Chairman of the Department of Pediatrics, University of California at Davis, gets the final word. "Spike" comments as follows:

"The apparent reversal of immunodeficiency in two 6-month-old male infants following administration of irradiated fresh-frozen plasma raises a number of interesting points. As the study was not designed to identify the factor(s) involved in the reversal of the immunologic deficiency state, there is much room for speculation. Three major areas should be considered.

"First, were these patients indeed immunologically deficient? As noted by the authors, the absence of symptoms such as thrush, diarrhea, or severe infections early in life is noted occasionally in combined immunodeficiency. Nonetheless, this is a somewhat unusual clinical story, and the significance of the laboratory abnormalities of immunodeficiency is, therefore, open to question. It is also noteworthy that although intractable diarrhea has rarely, if ever, been associated with secondary combined immunodeficiency, such a finding may not be impossible.

"Second, each of the patients had a set of variables and laboratory findings which would suggest that the etiologies of immunologic deficiency were different, hence making it difficult to implicate a single factor or set of factors in the apparent plasma response. In the first patient, immunologic deficiency occurred after the administration of antiseizure medications including phenobarbital and diazepam. Adrenocorticotropin in significant dosages also was administered prior to the episode of diarrhea and subsequent findings of immunologic deficiency. In the second patient, neutropenia and a peculiar radiation-sensitive mononuclear suppressor cell were present.

"Third, one can speculate as to the possible factor(s) in the plasma responsible for the reversal of the immunodeficiency. Substitution of an essential nutrient is unlikely in view of the intensive parenteral nutrition administered to each patient prior to the plasma therapy. The presence of a functional immunocompetent cell, perhaps of the T cell series, seems unlikely in view of the irradiation of the plasma prior to administration. Conclusive ruling out of such a cell type would depend on studies from an irradiated aliquot of the administered plasma to insure that no such cell type was functionally present. The possible addition of a factor of the complement system is also a consideration. Patients with intractable diarrhea are often deficient in functional complement activity and, in particular, have a deficiency of C1q. The extent to which irradiation with 1,500 rad would remove functionally active C1q in such patients is unknown and cannot necessarily be inferred from studies of hemolytic inactivation.

"The fourth area of interest is the suggestion that a therapeutic trial of irradiated fresh-frozen plasma might be indicated in similar patients. Although seemingly harmless, the routine administration of plasma in such situations might introduce an undesirable effect, such as the presence of hepatitis or cytomegalovirus or the possibility of immune complex formation with subsequent harmful effects. On the other hand, the avoidance of an extensive workup and potentially harmful therapy for the treatment of immunodeficiency is obviously desirable if provided by such a simple technique as administration of fresh-frozen plasma. Judgment regarding the wisdom of proceeding with such therapy in these patients must await the identification of which factors are involved in the clinical reversals noted."] ◀

3. Allergy and Dermatology

3–1 **Cow's Milk Proteins Cause Infantile Colic in Breast-Fed Infants: Double-Blind, Crossover Study.** Views have conflicted as to whether infantile colic in breast-fed infants can be related to consumption of cow's milk by the mother. Iréne Jakobsson and Tor Lindberg (Univ. of Lund) undertook a double-blind, crossover study in 66 mothers of breast-fed infants with infantile colic, defined as paroxysmal abdominal pain, persistent marked crying, abdominal distention by gas, and a wish to suck frequently. All the infants were otherwise healthy. Cow's milk was eliminated from the mother's diet for about a week initially and was then reintroduced twice. Mothers who continued on a diet free from cow's milk received a calcium supplement. Capsules containing either 200 mg of a powder of cow's milk whey proteins or potato starch were given in the double-blind trial. Three capsules were used four times a day. The whey protein corresponded with the amount of whey in about 80 ml of cow's milk.

Elimination of cow's milk from the mother's diet led to the disappearance of colic within 1 to 3 days in 53% of cases, and symptoms recurred within 1 to 8 hours of the reintroduction of cow's milk to the mother's diet in 23 of these 35 cases. A family history of allergy was present in half the infants who relapsed when their mothers drank cow's milk (table). The overall incidence of allergy in the family was 33%. Nine of 10 evaluable infants in the double-blind challenge study developed colic after their mothers' ingested cow's milk whey protein, and also when the mothers drank milk directly afterward. No reactions followed use of placebo capsules in these infants. One infant had colic when the mother ingested placebo capsules only and also when she drank milk. Colic resolved in 18 infants at a mean age of 15 weeks.

SURVEY OF 23 BREAST-FED INFANTS WITH RELAPSE OF COLIC WHEN THEIR MOTHERS WERE GIVEN COW'S MILK

	Infantile Colic	1st Elimination of Cow's Milk to Mothers	1st Positive Challenge* (N = 23)	Double-Blind Challenge (N = 16)	Negative Challenge (N = 18)
Range (wk)	1–12	1–16	2–20	3–28	7–40
Mean value (wk)	2.6	5.2	7.2	8.9	14.9

*Challenge = cow's milk given to mother.
Three infants had verified cow's milk protein intolerance; 2 were aged only 2 and 2½ mo.
(Courtesy of Jakobsson, I., et al.: Pediatrics 71:268–271, February 1983. Copyright American Academy of Pediatrics, 1983.)

(3–1) Pediatrics 71:268–271, February 1983.

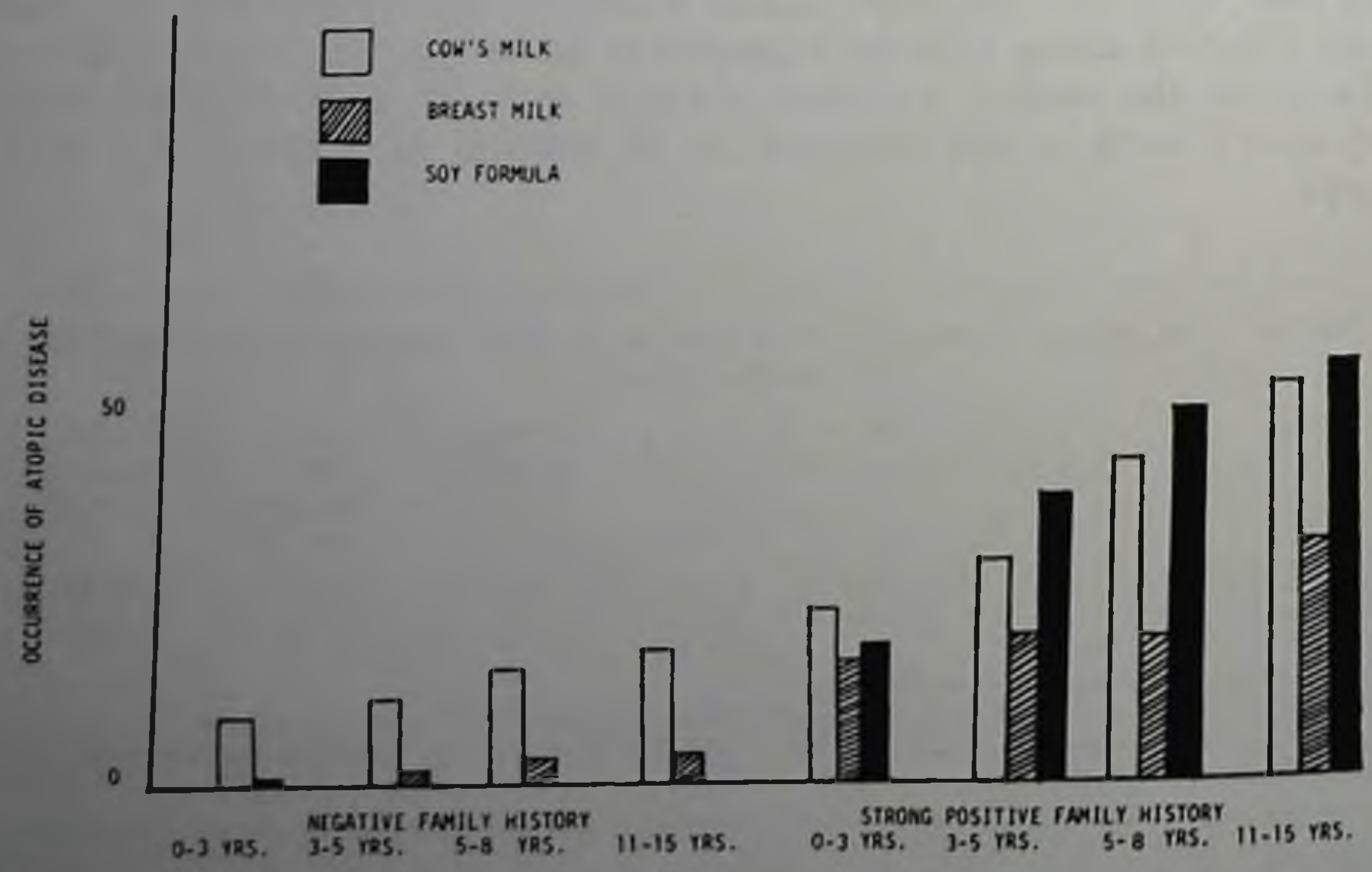
The findings support the suggestion that infantile colic can be a symptom of food intolerance even in breast-fed infants. A diet free from cow's milk is proposed for the mother as a first step in the management of infantile colic in breast-fed infants. The factor in cow's milk that produces infantile colic in breast-fed infants remains to be identified.

▶ [When Jacobsson and Lindberg described their original observations (*Lancet* 2:437, 1978, in 1980 YEAR BOOK, pp. 284–285) readers were divided into two camps—the converts and the cynics. This carefully controlled double-blind study should go a long way in converting the cynics. It is not unreasonable to assume that things the mother eats may produce abdominal discomfort in her breast-fed infant. It is always nice when your assumptions (read "prejudices") can be scientifically validated. Even if the removal of whole cow's milk from the maternal diet doesn't cure colic in every infant, and nobody claims that it does, it gives you something to try while this mysterious affliction runs its natural self-limited course. I, for one, am delighted that the cow has been made the villainess in the story. When things go wrong in early infancy, "Cherchez la vache."—F.A.O.] ◀

3–2 **Comparison of Breast, Cow, and Soy Feedings in Prevention of Onset of Allergic Disease: A 15-Year Prospective Study.** Frank L. Gruskay (Yale Univ.) prospectively studied children from birth through age 15 years to determine whether the food ingested during the first months of life is related to development of atopy in the offspring of allergic families.

Each of 328 children with a positive family history of allergy was assigned to one of three groups according to the feeding preference of the parents: 48 were fed breast milk; 79, soy-based formula; and 201, cow's milk formula. All groups had egg, citrus, tomato, and wheat restrictions and avoided inhalant allergens. These children were compared to a control group of 580 with no family history of allergy.

Fig 3–1.—Age of onset of initial atopic disease in children, related to family history of allergy and type of infant feeding. (Courtesy of Gruskay, F. L.: Clin. Pediatr. (Phila.) 21:486–491, August 1982.)



(3–2) Clin. Pediatr. (Phila.) 21:486–491, August 1982.

INCIDENCE AND AGE OF ONSET OF INITIAL ALLERGIC DISEASE IN GROUP WITH POSITIVE FAMILY HISTORY

Initial Allergic Disease	Type of Feeding	Followed 3 Years	5 Years	8 Years	15 Years	Total
Atopic dermatitis	Cow's milk	24/201	0/192	0/167	0/143	24
	Soy	9/79	0/76	0/69	0/66	9
	Breast	4/48	0/44	0/38	0/31	4
Asthma	Cow's milk	20/201	10/192	0/167	1/143	31
	Soy	7/79	7/76	1/69	1/66	16
	Breast	4/48	0/44	0/38	0/31	4
Allergic rhinitis	Cow's milk	6/201	11/192	1/167	3/143	21
	Soy	0/79	7/76	2/69	1/66	10
	Breast	0/48	0/44	0/38	1/31	1

(Courtesy of Gruskay, F. L.: Clin. Pediatr. (Phila.) 21:486–491, August 1982.)

The findings of 15% prevalence of major allergy in an unselected control group and 50% in those with a strong family history are consistent with prior studies. Among infants with a positive family history, those who were breast-fed for at least 3 months had about one-half the incidence of atopy of those given cow's milk or soy formula when all three groups were followed for up to 15 years (Fig 3–1). There was a three-fold increase in clinically apparent atopic disease in offspring of allergic families when compared with controls, but the increase was only twofold if the infant was breast-fed.

In the control group, two thirds of the allergic conditions that appeared by age 3 was atopic dermatitis, one-third was asthma, and none was allergic rhinitis. In older age groups, all the new atopic conditions in previously well children were allergic rhinitis. The same general trend is apparent in those with a positive family history of allergy (table).

The earlier age of onset of allergic disease in children with a strong family history of allergy points to genetic influence as a significant risk factor. Mean ages of onset of allergic disease in this study confirm those reported by Wittig et al. (1978) of 3.7 years with strong family history, 6.1 years with intermediate family history, and 8.7 years with negative family history.

The results support the hypothesis that breast-feeding and delay of exposure to known allergens may reduce the frequency of clinical allergic disease in offspring of allergic families. The substitution of soy formula for cow's milk for prevention of allergic disease does not seem to have any advantage.

▶ [We never will be presented with the results of a prospective, randomized study to determine the relationship of early infant practices to the subsequent development of atopic disease. Evidence has begun to accumulate that suggests that breast-feeding does reduce the incidence and delay the appearance of atopy. Until somebody else provides us with another 15-year follow-up, I'll stick to the conclusions reached by Gruskay. It is frustrating to realize that we have made so little progress in settling this controversy when it is remembered that in 1936 Grulee and Sanford (*J. Pediatr.* 9:223, 1936) suggested that there was a sevenfold decrease in the incidence of atopic dermatitis in infants who were fed a cow's milk-free diet during the first 6 months of life. A cow's milk-free diet doesn't mean, however, that soy-based formulas are the answer. This study and the work of others (see Easthan, E. J., et al.: ibid. 93:561, 1978; and Kjellman, N., et al.: *Clin. Allergy* 9:347, 1979) are but further examples of the fact that soy protein is not the panacea that commodity brokers would have us believe.

In the past year it was reported that the presence of specific IgE antibodies to cow's milk can be used to support a diagnosis of cow's milk allergy (Bjorksten, B., et al.: ibid. 13:119, 1983); that approximately 25% of infants will display positive blood basophil histamine release when their blood is incubated with cow's milk protein (McLaughlan, P., et al.: ibid., p. 1) and that allergy to cow's milk protein can result in recurrent mucoid impactions in the lung of an infant with asthma (Fruchter, L., et al.: *Ann. Allergy* 48:292, 1982). These adverse reports regarding cow's milk can't all be bull.—F.A.O.] ◀

3–3 **Adverse Pulmonary Responses to Aspirin and Acetaminophen in Chronic Childhood Asthma.** Thomas J. Fischer, Timothy D. Guilfoile, Hemant H. Kesarwala, John G. Winant, Jr., Gregory L. Kearns, Peter S. Gartside, and Charles J. Moomaw (Univ. of Cincinnati) used double-blind oral challenges to determine the frequency of adverse pulmonary responses to aspirin and acetaminophen in 25 patients, aged 8 to 18 years, with chronic, reversible obstructive airway disease. Most patients used one or two nonsteroid prophylactic agents daily. Tests were done with 600 mg of aspirin or acetaminophen and a lactose monohydrate placebo. Pulmonary function was measured at intervals for up to 4 hours after the challenge. Tests were considered to be positive if there was a 20% or greater reduction in 1-second forced expiratory volume or a 30% fall in maximal midexpiratory flow rate from baseline that was sustained over the 4-hour study period.

(3–3) Pediatrics 71:313–318, March 1983.

Four patients had positive aspirin tests and 2 had positive acetaminophen tests. One of the aspirin-positive patients also reacted to acetaminophen, and another was intolerant of placebo. The responses to acetaminophen were less intense than those to aspirin. Group mean pulmonary function responses to the active drugs and to lactose did not differ significantly.

It seems wise for chronically asthmatic children routinely to avoid aspirin-containing compounds. Acetaminophen appears to be a safe, although not entirely innocuous, substitute for aspirin in most children with chronic asthma. Noninvestigative aspirin challenges are not recommended for childhood asthmatics, but challenges may be useful for patients requiring aspirin or other nonsteroid anti-inflammatory medications. Challenge may help define mild adverse responses, particularly if there is a prolonged latent period between ingestion and an adverse reaction.

▶ [The incidence of aspirin sensitivity in children with asthma has been reported to range from .0% (Schull, J. F., and Pereyra, J. G.: *Clin. Allergy* 9:83, 1979) to a high of 28% (Rachelefsky, G. S., et al.: *Pediatrics* 56:443, 1975). This study, using sensitive techniques, splits the difference and comes up with a figure of 12% as the actual incidence of adverse pulmonary responses to aspirin. Acetaminophen did not get a completely clean bill of health but did produce fewer, and less intense, pulmonary responses.

There have been sporadic reports of actual clinical benefit from the use of aspirin in asthmatics, presumably via the inhibition of local pulmonary prostaglandin production. Cummings and Stark (*J. Allergy Clin. Immunol.* 71:245, 1983) treated 10 asthmatic children, after carefully excluding candidates with aspirin sensitivity, in a 9-week double-blind, crossover study using aspirin or placebo. Aspirin therapy did not reduce the number of wheezing episodes, the frequency of bronchodilator use or the administration of additional prednisone. No adverse effects were noted.

It would seem prudent, until proved otherwise, to avoid the use of aspirin or aspirin-containing compounds in children with asthma. The way things are going, it looks like aspirin is fast becoming "a drug on the market."—F.A.O.] ◀

3–4 **Epidemiologic Study of Insect Allergy in Children: II. Effect of Accidental Stings in Allergic Children.** Insect-allergic persons often have frightening anaphylactic reactions after being stung, but the appropriate way of using venom immunotherapy remains to be established. Kenneth C. Schuberth, Lawrence M. Lichtenstein, Anne Kagey-Sobotka, Moyses Szklo, Kathleen A. Kwiterovich, and Martin D. Valentine (Johns Hopkins Univ.) evaluated treatment in a series of 181 children, aged 3 to 16 years, with insect allergy who had had non-life-threatening reactions to insect stings and positive venom skin tests. Venom therapy was administered to 53; the other 128 were untreated and were followed clinically and immunologically for at least 2 years.

Many children in the study had skin test reactions to multiple venoms (Fig 3–2)! Immunotherapy led to a rise in IgG antibody against venom antigens in all cases. Titers declined over time in untreated subjects. About one third of each group was stung accidentally during follow-up. Both groups had low systemic reaction rates per sting and per patient stung; the difference was not significant. No reaction was more serious than the initial reaction had been. Seven of the nine

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(3–4) J. Pediatr. 102:361–365, March 1983.

systemic reactions resolved without administration of epinephrine. No significant differences were apparent between untreated patients who had systemic reactions after entry into the study and those who had local reactions only (Table 1). The course of skin test reactivity over time was comparable in the treated and untreated groups (Table 2).

TABLE 1.—Characteristics of "Systemic" vs. "Local" Reactors

	Systemic reactors (n = 8)	*Local reactors (n = 39)*	
Age (yr) (mean ± SE)	9.12 ± 3.2	9.34 ± 3.8	*P* = NS*
Percent males	75	76.9	*P* = NS
Original skin test score (mean ± SE)	3.12 ± 0.96	3.00 ± 0.88	*P* = NS
Presting yellow jacket RAST titer (mean ± SE)	276 ± 169	402 ± 643	*P* = NS
RAST rise with sting	6/8 (75%)	23/39 (58.9%)	*P* = NS
Presting yellow jacket IgG > 4.00 μg/ml	2/8 (25%)	10/39 (25.6%)	*P* = NS

*$P < .05$, Fisher's exact t test.
(Courtesy of Schuberth, K. C., et al.: J. Pediatr. 102:361–365, March 1983.)

TABLE 2.—Changes in Vespid Skin Test Sensitivity After One Year

Skin test sensitivity	*Treatment group*		*No-treatment group*		*Total*	
Increased	2 (7%)	1/2 (50%)	13 (21%)	9/13 (69%)	15 (16%)	10/15 (67%)
Same	6 (21%)	3/6 (50%)	18 (35%)	3/18 (17%)	24 (26%)	6/24 (25%)
Decreased	21 (72%)	5/21 (24%)	32 (44%)	14/32 (44%)	53 (58%)	19/53 (36%)
Total	29 patients	9 stung	63 patients	26 stung	92 patients	35 stung

(Courtesy of Schuberth, K. C., et al.: J. Pediatr. 102:361–365, March 1973.)

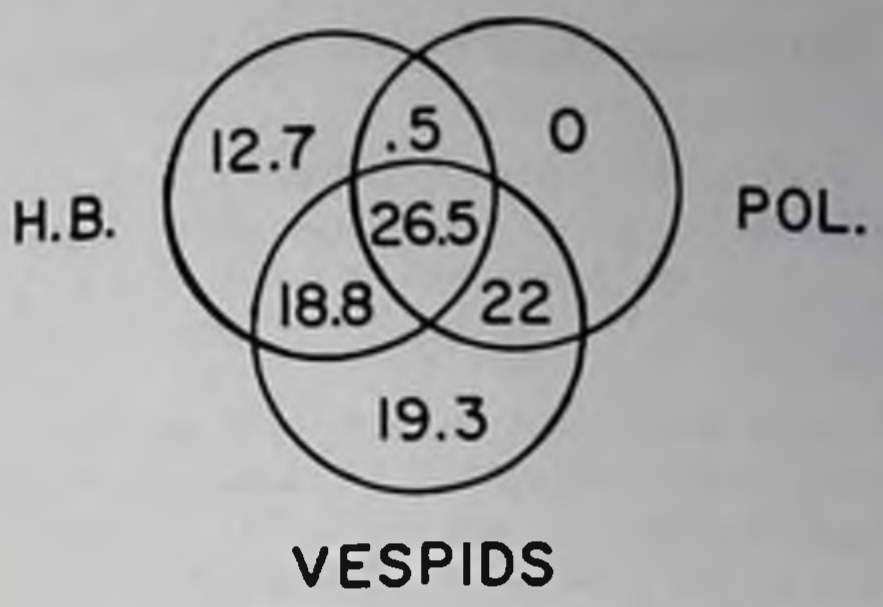

Fig 3–2.—Distribution of skin test sensitivity in children. *HB*, honeybee; *Vespids*, yellow jacket, white hornet, and yellow hornet; and *Pol*, *Polistes*. (Courtesy of Schuberth, K. C., et al.: J. Pediatr. 102:361–365, March 1983.)

Severe reactions to accidental stings are infrequent in insect-allergic children with a history of non-life-threatening systemic reactions, with or without venom therapy. Most have decreased skin test sensitivity over time. The findings should help physicians assess the risk of withholding treatment and may permit temporizing until more definitive data are available.

3–5 **Nasal Smear for Eosinophils: Its Value in Children With Seasonal Allergic Rhinitis.** Robert E. Miller, Jack L. Paradise, Gilbert A. Friday, Philip Fireman, and Dorothy Voith (Pittsburgh) report that nasal smears for eosinophils obtained by nose blowing or posterior nasopharyngeal swabbing, or both were stained with Wright's or Hansel's stains and read in three groups of children aged 4–15 years: 65 children with seasonal allergic rhinitis, 42 with perennial rhinitis and negative skin tests, and 70 nonallergic controls.

Of smears obtained by either or both methods, 69%, 11%, and 7% were positive (percentage of eosinophils $\geq$ 4%) in the seasonal allergic rhinitis group, the perennial rhinitis/negative skin test group, and the control group, respectively (table). Nearly identical results were obtained using only the nose-blowing method. Hansel's and Wright's stains were equally effective in identifying eosinophils, but the staining time for Hansel's stain was 1 minute, compared with 10 minutes for Wright's stain.

In children with seasonal nasal symptoms, the nasal smear for eo-

RESULTS OF NASAL SMEARS FOR EOSINOPHILS, BY GROUP*

	Nasal Smear	
	Positive†	Negative
Seasonal allergic rhinitis (N = 65)	45	20
Perennial rhinitis/negative skin test (N = 42)	5	37
Nonallergic control (N = 70)	5	65

*χ^2, df = 71, $P < .0005$. First *v* second group: χ^2, 1 df = 35, $P < .0005$. First *v* third group: χ^2, 1 df = 55, $P < .0005$.

†First nose blowing, nasopharyngeal swabbing, or subsequent noseblowing positive.

(Courtesy of Miller, R. E.: Am. J. Dis. Child. 136:1009–1011, November 1982; copyright 1982, American Medical Association.)

(3–5) Am. J. Dis. Child. 136:1009–1011, November 1982.

sinophils appears to be a reliable diagnostic test with moderately high sensitivity and high specificity.

► [I would encourage everyone to read this article and become proficient in the technique. I am afraid that this test, however, will never catch on as a diagnostic procedure. It is too simple and too inexpensive to ever become popular. Besides, how can you get a child to blow his nose onto a slide after his mother has brow-beaten him to always blow his nose into a tissue?

On the subject of allergic rhinitis, there is some good news for sufferers and their doctors. R. K. Chandra and co-workers (*Ann. Allergy* 49:131, 1982) have demonstrated, using a double-blind, controlled, crossover study, that repeated intranasal administration of a 4% sodium cromoglycate solution produced a significant reduction in symptoms and a decrease in consumption of antihistaminic drugs. One squirt in each nostril every 3 to 4 hours did the trick.—F.A.O.] ◄

3–6 **Heparin Liberation in Urticaria Pigmentosa.** Even minimal cutaneous lesions of urticaria pigmentosa can be associated with acute systemic effects of histamine liberation. Gerard Y. Guillet, Normand Dore (Johns Hopkins Univ.), and Jean Maleville (Bordeaux, France) report a paroxysmal coagulopathy presumably due to endogenous heparin release in a child with urticaria pigmentosa.

Boy, aged 4 years, presented with ecchymoses on the face and buttocks, suggesting abuse, but was active and behaved normally, and seemed to be in no distress. Skin lesions had been present since age 3 months. No medications were being taken. Brown macules were present, mainly on the trunk, and Darier's sign was positive, with spontaneous urticaria at sites of pressure. Ecchymoses were present all over the body and some petechiae on the trunk and knees. Clotting studies were negative. Biopsy of a pigmented lesion showed spindle-shaped cells in the upper dermis and around vessels; Giemsa staining showed red granules that were metachromatic with toluidine blue O. A bone marrow biopsy was normal. The coagulation time was prolonged after a hot bath, and the blood heparin level was increased to near the therapeutic anticoagulant range. Hematologic studies gave normal results 2 days later.

The ecchymoses in this patient could have been secondary to the combination of minimal trauma and a prolonged coagulation time. Histamine could be the primary mediator in some patients with mastocytosis, and overproduction of prostaglandin D_2 in others. The rare occurrence of ecchymoses in urticaria pigmentosa suggests that a carrier protein in serum could bind endogenous heparin and reduce its physiologic effects. Deficiency of such a carrier protein may have been present in this patient or, alternately, overproduction of heparin could have overcome the effect of a regulatory protein.

► [For those who wish to learn more about the mysterious mast cell, I would like to recommend the article by D. L. Marquardt and S. I. Wasserman entitled "Mast Cells in Allergic Diseases and Mastocytosis (*West. J. Med.* 137:195, 1982).—F.A.O.] ◄

3–7 **Cold Urticaria Associated With Infectious Mononucleosis.** L. Y. Frank Wu, J. Wesley Mesko, and Bruce H. Petersen (Indianapolis) encountered 2 patients with cold urticaria associated with infectious mononucleosis. A man aged 26 reported a week's duration of pruritus, erythema, urticaria, and lip swelling, first noted after ingestion of cold foods and then on exposure to cold air or after contact with cold surfaces. A cough and myalgia developed the week before onset of urticaria. Cold urticaria was confirmed by ice cube testing. Results of

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(3–6) Arch. Dermatol. 118:532–533, July 1982.
(3–7) Ann. Allergy 50:271–274, April 1983.

a Mono Spot test were positive, with a heterophil antibody titer of 224. The patient, who had mild perennial allergic rhinitis since childhood, had positive results on allergy skin testing. The other patient was a boy aged 17 who described symptoms of urticaria of 4 days' duration, with fever and myalgia for 1 day. A brother also had infectious mononucleosis, contracted 3 weeks earlier. The patient had bronchial asthma and hay fever. Cold urticaria was confirmed. In both patients, the duration of cold urticaria paralleled the course of infectious mononucleosis. Three similar cases were reported previously.

It is not clear whether an atopic constitution contributes to the development of cold urticaria in infectious mononucleosis. A clear relationship between cold urticaria and known cold-activated factors was not established in the 5 available reports of cold urticaria associated with infectious mononucleosis. A systematic search for cold-related factors that may occur in mononucleosis could provide an explanation for this association. Cold sensitivity may be more frequent in patients with infectious mononucleosis than has been recognized. Because cold urticaria may be life-threatening, patients who have urticaria and infectious mononucleosis must be examined carefully for cold sensitivity.

▶ [There has been a recent "rash" of reports describing the presence of cold urticaria in patients with Epstein-Barr virus infections (Tyson, C. J., et al.: *Med. J. Aust.* 1:33, 1981; Barth, J. H.: *Acta Derm. Venereal. (Stockh.)* 61:451, 1981; and Lemanske, R. F., Jr., et al.: *JAMA* 247:1604, 1982). Acute urticaria as an initial manifestation of infectious mononucleosis has been recognized for a much longer time (see Africk, J. A., et al.: ibid. 209:1524, 1969). It has been estimated that urticaria and other skin eruptions occur in about 5% of patients with mononucleosis. It is a nice diagnosis to keep tucked away in a place that you can remember.—F.A.O.] ◀

3–8 **Congenital Herpes Simplex Virus Infection Initially Resembling Epidermolysis Bullosa.** More than 50% of neonates infected with herpes simplex virus (HSV) have external involvement. Paul J. Honig and Diana Brown (Univ. of Pennsylvania) report the cases of 2 newborn infants with HSV infection with skin denudation resembling epidermolysis bullosa (Figs 3–3 and 3–4).

Transmission of congenital HSV infections is usually by contact with infected genital secretions during the birth process. Skin lesions appear 2–20 days after birth. If intrauterine infection occurs, lesions may be present at birth or within 24 hours. Intrauterine infection usually is thought to result from ascending infection related to prolonged rupture of the membranes. There is evidence that transplacental transmisson also may occur. Reports of congenital anomalies suggest infection of the fetus early in pregnancy.

Emphasis must be placed on early diagnosis to take advantage of the newer antiviral agents. Infants with congenital HSV infections may have large bullae and skin denudation, vesicles in a zosteriform distribution, pustules, purulent bullae, erythematous patches, or a generalized erythematous macular exanthem. It is recommended that Tzanck smears be performed immediately and that HSV cultures be

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(3–8) J. Pediatr. 101:958–960, December 1982.

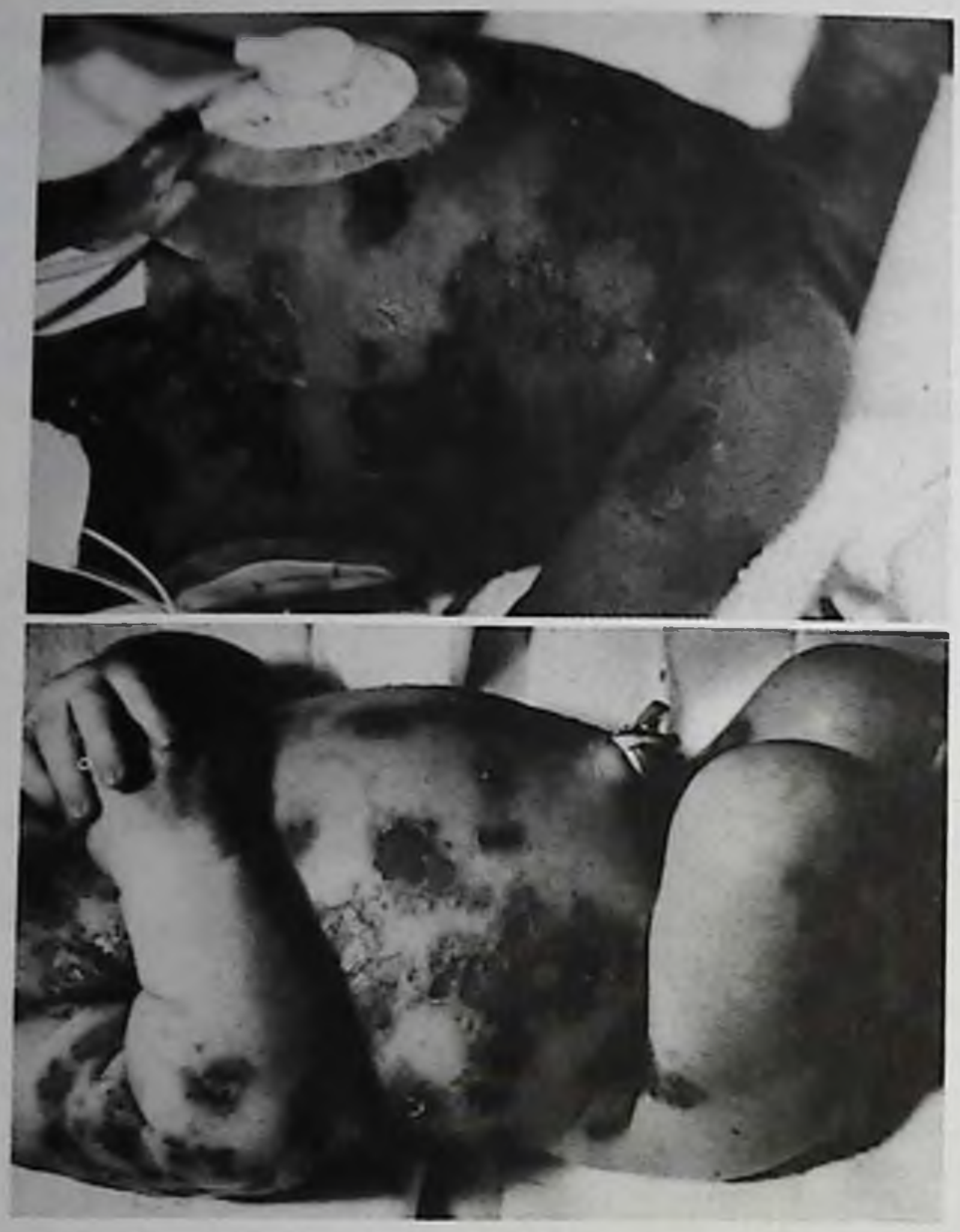


Fig 3–3 (top).—Three-day-old infant infected with herpes simplex virus type 1, showing denudation without intact vesicles or bullae.

Fig 3–4 (bottom).—Four-day-old infant with herpes simplex virus, type 2, infection, showing newly erupted vesicles, especially at the periphery of the denuded area of the abdomen.

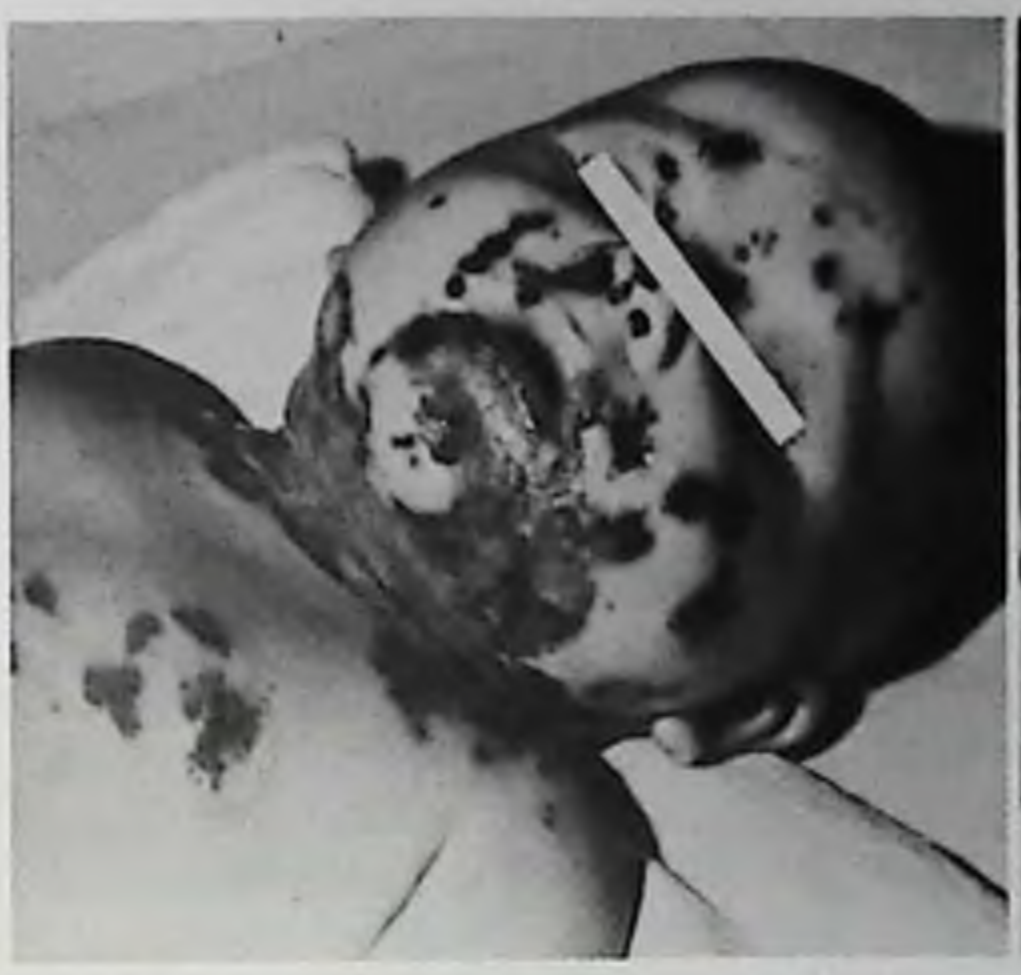
(Courtesy of Honig, P. J., and Brown, D.: J. Pediatr. 101:958–960, December 1982.)

obtained on all infants born with large bullae and areas of denudation.

3–9 **Sequential Bullous Impetigo and Cutaneous Herpes Simplex Virus Infection.** C. J. Harrison and M. I. Marks (Univ. of Oklahoma Health Sciences Center, Oklahoma City) report a case in which staphylococcal bullous impetigo appears to have predisposed an immunologically competent child to severe cutaneous herpes simplex virus (HSV) infection. Vesiculobullous lesions produced by staphylococci led to delay in recognition of the HSV. Rapid viral diagnostic techniques produced confirmation of HSV infection within 3 hours.

Male infant, aged 6 months, previously healthy, had culture-proved staphylococcal bullous impetigo in the diaper area. These lesions were nearly healed 5 days after beginning dicloxacillin, but 24 hours later, new small vesicles, noted on the lower abdomen, became disseminated (Fig 3–5). Fever (40 C) and lethargy developed. Further questioning of the mother revealed a history of "fever blisters," the last episode being less than 1 month before admission.

(3–9) Pediatr. Infect. Dis. 1:413–415, November 1982.



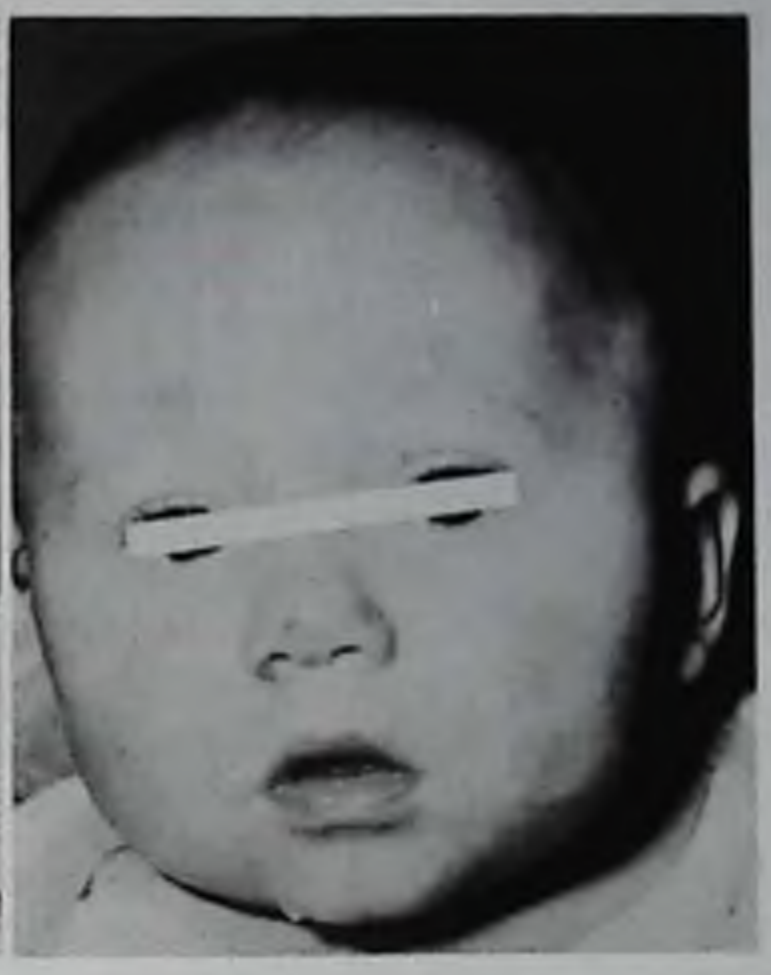


Fig 3–5 (left).—Disseminated lesions due to superinfection with herpes simplex virus in a male infant, aged 6 months, with bullous impetigo.

Fig 3–6 (right).—Patient 14 days after intravenous acyclovir therapy.

(Courtesy of Harrison, C. J., and Marks, M. I.: Pediatr. Infect. Dis. 1:413–415, November 1982.)

A Tzanck preparation of skin scrapings was inconclusive, but direct immunofluorescence was positive for HSV antigen. Electron microscopy of fluid aspirated from new nonpurulent vesicles showed virus particles consistent with herpes group viruses.

A 7-day course of acyclovir (750 mg/sq m/day) was begun. After 18 hours of therapy, the patient defervesced and was eating well and moving without pain. No additional lesions appeared after 72 hours of therapy, and viral cultures taken after 96 hours of acyclovir therapy were negative. Two weeks after hospital discharge, only mild superficial scarring and erythema remained (Fig 3–6). Complement-fixation titers for HSV were less than 1:8 in acute serum and 1:128 a month later.

▶ [This article and the preceding one should serve to heighten your suspicions regarding herpes infections. Bullous eruptions, or areas of denudation as a result of prior rupture of bullae, should trigger a diagnostic effort to identify herpes. Early diagnosis, particularly in a neonate, can prove lifesaving, given the availability of acyclovir therapy.—F.A.O.] ◀

3–10 **Tinea Capitis in Brooklyn.** Teresita A. Laude, Binita R. Shah, and Yelva Lynfield (Kings County Hosp.–Downstate Med. Center, New York) studied 144 patients with clinically diagnosed cases of tinea capitis presenting within a 12-month period; 96 (67%) had positive cultures. *Trichophyton tonsurans* grew in 89% and *Microsporum* organism in 11%.

The peak incidence was in the group aged 4–5 years. Boys and girls were affected equally. In many instances, several children in the same household were affected.

Of the culture-proved cases, 60% were noninflammatory and 40% were inflammatory (kerions). Of the 48 children with negative cultures, 26 (54%) had inflammatory lesions. In the group with kerions, 25 were girls and 13 were boys. None of the lesions fluoresced under a Wood's light. In 4 patients, the initial clinical manifestations were

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(3–10) Am. J. Dis. Child. 136:1047–1050, December 1982.

severe, diffuse, seborrhea-like scales and crusting of the scalp with minimal alopecia; *T. tonsurans* grew in the cultures of these 4 patients with noninflammatory tinea. More than half the patients with noninflammatory *T. tonsurans* tinea had "black dots"—an appear-

Treatment and Follow-up

Group*	Clinically Diagnosed Cases, No.	Culture-Proved Cases, No.	Culture-Proved Cases With Good Follow-up,† No.	Culture-Negative Cases With Good Follow-up,† No.	Duration of Griseofulvin Treatment to Cure, wk‡	
					Range	Mean
1	29	15	12	9	4-10	5
2	29	17	14	8	4-11	4.5
3	40	29	22	4	2-8	4.4
4	40	29	19	6	3-8	4.8
5	6	6	6	0	4-6	4.75
Total	144	96	73	27	. . .	. . .

*Group 1 had inflammatory lesions treated with griseofulvin alone; group 2, inflammatory, griseofulvin and erythromycin ethylsuccinate; group 3, noninflammatory, griseofulvin alone; group 4, noninflammatory, griseofulvin and topical antifungal agents; group 5, inflammatory, griseofulvin and prednisone.

†Patients returned for evaluation every 2 weeks.

‡Duration of griseofulvin treatment given for both culture-proved and culture-negative cases that were treated and followed-up.

(Courtesy of Laude, T. A., et al.: Am. J. Dis. Child. 136:1047–1050, December 1982; copyright 1982, American Medical Association.)

ance produced by the residual black stump of the diseased hair shaft after its fracture.

Marked cervical lymphadenopathic conditions were present in 53 cases. "Id" reaction was manifested as a generalized maculopapular rash by 7 patients with kerions. Concurrent tinea corporis was found in 24 patients.

Mycologic and clinical cure were obtained with a mean of 4.7 weeks of griseofulvin therapy (table). Griseofulvin was given as a micronized oral preparation (Grifulvin V), 10 mg/kg/day after breakfast. Neither systemic erythromycin, topical antifungal agents, nor systemic prednisone resulted in earlier eradication. However, prednisone (1 mg/kg/day orally for 1 week and then at a gradually reduced dosage for 1 more week) caused the inflammation of the kerions to subside dramatically; the patients in group 5 (see table) experienced complete subsidence of inflammation after a mean of 7 days. Lesions from which *Staphylococcus aureus* was cultured responded to griseofulvin as well as did those from which no *S. aureus* was cultured. The only adverse reaction to griseofulvin encountered was a mildly pruritic, generalized, maculopapular rash in 2 patients, which spontaneously disappeared after 2 days and did not preclude continued therapy.

Use of topical antifungal preparations may be indicated to prevent spread of infection to others. Use of systemic corticosteroids may be indicated in treating kerions.

▶ [Prevost (see 1981 YEAR BOOK, pp. 118–119) called attention to the fact of a change in the preponderant etiologic agent of tinea capitis from *Microsporum* to *Trichophyton tonsurans*. Prevost's study was based on experience in Charleston, South Carolina. These beasts are now in Brooklyn as well. They didn't know when they were well off. Of practical importance to the pediatrician is that *T. tonsurans* does not fluoresce with a Wood's light, whereas *Microsporum* organisms do. The Wood's light is no longer useful for screening purposes. Fortunately, the availability of dermatophyte test medium (DTM) makes culture of skin scrappings an easy procedure for office use. In the presence of an inflammatory lesion, the culture may be negative. Systemic steroids can produce dramatic improvement in kerions but griseofulvin is the mainstay of treatment. Remember, "black dots" don't always mean candy but are manifestations of *T. tonsurans*. They represent the residual black stump of the diseased hair shaft after its fracture. In Brooklyn, more than one half of the patients with noninflammatory *T. tonsurans* had "black dots." Do you think "Black Dots in Brooklyn" will ever rival "Red Sails in the Sunset"?—F.A.O.] ◀

3–11 **Treatment of Candidal Diaper Dermatitis: A Double-Blind, Placebo-Controlled Comparison of Topical Nystatin With Topical Plus Oral Nystatin.** Diane Munz, Keith R. Powell, and Chik H. Pai (McGill Univ., Montreal) conducted a prospective, double-blind study to evaluate the clinical resolution and incidence of relapse of candidal diaper dermatitis treated with combined oral and topical nystatin (group 1) as compared with topical nystatin alone (group 2). All patients were given cream containing nystatin, 100,000 units/gm, to be applied to affected areas 4 times a day for 10 days. The oral nystatin suspension contained 100,000 units/ml; 1 ml was given 4 times a day.

There was no difference in the clinical course between groups 1 and 2 (Table 1). About half the children needed topical treatment for as

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(3–11) J. Pediatr. 101:1022–1025, December 1982.

TABLE 1.—COMPARISON OF CULTURE-POSITIVE AND CULTURE-NEGATIVE DIAPER DERMATITIS

		*Group 1** (*n* = 16) (± *SD*)	*Group 2†* (*n* = 21) (± *SD*)
Initial evaluation			
Area of rash (cm²)		145.3 ± 112.7	155.5 ± 82.5
Redness‡		1.6 ± 0.6	1.6 ± 0.5
Pustules‡		3.0 ± 0.5	3.1 ± 0.7
Day 10 evaluation			
Area of rash (cm²)		64.3 ± 99.8	15.6 ± 28.5
Redness		0.4 ± 0.5	0.4 ± 0.5
Pustules		1.4 ± 1.2	1.2 ± 1.2
Isolation of *C. albicans*			
Skin	Day 1	16/16§	21/21
	Day 10	2/15	5/21
Stool	Day 1	8/16	9/17
	Day 10	5/15	7/18

*Skin positive for *Candida albicans*.
†$P < 0.05$ (no other significant differences).
‡Percent in parentheses.
§See Table 1 for scoring system.
(Courtesy of Munz, D., et al.: J. Pediatr. 101:1022–1025, December 1982.)

long as 3 weeks before clinical resolution was complete. A mycologic cure of the rash occurred in 78% of the children with candidal diaper dermatitis after 10 days of treatment, but gastrointestinal tract colonization persisted in two thirds of patients. About one third of the children in both treatment groups had a clinical recurrence within the following year.

The 11 children whose skin cultures (obtained on day 1) did not grow *Candida albicans* had had the rash for 6.4±7.5 weeks, compared with 1.8±2.7 weeks for those whose skin cultures yielded *C. albicans* ($P<.05$) (Table 2). When a diaper rash is characterized by intense erythema, especially in the groin creases and perianal skin, and by satellite papules and pustules, the recovery rate of *C. albicans* has been as high as 80% and was 77% in this series.

No difference was noted in the eradication of *C. albicans* from the skin or gastrointestinal tract between infants treated topically and those treated both topically and orally. Recurrence of a rash similar to the one studied occurred equally in patients treated with either regimen and with or without mycologic cure.

► [I realize that the following seems totally irrelevant, but I couldn't pass up the opportunity to share with you this news item, printed in its entirety, which appeared in the Aug. 10, 1983, issue of *USA Today*. We are talking about diapers—how is this for mental imagery?

"POLICE WORK TO PIN DOWN TRAVELING DIAPER MAN

"TEL AIR, Md.—Maryland state police Tuesday afternoon put out an alert for a 'white male wearing a diaper and driving a car with a large number of cans of whipped cream in the back seat.' A man, apparently the same one, startled a clerk in a York, Pa., convenience store Tuesday morning. A police report gave this account: The man walked into the store wearing only a disposable diaper and a T-shirt. He

TABLE 2.—Clinical and Mycologic Evaluations of Diaper Dermatitis in 37 Patients Seen in Follow-up

	Culture-positive(n = 37)*	*Culture-negative(n = 11)*
Average age (mo)	9.1 ± 6.2	6.4 ± 1.9
Duration of rash prior to treatment (wk)	1.8 ± 2.7	6.4 ± 7.5†
Area of rash (cm^2)		
At Day 1	151.1 ± 95.5	232.5 ± 124.1
At Day 10	36.6 ± 72.1	97.6 ± 130.1
Number of patients at day 10 with decrease in:		
Area of rash (cm^2)	34 (92)‡	10 (91)
Redness§	32 (86)	10 (91)
Pustules§	31 (84)	10 (91)

*Group 1, topical and oral nystatin.
†Group 2, topical nystatin alone.
‡Redness ratings: 0, none; 1, mild; 2, marked. Pustules ratings: 1, 1–5, pustules; 2, 5–20 pustules; 3, innumerable; 4, confluent pustules.
§Number positive/number cultured.
(Courtesy of Munz, D., et al.: J. Pediatr. 101:1022–1025, December 1982.)

picked up a can of whipped cream and took it to the checkout counter. 'What are you going to do with that?' the clerk asked.

"'The diaper or the whipped cream?' the man asked.

"'Both,' the clerk answered.

The man then shook up the can, opened it, and sprayed whipped cream around the store through a hose he had with him. Then he left the store and drove away in a car with Maryland tags. He headed south, toward the Maryland state line."—F.A.O.] ◀

3–12 **Incidence of Diaper Rash When Using Cloth and Disposable Diapers.** Howard Stein (SUNY, Stony Brook) evaluated the incidence of diaper rash in a blind, prospective, controlled study involving 200 infants over a 9-month period. Products studied included home-laundered cloth diapers, two marketed disposable diapers (Pampers and Johnson's Disposable Diapers), and a prototype disposable diaper from Johnson & Johnson.

There was no significant difference in severity of diaper rash at the initial visit in any of the groups (Table 1). The incidence of diaper rash noted at weekly visits was higher in infants who used cloth diapers than in those who used disposable diapers ($P < .01$) (Table 2). The percentage of infants with diaper rash in each group from week to week varied considerably within the four groups as well as between groups.

TABLE 1.—SEVERITY OF DIAPER RASH AT INITIAL VISIT (NUMBER OF INFANTS IN EACH CATEGORY)

		Disposable		
Severity	*Cloth*	*No. 1*	*No. 2*	*No. 3*
0—None	14	19	21	19
1—Minimal	21*	22*	22*	22*
2—Slight	11	6	5	7
3—Moderate	4	3	1	3
4—Severe	0	0	0	0
Total	50	50	49	51

Kruskal-Wallis chi square = 4.8; $P = .18$.
*Median severity.
(Courtesy of Stein, H.: J. Pediatr. 101:721–723, November 1982.)

TABLE 2.—NUMBER OF BABIES CLASSIFIED ACCORDING TO THE NUMBER OF RETURN VISITS DURING WHICH RASH WAS NOTED

		Disposable		
No. of return visits with rash	*Cloth*	*No. 1*	*No. 2*	*No. 3*
0	1	6	6	9
1	5	6	5	5
2	5	12	9	3
3	13	13*	9*	10*
4	9*	4	11	10
5	9	3	4	9
6	8	6	5	5
Total	50	50	49	51

Kruskal-Wallis chi square = 7.8; $P = .05$.
*Median number of visits.
(Courtesy of Stein, H.: J. Pediatr. 101:721–723, November 1982.)

(3–12) J. Pediatr. 101:721–723, November 1982.

► [A previous study (1981 YEAR BOOK, pp. 119–120) concluded that disposable diapers were more likely to produce a rash than were cloth diapers. Now we have an opposite conclusion. I wonder if the laundry detergents had anything to do with it? Most striking to me was the fact that the incidence of diaper rash ranged from 44% to 78% of infants using cloth diapers and from 37% to 63% for one of the disposable diaper groups. Diaper rash appears to be one of the rites of passage. I marvel at the number of hours grown men and women spend studying this problem.—F.A.O.] ◄

3–13 **Hazards Associated With Diaper Changing.** Mary A. McCormick, Peter G. Lacouture (Massachusetts Poison Control System), Pierre Gaudreault, and Frederick H. Lovejoy, Jr. (Harvard Med. School) studied the incidence of exposure to poisons occurring in children during diaper changing.

During the 3-month study period, the Massachusetts Poison Control System received 6,570 calls involving exposures to poison in children aged 3 years and younger; 138 exposures (2.1%) involved a child during diaper changing (study group), and 79% of the group was between the ages of 7 and 18 months. Of the poisonings, 42% occurred between 5 P.M. and 9 P.M. Powders accounted for 47% of the exposures (table). Symptoms occurred in one third of the exposures, were mild, and occurred most often with ingestion of powders.

Children are at increased risk of poisoning during diaper changing.

► [Please note that 42% of the poisonings occurred between 5 P.M. and 9 P.M. Was daddy responsible? I see another label in the offing: "A diaper change may be hazardous to your health." Are you prepared for informed consent?—F.A.O.] ◄

3–14 **Academy Rash: A Probable Epidemic of Erythema Infectiosum ("Fifth Disease").** Corstiaan Brass, Luella M. Elliott, and David A. Stevens reviewed the findings in an outbreak of febrile illness occurring in a private academy in Santa Clara County, California. The index case was in a boy, aged 11, with rash, fever, and meningismus. Sixty-nine children, or 13% of those enrolled, developed an erythematous, migratory rash over a period of a few weeks. The rash, which was most frequent on the extremities, was accompanied by fever or other systemic or respiratory symptoms. The fever lasted a mean of 4 days and the rash a mean of 11 days. The highest temperature reported was 39.3 C. Pruritus and sore throat were common; nuchal pain was uncommon.

FREQUENCY OF INHALED OR INGESTED SUBSTANCES IN 138 STUDY SUBJECTS

Substances	Subjects %
Powders	47
Ointments and creams	27
Baby wipes	16
Other	10
Baby oil, acetamimophen liquid, baby shampoo, and rubbing alcohol	

(Courtesy of McCormick, M. A.: JAMA 248:2149–2160, Nov. 5, 1983. Copyright 1982, American Medical Association.)

(3–13) JAMA 248:2159–2160, Nov. 5, 1982.
(3–14) Ibid., pp. 568–572, Aug. 6, 1982.

Cases occurred in all grades from kindergarten through ninth, with a peak in grades five to seven. More boarding than day students were affected. Secondary cases occurred in households of affected children and in adults from the school. No similar episodes occurred at other local schools. Eighty-eight attempts at virus isolation from 20 throat washings of affected children were unsuccessful. The index patient had a significant rise in titer to influenza A virus.

This illness was consistent with erythema infectiosum, a disease of unknown etiology that has occurred in epidemic form in schools and also sporadically. A second viral illness cannot be excluded as the cause of fever and systemic illness.

► [I know we have been misled before, but we finally may have the cause for erythema infectiosum (fifth disease). M. J. Anderson and co-workers (*Lancet* 1:1378, 1983) provide convincing evidence that this disease is caused by a human parvovirus infection. During the investigation of an epidemic in North London in two primary schools, serologic evidence was obtained using a parvovirus-specific IgM that demonstrated that antibody rises occurred in the children with the rash.

Parvovirus infection also has been implicated as the cause of the transient aplastic crisis observed in patients with sickle cell anemia and other congenital hemolytic anemias (see Duncan, J. R., et al.: ibid., p. 14).—F.A.O.] ◄

3–15 **Complete Resolution of Life-Threatening Hemangioma by Embolization and Corticosteroids.** Louis C. Argenta, Ellen Bishop, Kyung J. Cho, Alice F. Andrews, and Arnold G. Coran (Univ. of Michigan, Ann Arbor) report on a newborn infant with a massive hemangioma of the left thigh and hemipelvis, complicated by severe thrombocytopenia and refractory congestive heart failure.

Female infant, 3.09 kg at birth, was delivered after an uncomplicated pregnancy. A large hemangioma was noted at birth in the left gluteal area and the infant appeared to be in respiratory distress; a chest x-ray film showed massive cardiomegaly. Transferred to the neonatal intensive care unit at 6 hours of age, the child had a heart rate of 145, respiration rate of 66, temperature of 37 C, and blood pressure of 70/30. The precordium was hyperactive with an S_3 gallop, and a grade III/IV systolic murmur was heard on auscultation. The liver was palpable 4 cm below the costal margin. An 11×13-cm hemangioma involved the left buttock, labia, and thigh (Fig 3–7). Hemoglobin was 9.8 gm%, platelets 20,000, bilirubin 3.9/0.9, and fibrinogen 57. A chest x-ray film confirmed massive cardiomegaly. Treatment was begun with diuretics, digoxin, transfusion of packed cells, fresh-frozen plasma, and platelets. Intravenous methylprednisolone was given at 1 mg/kg every other day and external compression of the hemangioma was applied with Ace wraps.

Because of the progressive deterioration of the patient, umbilical artery catheters were inserted for angiography. The arteriogram showed a very large vascular mass on the left groin and gluteal region consistent with cavernous hemangioma with multiple feeding arteries. After the arteriogram, several 2×2-mm Gelfoam pellets were injected into the left internal iliac artery; immediate postembolization arteriograms showed marked decrease in blood flow to the mass. The next day, the lesion was softer and less violaceous (Fig 3–8). When respirations became fatigued on the fifth day of life, the infant was intubated and placed on a ventilator. Additional Gelfoam pellets were injected into the left internal iliac artery. Steady improvement followed; the patient was extubated and started on oral feedings, and the mass became

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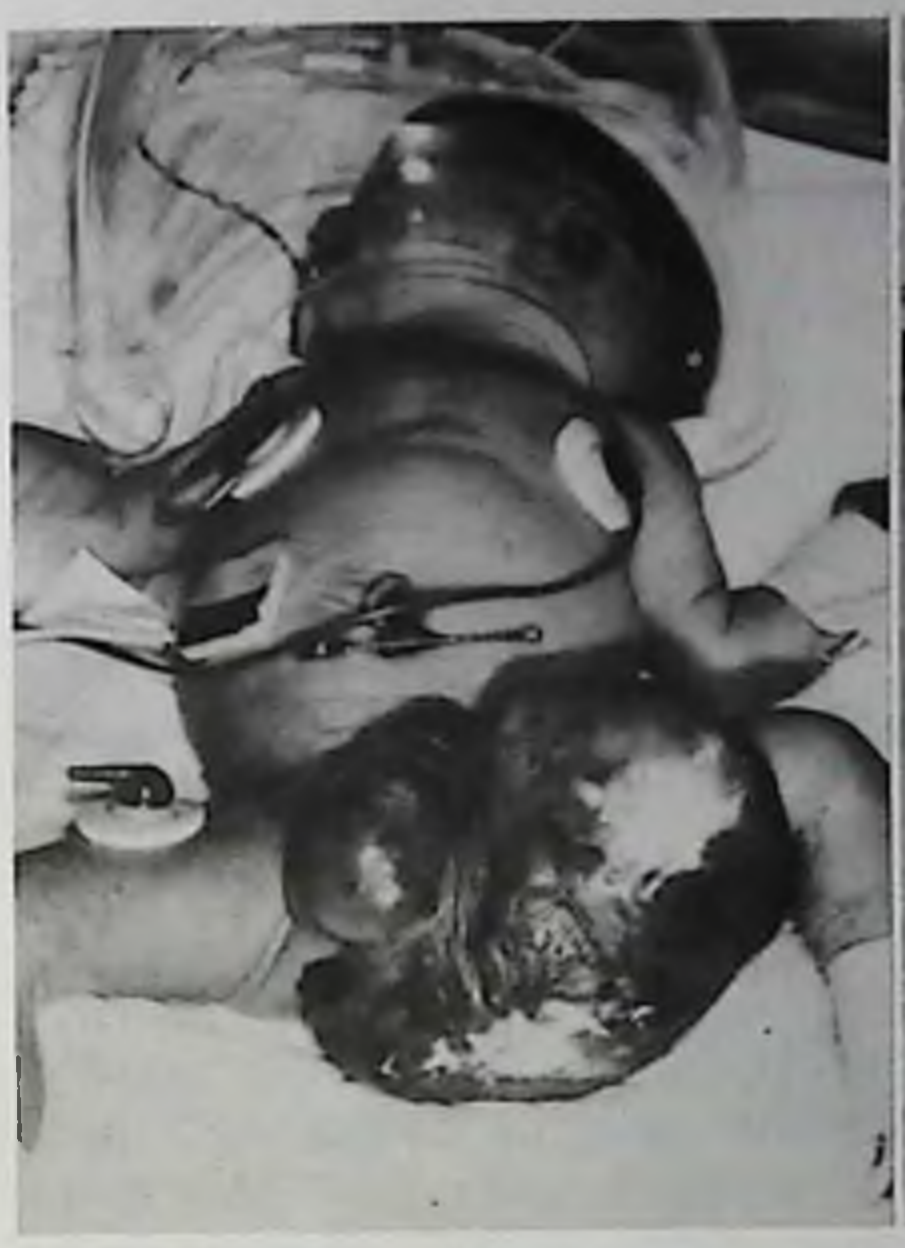
(3–15) Plast. Reconstr. Surg. 70:739–744, December 1982.



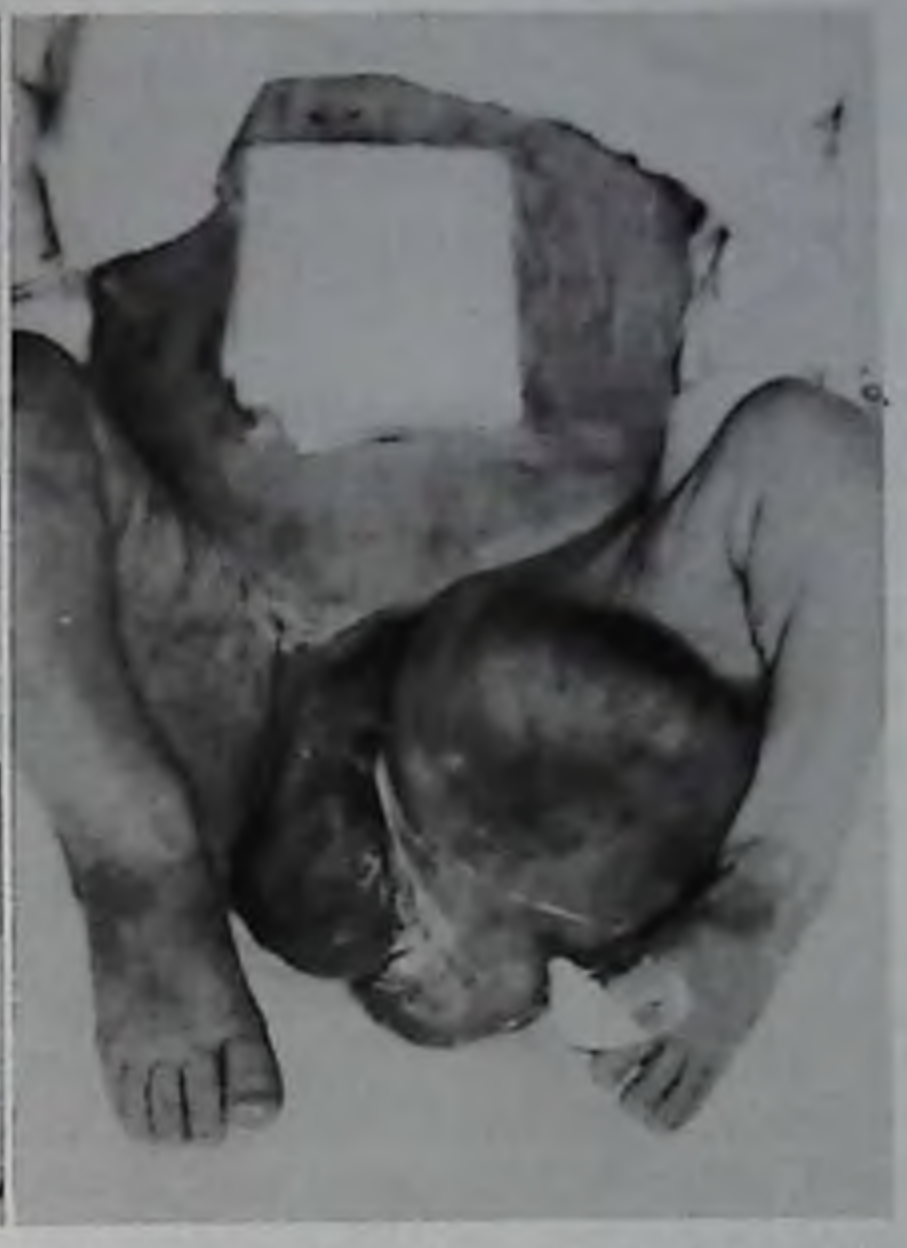
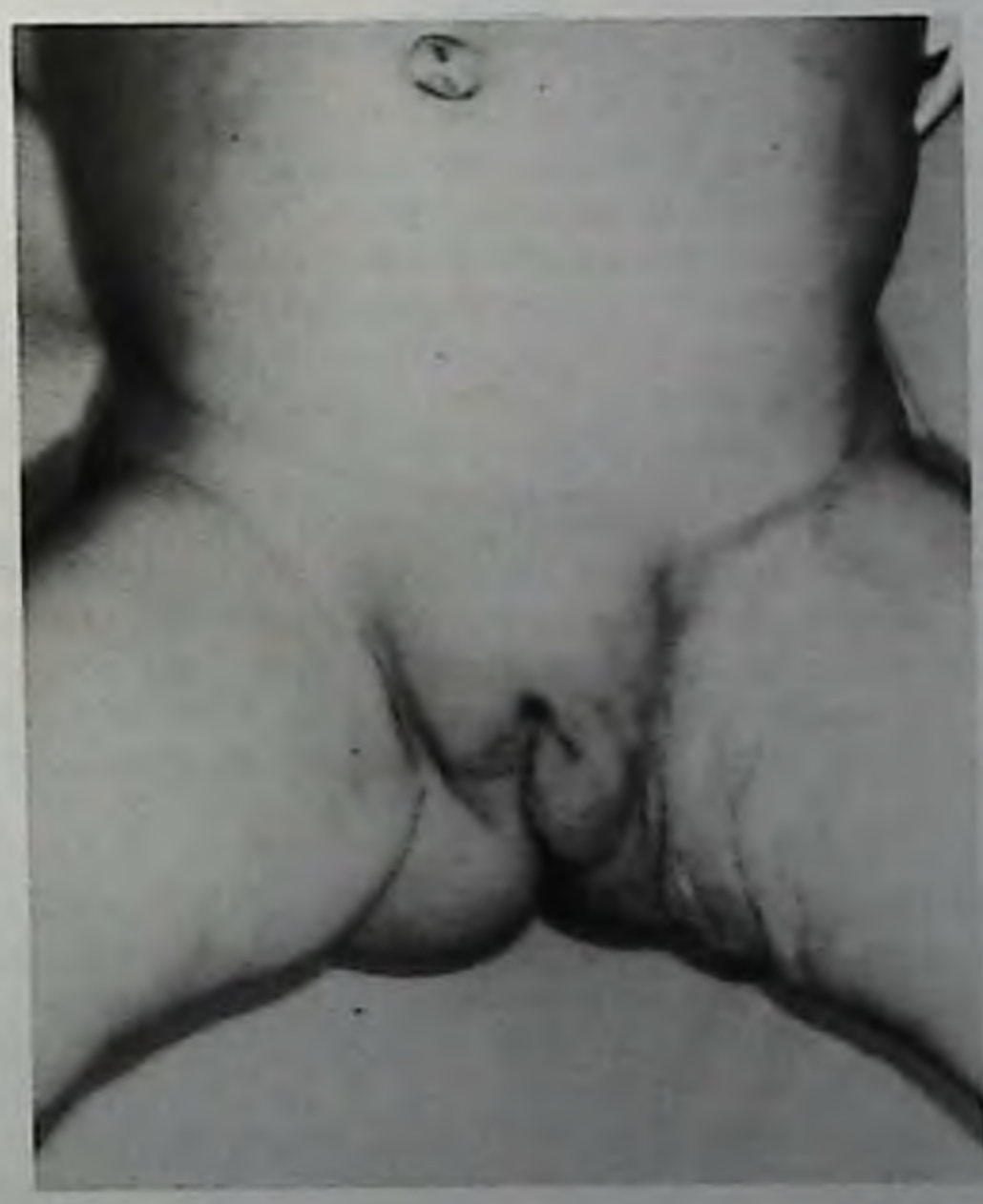


Fig 3–7 (left).—The patient at 12 hours of age had a massive hemangioma. White areas on the lesion are topical antibiotics applied to areas of impending skin breakdown.

Fig 3–8 (right).—One day after embolization, the lesion has decreased in size and vascular congestion.

(Courtesy of Argenta, L. C., et al.: Plast. Reconstr. Surg. 70:739–744, December 1982.)

Fig 3–9.—At 7 months of age, the patient demonstrates only a minimal amount of the lesion remaining in the left labia. (Courtesy of Argenta, L. C., et al.: Plast. Reconstr. Surg. 70:739–744, December 1982.)



smaller. At age 3 weeks, steroids were discontinued; at time of discharge of the patient at age 1 month, platelet count was 108,000/cu mm, fibrinogen 190, prothrombin time 11.8 seconds, and partial thromboplastin time 37.8 seconds. Discharge medications were digoxin, Aldactone, and Diuril. By the seventh month, the hemangioma was almost entirely involuted (Fig 3–9). By 15 months, the child had reached normal growth and could stand and walk normally.

Congestive heart failure is thought to be the result of increased cardiac output secondary to blood shunting through the arteriovenous malformations within the cavernous hemangioma.

The internal iliac artery was used for embolization as it is easily entered from the umbilical artery. One risk of Gelfoam embolization is that pellets could be carried to other parts of the body and the sudden respiratory deterioration on day 5 in this patient may have been caused by a pulmonary embolus.

3–16 **Café au Lait Spots in Schoolchildren.** R. G. Burwell, N. J. James, and D. I. Johnston (Queen's Med. Centre, Nottingham, England) examined 732 white schoolchildren aged 4–11 years for café au lait (CAL) spots 1 cm or more in diameter. The criteria were a discrete, flat light brown area with defined margins. Excluding 2 children with 5 CAL spots and 3 with 6 or more spots, 233 CAL spots were identified in 185 children. Three fourths of the children examined had no CAL spots. The 3 subjects with 6 or more spots were siblings and were presumed to have neurofibromatosis; 1 died of leukemia. In the other cases the number of CAL spots could not be significantly related to age or sex.

These findings provide some support for using the number of CAL spots as an empirical threshold for diagnosing neurofibromatosis. No significant increase in number of CAL spots between ages 4 and 11 years was confirmed in this study. Unlike freckles, CAL spots appear to be more prevalent on unexposed areas of the skin.

► [Previous studies that have enumerated the "normal" number of café au lait spots have involved neonates, children up to age 5 years, or adults. This study fills in the age gap. The conclusions seem the same—more than 5 café au lait spots should be viewed as abnormal and suggest the presence of neurofibromatosis. For more on this colorful topic, see the 1981 YEAR BOOK (pp. 113–115), where a survey of white neonates concluded that the presence of 2 or more spots in a newborn should arouse the suspicion of neurofibromatosis.—F.A.O.] ◄

► ↓Last year, Dr. Walter W. Tunnessen, Jr., prepared a summary for us of the highlights of the annual meeting of the Society for Pediatric Dermatology. We printed it and it proved to be a very popular addition to the YEAR BOOK. Tunnessen, Professor of Pediatrics, State University of New York, Upstate Medical Center, provided the following highlights of the eighth annual meeting of the Society for Pediatric Dermatology for his encore.—F.A.O. ◄

WHAT'S NEW IN PEDIATRIC DERMATOLOGY

The eight annual meeting of the Society for Pediatric Dermatology (a mixture of pediatricians, dermatologists, and an increasing number of double-boarded individuals) was held July 21–23, 1983. A few highlights of the meeting are abstracted here for your interest.

(3–16) Arch. Dis. Child. 57:631–632, August 1982.

Cat-Scratch Disease: An Etiologic Breakthrough?

Doctor Andy Margileth of the Uniformed Service University of Health Sciences provided evidence for a possible breakthrough in the etiology of cat-scratch disease during his presentation "Atypical Cutaneous Infections in Children." Doctor Margileth has pursued this feline-induced disease for years and has reminded us repeatedly that it is more common than we realize. Now he and Dr. Douglas Wear at the Armed Forces Institute of Pathology have discovered a gram-negative pleomorphic bacilli in pathologic sections of affected lymph nodes. Twenty-seven of 30 nodes from patients with cat-scratch disease demonstrated the organisms with Warthin-Starry agent, a silver stain, and 2 others with Brown-Hopps, a modified gram stain. Control specimens did not show these pleomorphic rods.

The organism has not yet been isolated; however, Doctor Margileth asks that if a node suspicious for cat-scratch disease is biopsied, you freeze part of the specimen without fixatives at −70 degrees and stain the other with either of the above agents. If the pleomorphic rods are found, call Doctor Margileth (202–295–3136) to facilitate shipment of the frozen specimen for isolation of the organism.

Ichthyosis: Fishing Around for the Answers

Doctors Lowell Goldsmith (University of Rochester) and Mary Williams (University of California, San Francisco) provided an update on ichthyosis. Lipids apparently are intimately involved with some types, and abnormalities in proteins are involved in others.

It turns out that ichthyosis vulgaris is much more common than most of us realize, with a prevalence of 1/250 to 1/1,000. Many cases are mild and easily missed, particularly since 74% have atopy, and, consequently, this aspect of the skin may receive the primary attention. Could it be that our recalcitrant atopics are combinations of the two?

Some cases may have plantar and palmar fissures as the main presentation. Propylene glycol (in concentrations as high as 60%) seems to work very well for the fissures and for ichthyosis vulgaris in general. Keep this in mind for cracked feet. Another helpful agent is 5% pyruvic acid (or citric or lactic acid) in an emollient such as Eucerin or Acid Mantle Creme.

Androgens and Acne

In the Apr. 28, 1983, issue of the *New England Journal of Medicine,* Marynick et al. reported results of measurement of androgens in 59 women and 32 men with long-standing cystic acne resistant to conventional therapy. Affected women had higher serum levels of dehydroepiandrosterone sulfate (DHEA-S), testosterone, and luteinizing hormone and lower levels of sex hormone-binding globulin (SHBG) than controls. Affected men had higher levels of serum DHEA-S and 17-hydroxyprogesterone and lower levels of SHBG. Dexamethasone

was given to men and dexamethasone and/or an oral contraceptive pill, Demulen, was given to women to suppress DHEA-S. After 6 months of treatment, 97% of the women and 81% of the men had resolution or marked improvement in their acne.

Anne Lucky, a pediatric endocrinologist and dermatologist at Yale University (now at Cincinnati Children's Hospital), reported her studies of androgen measurements in adult women with persistent acne and hirsutism. Fifty percent to 60% of the women had at least one androgen or androgen precursor abnormality. Free testosterone or DHEA-S levels or both were elevated in 33%, while the remaining had elevations in other precursors.

After years of searching for androgen excess in acne, it looks like the payoff is near. Suppression with small doses of steroids or estrogens seems to offer promise. Blocks in steroid hormone synthesis may lead to excessive production of androgens by the adrenal or ovaries. The next few years should prove exciting to us and therapeutically helpful to our patients.

Is Staphylococcus aureus Making a Comeback?

Many of us remember the epidemics of staphylococcal infections of the 1950s and 1960s, particularly those playing havoc with neonates. In the 1970s, staphylococci infections seemed to tame down a bit, with the notable exception of the toxic shock syndrome, which has received increasing attention. Now Dr. Jim Leyden of the University of Pennsylvania reports that he has noted increasing numbers of patients with furunculosis who seem to have a rapidly spreading type of disease. Leyden warns to be on the lookout for such cases and, more importantly, not to neglect looking at family and social contacts. He suggests examining all other close contacts for similar lesions. If the index case is the only one treated, the disease may "ping-pong" back and forth. Has the time for *Staphylococcus* reappeared?

Dermatomyositis

Doctor Arthur Norins, Chairman of Dermatology at the Indiana University School of Medicine, presented an update on childhood dermatomyositis. He pointed out that a wide spectrum of disease may be seen, with a very acute onset in some children and a slowly progressive course in others. The first marker of skin disease may be facial erythema, mistaken for sunburn, that persists. Generally, by history, subtle evidence of muscle weakness is present before the rash. Erythematous, scaly plaques (Gottron's sign) are characteristic over the knuckles, elbows and knees, but for some reason are not seen on the feet.

The prognosis of children with this disease has improved markedly in the steroid era. Before steroids, 30% of patients died, 30% had major residua, and 40% cleared. At present, the mortality is about 10%, with 15% developing major residua and 75% clearing.

Steroid pulse therapy (Medrol, 1 gram intravenously over 1 hour, on 5 consecutive mornings) has proved helpful in patients who seem resistant to oral steroids.

The Therapeutic Hotline

A panel of 5 experts fielded questions from the floor on a variety of sticky problems.

Atopic Dermatitis

Some children with atopic dermatitis seem to be resistant to standard therapy. Doctor Art Norins emphasized the importance of clothing. For recalcitrant cases he *strongly* recommends 100% cotton clothing. Although a bit more expensive (and harder to find) than synthetic-cotton combinations, this change can make a big difference in response.

Others reiterated the importance of treating skin infection, although the skin may not look infected clinically. Some use Dicloxacillin and others use erythromycin for 4 to 5 weeks routinely for tough cases.

An exchange developed about the dangers of home humidifiers. Apparently *Legionella pneumophila* loves to colonize these devices. Perhaps we need to think twice about their prescription!

Vitiligo

Considerable variation in the treatment of this relatively common problem was found. All panelists agreed that if the child with vitiligo is clinically healthy, has good growth curves, and a normal physical examination, there is no need for an endocrine workup.

Some use no active therapy for vitiligo, only cover-ups, while others use topical and even oral psoralins. The dangers of cataract formation with oral psoralens and sunlight exposure were discussed. Coal tar, applied topically, seems to work in some cases.

Perhaps the niftiest suggestion was the use of lime extract. Apparently certain plants, including lime, are well known to produce phototodermatitis. Ron Hansen, of Tucson, presented 2 patients with suspected child abuse who had irregular areas of hyperpigmentation (not bruising) on their trunks. Margarita mix was responsible. The day I returned to work after the meeting, I saw my first case. Perioral hyperpigmentation, recurrent for 2 summers, in a youngster who loved to chew on limes!

Warts

Unfortunately, there were no real therapeutic breakthroughs for wart sufferers, especially those who have extensive lesions. Some suggest sending the patient to your worst enemy. Many highlighted the

importance of placebo therapy. One paints fluorescein on the warts and then exposes them to a Wood's lamp. Another uses milk of magnesia by mouth.

Duofilm (a combination of lactic and salicylic acids in flexible collodion) was found to be suitable by many, but failures often result if the warts are not soaked for 5 minutes before the medication is applied. After application, the wart should be covered by waterproof tape. The next day, the wart should be brushed or filed with a pumice stone or emery board and the process reapplied. Six to 8 weeks may be necessary.

The problem of condyloma acuminata in children also was batted about. It was stated that the burden of proof on ruling out sexual abuse rests with us. Some felt that as many as 80% of the cases reflect sexual abuse, while others thought that 33% were. Nonetheless, venereal warts should create a high level of concern.

4. Dentistry and Otolaryngology

4–1 **Defects of Tooth Structure in Congenital Cytomegalovirus Infection.** Sergio Stagno, Robert F. Pass, Joe P. Thomas, Juan M. Navia, and Meyer E. Dworsky (Univ. of Alabama in Birmingham) studied 118 patients with congenital cytomegalovirus (CMV) infection, which was documented by isolation of virus from urine during the first 3 weeks of life. All patients were older than age 18 months at the time of dental examination. Typical signs and symptoms of congenital CMV infection were evident at birth in 25 patients; the remaining 93 had subclinical infection.

Tooth defects occurred in 10 of 25 (40%) children with the more severe form of infection and in 5 of 93 (5.4%) of those born with asymptomatic infections. The defect of tooth structure was generally more severe in infants with symptomatic infection at birth, because in these cases all or nearly all the teeth were affected.

In a significant number of children the anomaly derived from a defect of amelogenesis. The defect was characterized by generalized yellowish discoloration. The enamel was opaque and apparently hypocalcified, as some children had incisors with fractured borders (Fig 4–1). In many cases the enamel was absent, and affected teeth tended to wear down rapidly. Rampant dental caries was frequent. The group was too young to determine whether enamel defects will occur in permanent teeth.

Patients with congenital CMV infections should receive good dental

Fig 4–1.—Cytomegalovirus-affected teeth. Patient had clinically severe congenital infection. Fractured borders and opaque and hypocalcified enamel are seen. (Courtesy of Stagno, S., et al.: Pediatrics 69:646–648, May 1982. Copyright American Academy of Pediatrics 1982.)

(4–1) Pediatrics 69:646–648, May 1982.

preventive care, as they have high susceptibility to caries. Many may need orthodontic therapy.

▶ [I am not aware of anyone calling attention previously to defects of tooth structure in patients with congenital CMV infection. I am certain that I have seen young children with disturbances of enamel formation with yellowish or brown-colored stains on their teeth. Now we see that this can be due to congenital CMV infection. Apparently we still have much to learn about CMV and its effects on the body. If we give Doctor Stagno's group enough time, I am certain we will get all of the important information.—J.A.S., III] ◀

4–2 **Effects of Psychologic Preparation on Children Hospitalized for Dental Operations.** Although hospitalization of children for dental extractions and restorations with general anesthesia is sometimes useful, considerable anxiety is produced in most hospitalized children. Bruce H. Schwartz, Judith E. Albino, and Lisa A. Tedesco examined the effects of preoperative preparation by play therapy on young children hospitalized for dental surgery. Forty-five children aged 3 to 4 years were studied. Stress was quantified by the Manifest Upset Scale and Cooperation Scale. Control children given no preoperative preparation were compared with both a group that had a preoperative play session unrelated to the hospital or operations and a related-play therapy group in which the session focused on the hospital and operations. The same therapist participated in both play sessions. The sessions involved both provision of information to the child and the parent and role-playing by both the child and the parent.

The related-play group was more cooperative than either of the other groups; the controls were least cooperative. Uncooperative behavior was most marked at induction of anesthesia. The related-play group had less upset behavior than either of the other groups, and the control group displayed the most upset behavior. Upset behavior also was most marked at induction.

Systematic preparation by a hospital-operation-related play therapy session can benefit young children hospitalized for dental operations with general anesthesia. Provision of information about the procedures coupled with a rehearsal of the procedures can reduce anxiety and fears and help the young child cope more effectively with hospital procedures, especially at induction of anesthesia. Possibly children who react adversely to simulated mask inhalation induction would be less distressed by intravenous induction.

4–3 **Effect of Appointment Time, Age, and Gender on Children's Behavior in a Dental Setting.** Many have claimed that morning dental appointments are preferable to afternoon appointments for children. Mark H. Taylor, Ira N. Moyer, and Devereaux S. Peterson (Creighton Univ., Omaha, Neb.) examined the influence of appointment time, age, and sex on the behavior of children in a dental setting. A total of 437 randomly selected children aged 3–13 years participated in the study. Observations of behavior at the outset and at the times of injection and cavity preparation were made using the Frankl Behavior Rating Scale.

(4–2) J. Pediatr. 102:634–638, April 1983.
(4–3) ASDC J. Dent. Child. 50:106–110, Mar.–Apr. 1983.

Inappropriate behavior at the outset was much less frequent in children older than age 7 years, but was not influenced by the time of day or by gender. Both extremely negative and extremely positive behaviors were seen in younger children. During the injection period, older children exhibited significantly better behavior than younger ones. Children aged 3–6 and 10–13 years exhibited less negative behavior during afternoon appointments. Among older patients, boys behaved better than girls. During cavity preparation, children aged 10–13 years behaved somewhat better than the younger children. There was a trend toward better behavior during afternoon appointments in all age groups combined. Among children aged 7 and older, boys showed less negative behavior than girls.

Behavior generally tended to be better in the afternoon than in the morning in these children, especially during the injection and operative phases of the appointment. Younger children tended simultaneously to exhibit more extremely positive and extremely negative reactions. Among older children, boys behaved better than girls, especially in the injection and operative phases of the appointment.

▶ [The conclusions of this study seem to go against the "traditional wisdom" of getting the kids early in the day to the dentist. This study seems reasonably well enough designed, so I guess we have to say that little girls showing up at 8:30 A.M. are likely to set the pace for a bad day for their dentist.

You might recall that in the 1983 YEAR BOOK OF PEDIATRICS (page 129), we reviewed the results of a study reported in *Pediatrics* (68:418, 1981) that highlighted the problem of dental caries associated with sucrose-containing medicinals. Well, now we have one less burden to be concerned about. As a result of all of the hullabaloo with regard to sucrose in commonly used medicines, reformulation of at least some of these products has taken place. I think it would be wise to check these out for yourself. For example, Actifed, which was listed as one of the worst offenders back in 1981, was reformulated appropriately in 1982 in order to contain no sucrose. Hopefully, this one maneuver will contribute in some part to the reduction of dental caries in our children.—J.A.S., III] ◀

4–4 **Treatment and Prognosis of Nasal Polyps in Cystic Fibrosis.** Robert C. Stern, Thomas F. Boat, Robert E. Wood, LeRoy W. Matthews, and Carl F. Doershuk (Cleveland) report that nasal polyposis complicated the course of cystic fibrosis (CF) in 157 (26%) of 605 patients. Onset before age 5 years or after age 20 years was rare.

Polyps were almost always multiple and bilateral. Polyposis was the initial symptom of CF in 13 patients. Common symptoms included obstruction to nasal air flow, mouth breathing, epistaxis, and rhinorrhea. Of the patients with nasal polyps, 56 (36%) had no allergic symptoms or history of allergy in the immediate family. No evidence was found for a familial predisposition for the occurrence of nasal polyps when more than 1 child had CF.

Intranasal and oral corticosteroids and antihistamines were ineffective in preventing recurrences but occasionally afforded symptomatic relief of obstruction. Polyps continued to be a problem in 4 of 6 patients who received allergy hyposensitization treatment. Of 62 patients who never had surgical or specific medical treatment, 19 (31%) had spontaneous, permanent disappearance of polyps.

(4–4) Am. J. Dis. Child. 136:1067–1070, December 1982.

Simple polypectomy was an adequate procedure for patients with substantial nasal symptoms. There were no visual complications. Other surgical complications were rare. However, recurrences were fairly common and occasionally rapid.

Children, adolescents, and young adults with nasal polyps should be tested for CF by pilocarpine-induced sweating and chemical analysis of sweat chloride. The data indicate that, contrary to previous prediction, the incidence of nasal polyps will not increase as life expectancy in CF increases.

▶ [Nasal polyposis has been a recognized complication of cystic fibrosis for over 30 years, yet the exact pathophysiology of why they appear with this disorder is unknown. The extremely high incidence of nasal polyps in cystic fibrosis cannot be explained by allergy alone. The overall incidence of polyps as seen in this study was about 25%. What to do with them is even more "ify." Intranasal corticosteroids and antihistamines may produce transient relief but, if obstruction is not present, they are probably better left alone. There is a fairly high incidence of recurrence after surgery, so if they are not producing a problem they may be better not meddled with. I tend to agree with the authors' suggestion that children, adolescents, and young adults with nasal polyps should be tested for cystic fibrosis. You may say that that is stretching a point, since the most common cause of nasal polyps in the general population is simple allergy. However, one large series of allergic patients found an incidence of nasal polyps of 5 per 1,000 patients (Kaplan, I., et al.: *Ann. Allergy* 29:631, 1971). When you do run across somebody who is known to have allergies and also has nasal polyps, there is a fairly high chance that that patient will also be aspirin intolerant. This association has been known now for 5 or 6 years.—J.A.S., III] ◀

4–5 **Eosinophilic Nonallergic Rhinitis in Children.** From a group of 16 patients, Garry H. Rupp and Roger A. Friedman (Columbus Children's Hosp., Ohio) identified 12 children aged 6–17 years as having eosinophilic nonallergic rhinitis (ENR). Physical examination revealed pale, boggy membranes with clear nasal discharge in 10 of the 12 patients. All patients had normal serum IgE concentration. Nasal smears were taken from all patients several times during the year but especially during the winter months that are considered to be free of pollen and mold in Ohio. The percentage of eosinophils noted in each patient, ranging from 10%–50%, was present in several seasons, including the winter. All patients were skin tested to a standard battery of 60 seasonal and perennial antigens. Nine of the 12 patients had completely negative skin tests by prick and intradermal techniques. The 3 other patients had 1 positive skin test that would not account for the year-round rhinitis.

Initially, all patients received a decongestant or antihistamine-decongestant which led to subjective improvement in 7; the remaining 5 patients were placed on a regimen of either topical or systemic corticosteroids and all showed great improvement of symptoms.

Eosinophilic nonallergic rhinitis can be differentiated from other forms of rhinitis by a nasal smear indicating presence of eosinophilia, which may help separate allergic rhinitis and ENR from vasomotor rhinitis. Histories, skin testing, and IgE concentrations will further separate ENR from seasonal, local, or perennial allergic rhinitis.

Whereas the incidence of ENR in the adult population may be as high as 10%–15% of those complaining of chronic rhinitis, our expe-

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(4–5) Pediatrics 70:437–439, September 1982.

rience points to an incidence of approximately 1%—5% among pediatric patients with perennial rhinitis.

Patients with ENR have a fairly poor response to antihistamines and decongestants, although they remain the drugs of choice for daily use. During periods of severe bouts, topical or systemic corticosteroids, given over a short period, afford excellent relief. In the present study, Decadron (Turbinaire) was used as the topical steroid because it presently is approved for intranasal use. Beclomethasone may be less harmful for prolonged administration and may become the drug of choice once it is approved for intranasal use.

▶ [The presence of eosinophils in nasal secretions of a patient with rhinitis does not confirm an allergic cause. Many patients perennially afflicted with nasal congestion from nonallergic causes have a pale blue edematous nasal mucosa with over 20% eosinophils on smears that is typical of allergic rhinitis. But here the similarity with allergic congestion ends. Patients with nonallergic rhinitis have no seasonal pattern to their symptoms and have negative skin test results to inhaled antigens. The patients are usually older, and this is the first report of any significant number of pediatric-aged patients. Although sinusitis and nasal polyps have not been noted in children with eosinophilic nonallergic rhinitis, these are common as patients get older, in adulthood. The diagnosis of eosinophilic nonallergic rhinitis is based on a history of perennial rhinitis, the presence of the aforementioned mucous membranes, nasal eosinophilia, a negative skin test, and a normal serum immunoglobulin E level.

It's hard for me to imagine that this disorder isn't somehow allergic in origin no matter what all the reports say. Frankly, I am disappointed by this, the first report in the pediatric literature of eosinophilic nonallergic rhinitis, inasmuch as one of the studies in the adult literature had a much better name for the problem. Jacobs et al. (*J. Allergy Clin. Immunol.* 67:253, 1981) called this "the nonallergic rhinitis with eosinophilia syndrome." In case you can't figure out how to abbreviate the latter, it spells NARES! For once, we have a syndrome that's easy to remember.!—J.A.S., III] ◀

4–6 **Pediatric Tracheostomy: Experience During the Past Decade.** Ralph F. Wetmore, Steven D. Handler, and William P. Potsic (Univ. of Pennsylvania) reviewed 420 pediatric tracheostomies performed between 1971 and 1980. A male predominance of 1.4:1 was evident. Forty-seven percent of patients were younger than age 1 year. Disorders of the CNS and of the upper airways were most frequent. Tracheostomies were done more often in conjunction with elective craniofacial procedures, CNS disorders, and respiratory distress over the review period and less often in patients with congenital heart disease. Prolonged ventilation was the indication for tracheostomy in 53% of cases and upper airway obstruction in 39%. The duration of tracheostomy averaged about 180 days.

A total of 341 complications occurred in 204 children. Early complications are listed in Table 1 and late complications in Table 2. The most common late complications were persistent tracheocutaneous fistula and accidental decannulation. Complications appeared to be more frequent in patients with upper airway obstruction and respiratory distress syndrome. Average duration of tracheostomy in children with complications was 305 days. Overall mortality was 28%. Eight deaths were attributed to tracheostomy, half to an obstructed tube and 2 to accidental decannulation. One death was attributed to massive tracheal hemorrhage and 1 to sepsis from erosion by the tube.

(4–6) Ann. Otol. Rhinol. Laryngol. 91:628–632, Nov.–Dec., 1982.

TABLE 1.—EARLY COMPLICATIONS (N = 119)

Accidental decannulation	29	(24%)
Pneumonia	24	(20%)
Pneumothorax	11	(9%)
Subcutaneous emphysema	11	(9%)
Obstructed tube	8	(7%)
Hemorrhage	8	(7%)
Stomal infection	7	(6%)
Tracheitis	7	(6%)
Pneumomediastinum	5	(4%)
Other	9	(8%)

(Courtesy of Wetmore, R. F., et al.: Ann. Otol. Rhinol. Laryngol. 91:628–632, November 1982.)

TABLE 2.—LATE COMPLICATIONS IN 222 PATIENTS

Tracheocutanous fistula	42	(19%)
Accidental decannulation	40	(18%)
Tracheal granuloma	30	(14%)
Excessive stomal granulation	24	(11%)
Obstructed tube	23	(10%)
Hemorrhage	22	(10%)
Stomal infection	18	(8%)
Tracheomalacia	12	(5%)
Other	11	(5%)

(Courtesy of Wetmore, R. F., et al.: Ann. Otol. Rhinol. Laryngol. 91:628–632, November 1982.)

A relative increase in tracheostomies in children younger than age 2 appears to parallel an increase in survival of children with bronchopulmonary dysplasia and other congenital disorders. Disorders of the CNS have occurred with increasing frequency in children undergoing tracheostomy in the past decade. Both the length of hospitalization and the duration of tracheostomy have increased substantially. About half the patients in this series had complications. Operative complications can be minimized by good technique. Postoperative complications often reflect the complexity of overall medical care. Mortality from complications can be limited by good training and equipment, humidification, and appropriate monitoring.

▶ [I was just amazed at seeing the number of tracheostomies performed at one institution over a 10-year period. However, when I read the details of this report, it was clear what was going on. Although there are not as many tracheostomies performed for common upper airway obstructive problems (presumably, short-term endotracheal tube placement has taken care of that problem), there are many more tracheostomies being performed for children with disorders that may not have permitted long-term survival a decade or more ago. In particular, I am speaking of infants born prematurely who survived the rigors of the first few months of life but remained ventilator dependent.

Obviously, placing a tracheostomy in a younger patient creates a tremendous commitment on the part of parents and support personnel and is something to be

avoided, if at all possible. There have been a few innovations worth mentioning that have whittled away at the need for tracheostomy in recent years. A number of pediatric ear, nose, and throat specialists are now quite competent in laser treatment of benign lesions of the pediatric airway (Simpson, G. T., et al.: *Ear, Nose Throat J.* 61:33, 1982). Juvenile laryngeal papillomatosis of the upper airway, known to be due to human papillomavirus, is now being managed on a semiexperimental basis with interferon. In some cases, the need for tracheostomy is avoided. Obstructive sleep apnea syndrome has been shown to be caused in some patients by testosterone administration. Eliminating the drug cured the problem (Sandblom, R. E., et al.: *N. Engl. J. Med.* 308:509, 1983). The pickwickian syndrome (now frequently called "the obesity hypoventilation syndrome") may be associated with high levels of CNS endorphins. As we all know by now, endorphins are naturally produced endogenous opioid substances that are more potent than morphine. If produced in high levels by our bodies, they act like morphine to suppress the CNS. They have also been incriminated in the "highs" experienced by heavily committed joggers. In any event, at least one case has been reported of a 20-month-old girl with the pickwickian syndrome who improved remarkably when given an infusion of the opiate antagonist naloxone. Since some of these patients would otherwise ultimately require tracheostomy and perhaps ventilation, these procedures may be able to be avoided with an oral narcotic antagonist such as naltrexone (Orlowski, J. P., et al.: *Crit. Care Med.* 10:604, 1982). Finally, if upper airway obstruction is really upper upper, such as occurs in the Pierre Robin syndrome, then the ideal way to manage this is not by tracheostomy, but with a nasopharyngeal tube placed in one nostril and changed every 2 weeks, as demonstrated by Haef et al. (*J. Pediatr.* 100:698, 1982).

As ominous as the opening of this commentary was because of the risks of death due to tracheostomies, this risk appears to be diminishing now. Tracheostomy teams have been established within many hospitals and also provide adequate support for home tracheostomy. There is now increased availability of airway occlusion monitors of the type used to follow children at risk for sudden infant death syndrome from upper airway obstruction. To show how effective all these methods are, Ruben et al. (*Ann. Otol. Rhinol. Laryngol.* 91:633, Nov.–Dec. 1982) have reported that their death rate in infants and children with tracheostomies is now down to 0.13 deaths per 100 months of tracheostomy. This is a tremendous accomplishment, and all the individuals who participated in making these kinds of data possible are to be congratulated. This includes the parents of these children, because these data were based totally on home care of pediatric patients with tracheostomies.—J.A.S., III] ◀

4–7 **Steroid Treatment of Pseudocroup.** K. E. V. Mühlendahl, D. Kahn, H. L. Spohr, and F. Dressler (West Berlin) conducted a randomized, controlled, double-blind trial in 349 children with stage I or II pseudocroup (children with somnolence or cyanosis were excluded); none had bacterial epiglottitis. The children were treated orally with either 6 mg of dexamethasone or placebo. Further treatment varied. Symptoms were scored on admission and at 6, 12, and 18 hours after treatment.

Bronchopneumonia or obstructive bronchitis developed within 24 hours in 24 children, of whom 20 had received placebo and 4 had received dexamethasone. The rate of recovery during the first 12 hours was nearly identical in both groups, and after 18 hours, most scores in both groups had become very low (Table 1). If, however, only the more seriously affected patients are considered, improvement was significantly faster in the steroid-treated group (Table 2).

Steroids appear to be useful in the routine treatment of simple, uncomplicated pseudocroup even though the benefit is not very impressive. They may be even more useful in more severely affected pa-

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(4–7) Helv. Paediatr. Acta 37:431–436, November 1982.

TABLE 1.—EFFECT OF DEXAMETHASONE ON RECOVERY FROM ACUTE PSEUDOCROUP*

All patients	Verum		Placebo	
	n	mean ± SEM	n	mean ± SEM
Score at admission	176	3.83 ± 0.14	173	4.40 ± 0.14
Score after 6 h	176	0.69 ± 0.13	173	1.40 ± 0.13
Score after 12 h	75	0.52 ± 0.13	112	1.35 ± 0.17
Score after 18 h	25	0.94 ± 0.36	72	1.09 ± 0.20
Patients with a score of ≥4 at admission:				
score at admission	99	5.07 ± 0.12	106	5.67 ± 0.11
score after 6 h	99	0.78 ± 0.21	106	1.89 ± 0.17
score after 12 h	43	0.72 ± 0.15	73	1.44 ± 0.23
All patients:				
time until score 0 is reached (h)	176	7.0 ± 0.5	173	12.3 ± 1.0
time until score 1 is reached (h)	176	6.0 ± 0.4	173	8.5 ± 1.0

*Median values ± SEM. All differences between verum and placebo are significant at least at the 0.01 level.

(Courtesy of Mühlendahl, K. E. v., et al.: Helv. Paediatr. Acta 37:431–439, November 1982.)

TABLE 2.—EVOLUTION OF DISEASE IN MORE SEVERELY AFFECTED PATIENTS, WITH SCORE OF ≥4 AT ADMISSION*

Score	After 6 hours		After 12 hours	
	verum	placebo	verum	placebo
0–1	70%	40%	79%	52%
2–3	25%	36%	19%	27%
≥4	5%	24%	2%	21%

*Percentage of children who have reached a score of ≤1 or of 2–3 after 6 and 12 hours and of children who have remained at a score of ≥4. All differences between verum and placebo are significant at least at the 0.01 level.

(Courtesy of Mühlendahl, K. E. v., et al.: Helv. Paediatr. Acta 37:431–439, November 1982.)

tients. Close supervision remains important in this nearly always benign, but potentially dangerous, condition.

▶ [When a patient with croup arrives on the inpatient services at our hospital, our pediatricians go after steroids the same way that a Kentucky hound dog goes after his bone. We did a little study 5 years ago that brought about this conviction (Leipzig, B., et al.: *J. Pediatr.* 94:194, 1979). That particular study showed significant improvement with the use of 0.6 mg of dexamethasone per kilogram administered within the first few hours of admission for croup. The study itself came under fire for failing to discriminate between spasmodic croup and laryngotracheobronchitis. The authors of this study also make the same error, if it is an error, and appear to group the two disorders under one term, which they prefer to call "pseudocroup." It should be noted that this study is from Germany and the term acute "spasmodic croup" is not a nosologic entity currently accepted or generally used in Germany. This statement is also true of most other parts of the world except for the United States. The reason why individuals do not separate these two disorders is largely based on difficulties of establishing clinical criteria to do it adequately. I, personally, am a lumper in this regard, rather than a splitter, and therefore can accept the validity of this German study when it states that steroids produce a small but statistically significant improvement in the course of mild to moderate croup. I accepted these results even more when I saw that G. Koren et al. produced similar data at the spring meetings of the Society for Pediatric Research last year. These investigators working in Israel and in

Toronto showed that dexamethasone improved the clinical course of spasmodic croup. No improvement was seen with laryngotracheobronchitis, but the authors admitted that there were a number of borderline cases in which the distinction between these two was not clear-cut. It always struck me as a little funny that there are so many, albeit soft, studies suggesting that steroids may be of help, yet many tend to be so conservative with their use even though the side effects of administering one or two doses are almost inconsequential.—J.A.S., III] ◀

4–8 **Middle Ear Disease and the Practice of Pediatrics: Burden During the First Five Years of Life.** Although acute otitis media and middle ear effusion are among the most common childhood illnesses, the precise extent of the problem is unclear. David W. Teele, Jerome O. Klein, Bernard Rosner, Lorna Bratton, Gilbert R. Fisch, Owen R. Mathieu, Philip J. Porter, Sidney G. Starobin, Lloyd D. Tarlin, and Robert P. Younes assessed the burden imposed by middle ear diseases on pediatricians by analyzing data on 2,570 children followed prospectively from birth at five centers in Boston suburbs and inner-city neighborhoods. The proportion of all visits made for middle ear disease rose from 22.7% in the first year of life to about 40% in years 4 and 5. About one in three visits made for illness of any type led to a diagnosis of middle ear disease, and about three fourth of all follow-up visits for illness were for middle ear disease. Middle ear disease was diagnosed in 5% to 10% of all well-baby visits. The proportions of visits attributable to middle ear disease were similar in private practice and neighborhood health center settings. Fewer follow-up visits, however, were made to private offices for either acute otitis media or asymptomatic middle ear effusion.

Pediatric training programs should make a special effort to train residents in the diagnosis and management of middle ear diseases. Any measures that reduce the incidence of acute otitis media or speed the resolution of middle ear effusions would substantially reduce the costs of providing care to children and might decrease the number of practitioners needed.

4–9 **Acute Otitis Media: One Year in General Pediatric Practice.** Acute otitis media (OM) is one of the most common reasons for pediatric sick visits. Virgil M. Howie and Richard H. Schwartz, reviewed experience with OM over a 1-year period in a pediatric practice in which tympanography and myringotomy were used to validate otoscopic diagnoses. Pneumotoscopy was performed routinely, and acute OM was diagnosed if the tympanic membrane contour bulged or a fluid level was present with acute pain or fever; a yellow, red, or gray membrane was present with dilated intratympanic capillaries; and reduced or absent membrane mobility was seen on pneumomassage. Acute OM was diagnosed in 18% of a total of 4,602 office visits for sickness. Another 14% of visits were for follow-up of OM.

The incidence of acute OM was highest in March and lowest in July and August. A total of 830 episodes occurred in 677 children. Forty percent of patients were aged 2 years or younger, whereas 12% were aged 5 years or older (Table 1). The characteristics of the involved

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(4–8) JAMA 249:1026–1029, Feb. 25, 1983.
(4–9) Am. J. Dis. Child. 137:155–158, February 1983.

TABLE 1.—AGE AT DIAGNOSIS OF ACUTE OTITIS MEDIA

Age	No. (%) of Episodes
0-6 mo	71 } (21)
7-12 mo	107 }
13-23 mo	145 (18)
2 yr	128 (16)
3 yr	69 (8)
4 yr	75 (9)
5 yr	49 (6)
6-8 yr	110 (13)
≥9 yr	76 (9)
Total	**830 (100)**

(Courtesy of Howie, V. M., et al.: Am. J. Dis. Child. 137:155–158, February 1983; copyright 1983, American Medical Association.)

TABLE 2.—CHARACTERISTICS OF TYMPANIC MEMBRANES OF 677 CHILDREN WITH 830 ATTACKS OF ACUTE OTITIS MEDIA IN 1 YEAR

Tympanic Membrane*	No. (%) of Episodes
Contour	
Bulging	441 (53.1)
Full	294 (35.4)
Segmental disease†	
Fluid line	74 (8.9)
Perforated	3 (0.4)
Not noted	18 (2.2)
Total	**830 (100)**
Color	
Yellow	464 (55.9)
Red	146 (17.6)
Gray	85 (10.2)
"Straw"	59 (7.1)
Mixed	5 (0.6)
Not noted	71 (8.6)
Total	**830 (100)**

*Motion was reduced or absent in 100% of cases of acute otitis media as determined by pneumotoscopy.

†Segmental disease is defined as segmental areas of apparent purulent exudate, presence of fluid lines, or presence of bubbles within a thin, yellow effusion, accompanied by pain, fever, or both.

(Courtesy of Howie, V. M., et al.: Am. J. Dis. Child. 137:155–158, February 1983; copyright 1983, American Medical Association.)

TABLE 3.—HIGHEST TEMPERATURE FOUND AT OFFICE VISITS AT WHICH ACUTE OTITIS MEDIA WAS DIAGNOSED IN ONE YEAR

Temperature, °C	No. (%) of Office Visits
<38.3	587 (74.5)
38.3	66 (8.4)
38.9	53 (6.7)
39.4	48 (6.1)
40	29 (3.7)
40.6	5 (0.6)
Subtotal	**788 (100)**
Not recorded	42
Total	**830 (100)**

(Courtesy of Howie, V. M., et al.: Am. J. Dis. Child. 137:155–158, February 1983; copyright 1983, American Medical Association.)

TABLE 4.—TREATMENT OUTCOME OF 830 EPISODES OF ACUTE OTITIS MEDIA IN 1 YEAR OF PEDIATRIC PRACTICE*

Results of Reevaluation Visit	No. (%) of Episodes
Tympanic membrane healed in 10-14 days	335 (40)
Otitis media with effusion†	256 (31)
Continuing acute otitis media‡	59 (7)
Did not return for follow-up	180 (22)
Total	**830 (100)**

*Follow-up visits were recommended 10 da to 2 wk after initial office visit at which diagnosis of acute otitis media was made and antibiotic treatment was begun.

†Tympanic membrane in neutral position or retracted with reduced or absent mobility.

‡Eardrum still bulging.

(Courtesy of Howie, V. M., et al.: Am. J. Dis. Child. 137:155–158, February 1983; copyright 1983, American Medical Association.)

tympanic membranes are categorized in Table 2. Bilateral OM was diagnosed in 37% of the 800 episodes evaluated. Fever was present in about one fourth of episodes (Table 3). Several antimicrobial drugs were prescribed, but ampicillin or amoxicillin was used in 91% of cases. The outcome of treatment is given in Table 4. Tympanography was done in about half of 260 children with otoscopic evidence of OM with effusion, and a type B or flat record was obtained in 95% of cases. A bulging drum suggesting an ongoing acute process was seen at follow-up in 9% of children who returned for follow-up. They received a different antimicrobial, and none had a bulging drum subsequently.

The findings in this study of a suburban pediatric practice suggest that acute OM occurs most often in infancy and is best diagnosed by the presence of a bulging, poorly mobile or immobile tympanic membrane. Neither pain nor fever is an invariable accompaniment of acute OM. Half the children followed had otoscopic or tympanometric evidence of OM with effusion. The estimated cost of diagnosis and treatment of these episodes exceeded $25,000.

▶ [This article and the preceding one are included in the YEAR BOOK to bring us all up to date with the current status of the impact of middle ear disease on the office practice of pediatrics. I wonder if the data in these studies correlate with what your impression has been. There doesn't seem to have been much of a changeover in the past decade or so in the frequency of visits for this problem. Middle ear disease constitutes the single most common cause of a visit to the office. Both studies are fine examples of what tremendously useful information can be gained from examining the experiences of a private practice setting. The importance of the data accumulated in these two studies is obvious. As Teele et al. state, any intervention to decrease the incidence of acute otitis media or to hasten the resolution of middle ear effusions would reduce the costs of providing care to children substantially and perhaps might impact remarkably on the number of required pediatricians and family practitioners. Other practice trends also could make a difference. Take, for example, the recommendations of Dr. Jack Paradise when talking about the role of tympanometry in the office setting (*N. Engl. J. Med.* 307:1074, 1982). He suggests that we may be able to substitute tympanography for an otoscopic examination at many, if not most, of the follow-up visits for acute otitis media. Basically, Doctor Paradise is saying that once a diagnosis of otitis media already has been established, the tympanogram tells us all we really need to know in terms of complete resolution of the process, including the effusion. If this is true, we would not even need to look inside the ear if the tympanogram is normal. Because effusions commonly persist beyond the completion of the antibiotic course (as discussed elsewhere in this chapter), this also would imply that the custom of a routine follow-up visit after the initial 10 days of antibiotics would no longer be necessary. The repeat visit might be better had at 6 weeks or so down the line rather than 1½ weeks or 2 weeks. That is around the time when effusions that are going to go away on their own usually have disappeared. I am not totally satisfied with this type of approach, since one would like to know if the ears are still red at the end of the antibiotic treatment cycle. This would require a look at the drums. A tympanogram wouldn't help a great deal because it probably would be abnormal whether the drums were red or not.

If I were giving advice to somebody during their residency program about things they should learn about office practice, I would suggest two things. One would be to learn the most they could about otitis media. About one third of their livelihood might be dependent on that knowledge. Secondly, I would encourage them to read everything that the parents of the children coming to their office read, including Erma Bombeck. For example, one of Erma's caveats to parents that you should be aware of is, "Never take your child to a pediatrician who has dead tropical fish in the aquarium of the waiting room."—J.A.S., III] ◀

4–10 **Acute Otalgia in Children: Findings and Diagnosis.** Acute otitis media (AOM) is one of the most common complications of upper respiratory tract infection in children. The symptoms vary and are nonspecific and sometimes directly misleading. Leif Ingvarsson (Univ. of Lund, Malmö, Sweden) reviewed the findings in 171 children aged 14 or younger, seen in a 3-month period, to determine whether otalgia or other symptoms are closely enough related to AOM to render diagnostic otoscopic examination unnecessary. Children with middle ear disease and those given antibiotics in the past month were excluded. Acute otitis media was diagnosed in 46% of patients, otitis simplex in 15%, and serous otitis media in 17%. Seventy-three children with AOM were treated with potassium penicillin V and 6 with erythromycin. All received oximetazolin, a nasal decongestant, as well, and analgesics as needed.

Most patients with all types of otitis had signs of upper respiratory infection. Nearly 80% of patients had had otalgia for less than 24 hours when evaluated. About half the children were febrile. More than 80% of children younger than age 8 years with AOM were febrile. Otorrhea was noted in 30% of children with AOM and in 44% of children younger than age 2 years. None of the children with AOM was completely healed within 10 days, although all showed some healing. Three children with otitis simplex returned within 48 hours with features of AOM and were treated with penicillin. The other 22 with otitis simplex had normal or nearly normal eardrums 2–5 days after initial evaluation, and none of them developed AOM over the next 3 months.

All the symptoms of AOM can occur without AOM, even otorrhea. A probable diagnosis is warranted only if both otorrhea and fever are present. In other cases, otoscopy is necessary. Physicians without experience in otoscopy should refer patients to an otologist without delay, especially children younger than age 2–3 years.

▶ [Some of the things discussed in this article are quite peculiar, as you can tell from the abstract. However, there are some interesting aspects to this report that are worthwhile emphasizing. What Doctor Ingvarsson has done is to see if there are sufficient historical findings present during the course of an illness that might be associated with otitis media to make a diagnosis of otitis media correctly without actually looking in the ears. What he found was that earache was a most unreliable symptom in its own right. However, if you added fever to that symptom in a child younger than age 2 years, about 75% will have otitis media on physical examination with otoscopy. In the children who had otalgia without acute otitis media, various causes were found, including pharyngitis, tonsillitis, teething, and rare cases of lesions in the supply areas of the trigeminal, glossopharyngeal, vagus, great auricular, and lesser occipital nerves.

I sense that pediatricians in Sweden may not think of otitis media in quite the same way we do if this report is a reflection of the thinking in that country. It concerns me when a report such as this appears suggesting that there are physicians providing primary care who may not have otoscopic experience and, because of this inadequacy, have to refer patients to otologists for the management of what may very well turn out to be simple acute otitis media. The study does teach us, however, that when a patient complains of earache alone, he or she will have to be seen for a correct diagnosis to be made.—J.A.S., III] ◀

(4–10) Acta Paediatr. Scand. 71:705–710, September 1982.

4–11 **Recurrent Acute Otitis Media in Infants: Role of Immune Complexes Acquired In Utero.** Many workers have proposed that altered immune responses may have a role in recurrent middle ear infections and chronic effusions, and prolonged breast-feeding has been recommended in atopic families. William H. Wilson (Denver) examined the possible role of immune complexes, acquired in utero through the mother's allergic diathesis, in 10 infants who had recurrent episodes of acute otitis media and effusion while receiving human breast milk. Seven children were taking breast milk when first seen. Age range was 5 to 22 months. Seven infants had middle ear effusion when first examined, 6 bilaterally. All infants but 2 had regurgitated breast milk. All the mothers had a personal history of allergic diathesis.

Challenges were carried out after 4 days without the food to be challenged. Five nursing mothers had definite allergic manifestations when challenged with corn, and in each instance the infant reacted in some way when next nursed. Clinical reactions also were obtained with cow's milk, peanuts, soy, yeast, chocolate, and tomato. Episodes of acute otitis and otitis with effusion ceased in 5 instances as proved offenders were eliminated from the mother's diet. Two mothers could not deny their children cow's milk despite proved hypersensitivity, but 1 of these children remained free from otitis with effusion. The only child continuing breast milk required placement of tympanostomy tubes.

Infants of allergic mothers may acquire specific immune complexes in utero or neonatally. Food antigens may reach the infant through human breast milk and combine with specific antibodies to initiate allergic responses in many body regions, including the eustachian tube and middle ear. Elimination of responsible food products from the mother's diet may lead to the cessation of acute otitis media and otitis with effusion in the infant. It may prove to be feasible to reintroduce offending foods on a rotary basis as the child progresses into the second year of life.

▶ [I wish investigators would get their act together when talking about the role of breast-feeding and the risk of middle ear disease. For a long time now, we've been made to feel comfortable with the fact that breast-feeding is protective of many different problems during the first year of life. There are studies, in which God's foot was on the treadle of the loom that designed them, that have shown that breast-feeding is prophylactic against recurrent otitis media in the first year of life. Now we see the suggestion from this study by Wilson that infants may acquire immune complexes in utero from their mothers and that the same infants, when they breast-feed may have middle ear problems if their mothers are exposed to offending antigens. Truly, nothing seems to be sacred anymore, not even mother's milk. It seems reasonable to suggest that allergic mothers should try to avoid substances they react to when they are breast-feeding. It is unreasonable to suggest that they stop breast-feeding.—J.A.S., III] ◀

4–12 **Longitudinal Study of Respiratory Viruses and Bacteria in Etiology of Acute Otitis Media With Effusion.** Frederick W. Henderson, Albert M. Collier, Margaret A. Sanyal, Jessie M. Watkins,

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(4–11) Laryngoscope 93:418–421, April 1983.
(4–12) N. Engl. J. Med. 306:1377–1383, June 10, 1982.

Diane L. Fairclough, Wallace A. Clyde, Jr., and Floyd W. Denny (Univ. of North Carolina, Chapel Hill) prospectively studied respiratory viral infection and nasopharyngeal colonization with *Streptococcus pneumoniae* and *Hemophilus influenzae* to determine their importance as factors influencing occurrence of otitis media with effusions (OME). From 1966 to 1980, 83 study children completed at least 2 years and 5 months of day care before reaching age 3. Among their more than 2,000 respiratory illnesses, this group had 474 episodes of OME. The boy-to-girl ratio was 1.09:1.

Antecedent (within 14 days preceding) or concurrent viral respiratory infection was identified in 124 of 472 episodes of OME (26.3%). When initial episodes of OME were considered separately, an associated viral infection was demonstrated in 38.8%. Middle ear effusions occurred in 6.6% of the 2-week periods in which no viral infection was identified. Incidence of OME was increased during the 14 days after isolation of respiratory syncytial virus, adenoviruses (usually types 1, 2, and 5), influenza viruses types A and B, parainfluenza and mumps viruses, and enteroviruses. Peaks in the isolation of respiratory syncytial virus and adenoviruses were consistently associated with elevated rates of OME, whereas major outbreaks of parainfluenza and enterovirus infections were associated with smaller increases in OME. Average risk of OME among children with viral respiratory infections was 3.2 ($P < .0001$).

Only 2-week periods which were negative for virus were examined for the relation of OME to nasopharyngeal bacteria. Cultures were examined for either *S. pneumoniae*, *H. influenzae*, neither, or both. The incidence of *H. influenzae* was influenced with *S. pneumoniae* be-

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OCCURRENCE OF ACUTE OTITIS MEDIA WITH EFFUSIONS (OME) IN CHILDREN WITH VIRAL INFECTIONS, ACCORDING TO NASOPHARYNGEAL BACTERIOLOGY AT TIME OF INFECTION

VIRAL INFECTION	SYNDROME	NASOPHARYNGEAL BACTERIOLOGY *		
		neither *Str. pneumoniae* nor *H. influenzae*	*Str. pneumoniae* only	*H. influenzae* with or without *Str. pneumoniae*
Group 1				
Respiratory syncytial virus, adenovirus & influenza A or B	Not OME	46	76	34
	OME	16 (25.8)	32 (29.6)	22 (39.3)
Group 2				
Parainfluenza viruses 1–3, mumps virus, rhinovirus, enterovirus, & herpes simplex virus	Not OME	74	150	66
	OME	6 (7.5)	35 (18.9)	12 (15.4)

*Number of infections (percent diagnosed as OME in parentheses).

(Courtesy of Henderson, F. W., et al.: N. Engl. J. Med. 306:1377–1383, June 19, 1982.)

cause there were no differences in incidence of OME between these. Acute OME occurred 1.35 times more often with *S. pneumoniae* alone than when neither organism was present ($P < .05$). Average relative risk of OME with *H. influenzae* with or without *S. pneumoniae* was 1.76 ($P < .01$). Incidence of OME when both viral infection and bacteriologic activity were present is shown in the table. Earlier infection with viruses was closely associated with more frequent OME, whereas age at colonization of bacteria was not associated with frequency of OME.

▶ [The research carried out in this study was conducted in a day-care center and begins to clarify the role of viral infection in the complex etiology of otitis media. Any practicing pediatrician could testify to the fact that viruses play some role in otitis media. It is typically 1 or 2 days or more into a viral-type illness that a child begins to complain of the earaches and the parents call you in the middle of the night. What this study does, however, is to polish our information base and tell us which viruses are likely to set the middle ear up for a bacterial infection and which ones are not likely to do so. Respiratory syncytial virus, adenovirus, and influenza virus will do this, whereas parainfluenza, enterovirus, and rhinovirus are not likely offenders. None of this means that viral pathogens do not actually cause the middle ear problem directly on occasion. These investigators did not perform tympanocentesis and culture virus. B. S. Klein et al., however, did (*J. Pediatr.* 101:16, 1982), and they found that about 25% of children with otitis media had virus in their middle ear fluid. In the vast majority of cases, the offending virus was respiratory syncytial virus. It took the group in North Carolina some 14 years to identify the relationship between viruses and bacteria in the etiology of middle ear disease. With that much effort, one would hope that some useful purpose could be made with these data. Unfortunately, the knowledge gained from this study will have to sit on somebody's back burner because the appropriate use of it would be to have this information as a stimulus to accelerate programs for the development of vaccines for common viral pathogens. Unfortunately, that is not likely to happen quickly. It would be nice, though, to prevent many of the causes of a common cold in order to prevent the sequelae of bacterial otitis media. I don't know about you, however, but no cold of mine ever really seemed common to me.—J.A.S., III] ◀

4–13 **Use of an Antihistamine-Decongestant in Conjunction With an Antiinfective Drug in the Treatment of Acute Otitis Media.** Donald M. Moran, Kelly D. Mutchie, Martin D. Higbee, and L. Dixon Paul (Salt Lake City) evaluated the efficacy of an antihistamine-decongestant combination as adjunctive therapy for acute otitis media with effusion. In a randomized study, 53 children with acute otitis media were treated with the broad-spectrum antibiotic amoxicillin and either Naldecon or placebo for 14 days.

Amoxicillin suspension was given orally at 50 mg/kg/day (to a maximum of 750 mg/day) in 3 divided doses. Naldecon syrup was administered orally at a dose proportioned to deliver phenylephrine, about 1 mg/kg/day; phenylopropanolamine, 3 mg/kg/day, chlorpheniramine, 0.350 mg/kg/day; and phenyltaloxamine, 1 mg/kg/day, in 4 divided doses. Patients were evaluated by tympanometry and pneumotoscopy. Follow-up evaluation was performed at days 7 and 14 of therapy.

The antihistamine-decongestant prescription influenced both the duration of nasal congestion and the course of middle ear effusion (Fig 4–2). Naldecon-treated subjects were symptomatic with nasal congestion for an average of 6 days, as compared with 9 days reported

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(4–13) J. Pediatr. 101:132–136, July 1982.

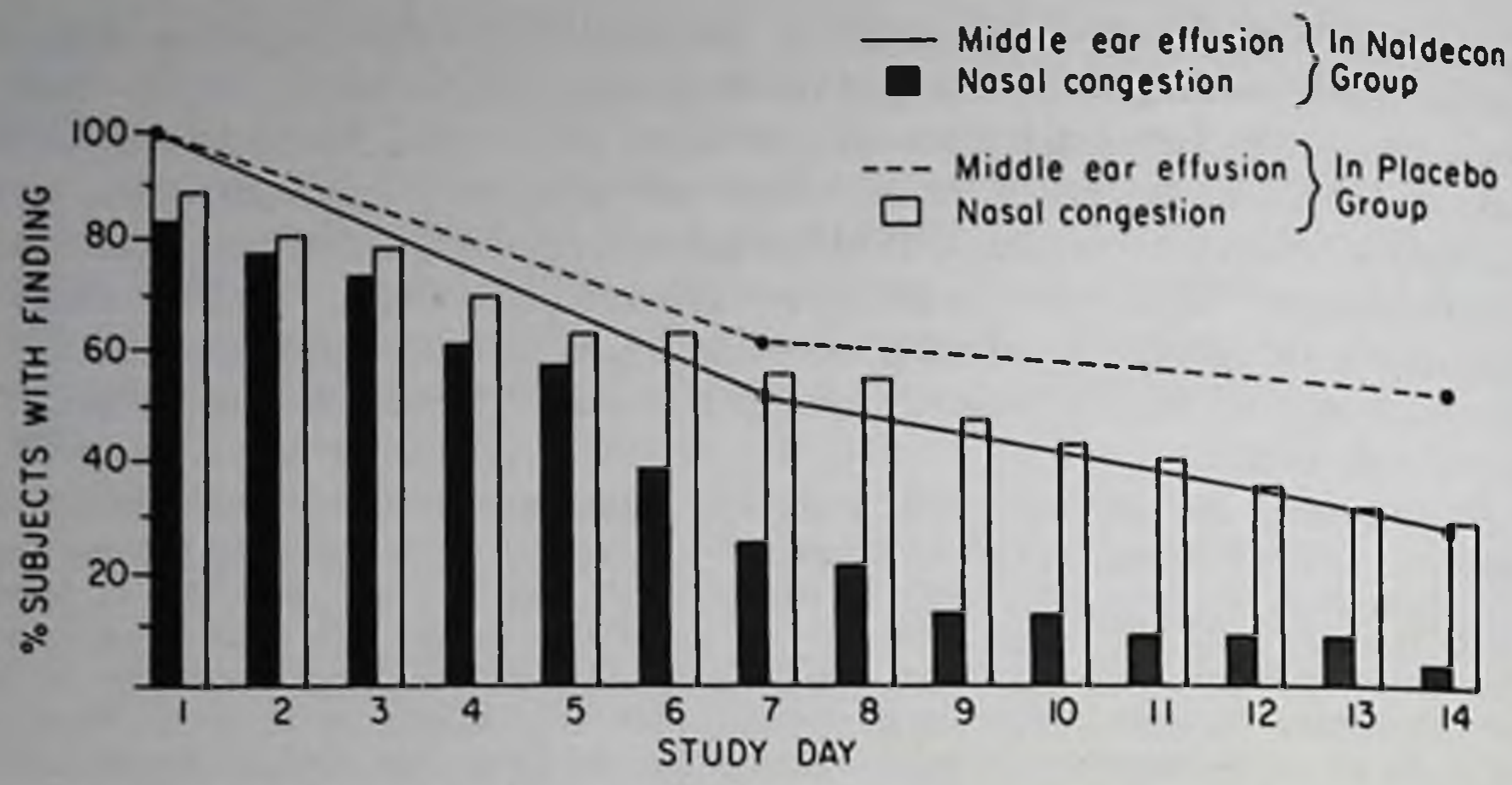

Fig 4–2.—Comparison of middle ear effusion and nasal congestion in two treatment groups. (Courtesy of Moran, D. M., et al.: J. Pediatr. 101:132–136, July 1982.)

by those given placebo. The risk of persisting middle ear effusion was about 2 times greater in the placebo-treated group when evaluated by tympanometry. At day 14, 28% of Naldecon-treated subjects compared with 54% of placebo-treated subjects had tympanometric criteria for effusion. There was no significant difference between study and placebo groups with respect to mean duration of earache or cough.

Adverse reactions thought to be related to Naldecon administration included abrupt onset of extreme somnolence, dry mouth, and blurred vision in one patient, necessitating discontinuation of the drug, and extreme irritability in another patient, which resolved with the reduction of the dosage.

4–14 **Lack of Efficacy of Decongestant-Antihistamine Combination for Otitis Media With Effusion ("Secretory" Otitis Media) in Children: Results of Double-blind, Randomized Trial.** Erdem I. Cantekin, Ellen M. Mandel, Charles D. Bluestone, Howard E. Rockette, Jack L. Paradise, Sylvan E. Stool, Thomas J. Fria, and Kenneth D. Rogers (Univ. of Pittsburgh) conducted a double-blind, placebo-controlled trial to assess the widely held belief that oral decongestant-antihistamine combinations are effective in the treatment of otitis media with effusion. The trial used stratified random allocation of subjects to provide balanced distribution of important variables, valid criteria for the presence or absence of middle ear effusion, and measurement of drug compliance.

A total of 553 children, aged 7 months to 12 years, who had otitis media with effusion were treated for 4 weeks with 4 mg of pseudoephedrine hydrochloride per kg per day and 0.36 mg of chlorpheniramine maleate per kg per day or with placebo.

Among children with initially unilateral disease, resolution of middle ear effusion occurred at 4 weeks in 34% of those actively treated

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(4–14) N. Engl. J. Med. 308:297–301, Feb. 10, 1983.

and in 38% of those treated with placebo ($P = .74$). Among children with initially bilateral disease, the corresponding proportions were 21% and 19%, respectively ($P = .67$). No relation was found between outcome and age, race, socioeconomic status, season of the year, adenoid size, history of recent use of a antimicrobial agent, or presence of upper respiratory tract infection when treatment was begun. Reexamination at 8 weeks of 94 of the 134 children who were effusion free at 4 weeks showed effusion in 43% of drug-treated children and in 26% of placebo-treated children, giving no support to the hypothesis that decongestant-antihistamine treatment may have a beneficial but delayed effect. Side effects occurred more often ($P < .001$) among drug-treated than among placebo-treated patients.

Of subjects with initially unilateral involvement, the proportion who were effusion free at the 4-week end point was about twice that of subjects with initially bilateral disease. Among subjects with initially unilateral involvement, development of effusion in the contralateral ear was closely related to the outcome in the initially involved ear. Middle ear effusion was less likely to have resolved if upper respiratory tract infection was present.

Decongestant-antihistamine combinations are apparently ineffective for treatment of otitis media with effusion. Because they are costly and sometimes accompanied by side effects, their administration for middle ear effusion in children appears to be inappropriate and inadvisable. This study does not exclude the possibility that patients without effusion but with eustachian tube obstruction might benefit from such treatment.

▶ [Obviously, this study and the preceding one examining the same question reached differing conclusions. This study from Pittsburgh that failed to find any efficacy for decongestant-antihistamine combinations seems better designed and had 10 times as many patients under observation. If there is any effect of decongestant-antihistamine combinations on middle ear effusion, the effect seems small at best and perhaps not worth the side effect of the drugs.

Anyone who isn't confused by all this is clearly uninformed.—J.A.S., III] ◀

4–15 **Duration of Effusion After Antibiotic Treatment for Acute Otitis Media: Comparison of Cefaclor and Amoxicillin.** Ellen M. Mandel, Charles D. Bluestone, Howard E. Rockette, Mark M. Blatter, Keith S. Reisinger, Frederick P. Wucher, and James Harper (Univ. of Pittsburgh) undertook a double-blind randomized study comparing cefaclor and amoxicillin in the treatment of acute otitis media with effusion in 293 ears of 214 children aged 2 months to 16 years without serious underlying disease or concomitant infection. Diagnostic tympanocentesis was performed in all cases. Subjects received cefaclor or amoxicillin in a dose of 40 mg/kg daily in 3 divided doses for 2 weeks. No other medication was used. The treatment groups were clinically comparable at the outset.

Only 4 of 112 cefaclor-treated children were considered treatment failures, as were 4 in the amoxicillin group. The middle ear status following treatment is related to the bacteriologic findings in the initial middle ear aspirate in the table. There were 6 ampicillin-resis-

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(4–15) Pediatr. Infect. Dis. 1:310–316, September 1982.

STATUS OF OTITIS MEDIA WITH EFFUSION AFTER 14 DAYS OF TREATMENT RELATED TO INITIAL MIDDLE EAR ISOLATE AND ANTIBIOTIC RECEIVED

Isolate	Cefaclor					Amoxicillin					Total Ears	
	No OME	OME	P/E*	Total		No OME	OME	P/E	Total			
Streptococcus pneumoniae	21	20	3	44	(32.1)†	19	28	3	50	(40.3)	94	(36.0)
Haemophilus influenzae (S)	9	5		14	(10.2)	8	11	2	21	(16.9)	35	(13.4)
H. influenzae (R)	2	1		3	(2.2)	0	0		0		3	(1.1)
Streptococcus pyogenes	3	2		5	(3.6)	3	2	1	6	(4.8)	11	(4.2)
Staphylococcus aureus (R)	2	0		2	(1.5)	0	0		0		2	(0.8)
Branhamella catarrhalis (S or ?)	9	1		10	(7.3)	6	3		9	(7.3)	19	(7.3)
B. catarrhalis (R)	0	1		1	(0.7)	0	1		1	(0.8)	2	(0.8)
Mixed pathogens	3	4		7	(5.1)	0	1	1	2	(1.6)	9	(3.4)
Sterile or nonpathogen	25	22	4	51	(37.2)	16	19		35	(28.2)	86	(33.0)
All ears receiving tympanocentesis	74 (56.9)	56	7	137	(100.0)	52 (44.4)	65	7	124	(100.0)	261	(100.0)
Ears with acute OME not receiving tympanocentesis	15	5	1	21		4	7	0	11		32	
Total	89 (59.3)	61	8	158		56 (43.8	72	7	135		293	

*P/E, perforation or excluded; S, ampicillin sensitive; R, ampicillin resistant; ?, sensitivity not tested.
†Numbers in parentheses are percentages.
(Courtesy of Mandel, E. M., et al.: Pediatr. Infect. Dis. 1:310–316, September 1982.)

tant organisms in the cefaclor group and only 1 in the amoxicillin group. No cefaclor-resistant organisms were isolated. Nearly two thirds of cefaclor-treated children were effusion-free or "improved" from their original status at 14-day follow-up, compared to about 45% of those given amoxicillin. By 42 days, about two thirds of both groups were without effusion or "improved." No serious side effects occurred with either treatment.

Both cefaclor and amoxicillin led to improvement in about two thirds of cases of acute otitis media with effusion in this study. Amoxicillin probably is adequate for children with infrequent attacks, but cefaclor therapy would appear reasonable for those with frequent episodes. More children in the present study who had unilateral acute otitis with effusion were free of effusion after cefaclor therapy, and more with bilateral disease were free of effusion in at least one ear.

▶ [Otitis media with effusion (OME) is being looked at in a new light these days. Not only is acute OME an immediate concern to the parent and physician because of its acute symptoms, its long-term sequelae also are now being probed. Recently, the impact of OME and its concomitant hearing impairment on learning and development has been receiving increasing attention. For this reason, rapid clearance of middle ear effusion after infection may be a desirable end. What these investigators have done is to determine whether cefaclor and amoxicillin had differing abilities to clear effusions associated with otitis media. Both drugs would be expected to treat the acute bacterial phase of the illness comparably, and that was not a concern of the study. At the end of 2 weeks of treatment with antibiotics, two thirds of cefaclor-treated ears were free of effusions, whereas this was true of less than half of those treated with amoxicillin. By 6 weeks from the original start of antibiotic therapy, there was no longer a difference in the rate of effusion between the two groups. What does all this mean? Only tentative speculations may be made. If there is a basis for the growing concern that there may be a critical age at which mild-to-moderate hearing loss may be detrimental to a child's cognition, then the difference in the effusion rates between amoxicillin and cefaclor might be significant clinically. Unfortunately, we don't know what the average time to clearance of the effusions was for the amoxicillin group. It is conceivable that no difference might have been noted had effusions been checked at, say, 18 or 21 days. I don't think anyone would go out on a limb and say that 4 or 7 days' difference in the length of effusion makes it likely that a child will be permanently damaged cognitively. Of more importance, perhaps, is the possibility that even a few days of extra effusion associated with amoxicillin might be the culture medium for a recurrent episode of otitis media. Then, the difference in number of days with effusion in the two treatment groups actually might be the window of vulnerability during which reinfection might occur. I don't know if this "window of vulnerability" theory has any greater substance than when it was used to argue for the MX missile.

There are a couple of other comments about cefaclor worth mentioning. One is the warning that this antibiotic probably never should be used for invasive *Hemophilus influenzae* disease. Meningitis has been reported during cefaclor therapy for otitis media (Raucher et al.: *Am. J. Dis. Child.* 136:745, 1982). If there is any suspicion that a child with otitis media has seeding someplace else or even bacteremia, a full evaluation would be necessary and an antibiotic appropriate for invasive resistant *H. influenzae* might be in order. This penetrating ability of cefaclor actually also includes the noninflamed middle ear. A nifty little study was reported a couple of years back, in the *Journal of Infectious Disease* (145:815, 1982), in which children undergoing elective myringotomy for tube placement were given antibiotics shortly before the procedure and the antibiotic level was determined on the middle ear fluid. Amoxicillin was the hands-down winner in terms of penetrating ability when compared to cefaclor, trimethoprim-sulfamethoxazole, or erythromycin-sulfisoxazole. Unfortunately, this study was done in children who had simple ear effusions. One would like to have seen data for children who had inflamed ears at the time the antibiotic levels were sampled.

I have come to the conclusion that we are going to have to put up with a continuing barrage of studies looking at various combinations, integrations, and permutations of antibiotics for OEM until something definitive is done about *H. influenzae*. Come on, you vaccine developers, let's get an effective vaccine on the market soon.—J.A.S., III] ◄

4–16 **Sulfisoxazole Chemoprophylaxis for Frequent Otitis Media.** Chemoprophylaxis with sulfisoxazole has been shown effectively to prevent recurrences of otitis media in children younger than age 6 years. Thomas E. Liston, William S. Foshee, and Wayne D. Pierson reevaluated this approach in children with frequent otitis in a double-blind, crossover comparison of sulfisoxazole with placebo. Thirty-five children, aged 6 months to 5 years, who had had at least three episodes of otitis media and at least one episode every 2 months were entered into the study. Sulfisoxazole was given in a dosage of 75 mg/kg daily for a 3-month period. Patients with diagnosed otitis were treated with amoxicillin in a dosage of 40 mg/kg daily, or with erythromycin ethyl succinate and sulfisoxazole for those allergic to penicillin. Thirty-five patients completed 102 months of sulfisoxazole and 34 completed 102 months of placebo.

Seventeen patients had 25 episodes of otitis while taking sulfisoxazole, and 20 had 43 episodes while taking placebo. A 40% reduction in the rate of otitis occurred during sulfisoxazole administration.

EPIDEMIOLOGIC FACTORS AND RATE OF OTITIS MEDIA IN PLACEBO VS. SULFISOXAZOLE GROUPS

Epidemiologic Factor	No. of Patients	Rate		% Reduction in Rate
		Placebo	Sulfisoxazole	
Age				
0–1 yr	21	0.51	0.27	47*
2–4 yr	14	0.28	0.21	25
Sex				
Male	17	0.47	0.24	49
Female	18	0.37	0.25	32
No. of preceding episodes				
1–2	20	0.37	0.22	41
3–4	15	0.49	0.28	43
Day care attendance				
Yes	17	0.47	0.27	43
No	18	0.35	0.23	38
Allergy history				
Yes	25	0.38	0.24	38
No	10	0.50	0.27	46
Sulfisoxazole treatment began				
Dec–May	22	0.43	0.24	44
June–Nov	13	0.41	0.25	39

*$P < .05$; $\chi^2 = 4.60$.

(Courtesy of Liston, T. E., et al.: Pediatrics 71:524–530, April 1983. Copyright American Academy of Pediatrics 1983.)

(4–16) Pediatrics 71:524–530, April 1983.

Comparable numbers of patients had no episodes of otitis while receiving active drug and placebo. The rate of otitis is related to various epidemiologic factors in the table. No significant differences in species or sensitivity patterns of isolates were found between the sulfisoxazole and the placebo groups. Serial tympanography indicated significantly improved tube function in sulfisoxazole-treated patients. No toxicity from sulfisoxazole was observed. Overall compliance was 87%.

The findings indicate that chemoprophylaxis with sulfisoxazole has a role in the management of children with recurrent otitis media. Patients with frequent episodes of otitis may have up to a two-thirds reduction in the rate of episodes, and about half of patients may be expected to become free from otitis media. Most patients have satisfactory tube function during prophylaxis. The use of sulfisoxazole appears to be safe. A trial of sulfisoxazole is suggested before tympanostomy tubes are placed.

▶ [The purpose of chemoprophylaxis for frequent otitis media is to reduce the recurrence rate of acute otitis media and to shorten the course of middle ear effusion so commonly seen in association with the acute disorder and, for some period, afterward. On both counts, sulfisoxazole seems to do the job for many children. There was an approximate 40% reduction rate in episodes of otitis media, with slightly more than half the children having no further recurrences compared to the placebo-treated group. Another benefit of chemoprophylaxis was improvement in the tympanogram patterns during the study, suggesting decrease in the presence of effusions. The requirements for successful specific-pathogen chemoprophylaxis were outlined nicely in a review by David Scheifele recently (*Pediatr. Infect. Dis.* 1:420, 1982). He notes that as far as the pathogen is concerned, it must pose a predictable high risk, implant at a predictable site, be predictably antibiotic susceptible, and remain antibiotic sensitive during treatment. As far as the antibiotic is concerned, it must reach the pathogen effectively, eliminate the organism, have minimal side effects, and be palatable and convenient to use. If these are the criteria for chemoprophylaxis of recurrent otitis media, sulfisoxazole fits the bill. Evaluations of chemoprophylaxis of recurrent otitis media have been limited in number, duration, and scope. These studies have included ampicillin, sulfonamides, and trimethoprim-sulfamethoxazole. The largest single study of sulfisoxazole previously was that of Perrin et al. more than 10 years ago (*N. Engl. J. Med.* 291:664, 1974). Although the numbers differed somewhat in that study, approximately the same results were obtained as in the investigation by Liston et al. R. H. Schwartz et al., in a small study, also suggested that low-dose sulfonamide prophylaxis be considered for any child with otitis who has had at least three episodes in the past 6 months, especially during the winter (*Arch. Dis. Child.* 57:590, 1982).

Although all sulfa preparations sort of sound the same, of course they are not. One study recently found trimethoprim-sulfamethoxazole to be helpful in preventing recurrent acute otitis media when given for a 2-week period after completion of the initial 10 days of amoxicillin therapy (Schwartz, R. H., et al.: *Pediatr. Infect. Dis.* 1:333, 1982). How safe this drug is compared with sulfisoxazole or sulfamethoxazole is something you might be concerned about. Clearly, trimethoprim-sulfamethoxazole has more-established uses, such as in the management of recurrent urinary tract infections. It may even be helpful in the prevention of travelers' diarrhea (Dupont, H. L.: *Gastroenterology* 84:75, 1983). I am not sure how long I would use it, however, for chemoprophylaxis of otitis media. In the 1983 YEAR BOOK, we saw the hematologic side effects of a short course of trimethoprim-sulfamethoxazole. It recently has been reported also to cause intrahepatic cholestasis (*Clin. Pediatr.* (Phila.) 22:212, 1983). Some pneumococcal resistance has developed against this agent (*JAMA* 248:3011, 1982). A case of acute interstitial nephritis after the use of trimethoprim-sulfamethoxazole has been noted (*Ann. Allergy* 49:323, 1982). Recall also that trimethoprim is a folic acid antagonist. This is not usually of much significance to the person taking this drug combination, but persons with the fragile X chromosome (*Science* 197:265,

1977) have a form of mental retardation that is folate sensitive. One child with this syndrome had severe clinical regression of motor development when he was treated with trimethoprim (Lejeune, J.: *Ann. Genet. (Paris)* 25:149, 1982).

All in all, I think we have much more to learn about chemoprophylaxis of otitis media. Questions of timing, safety, and true benefit deserve a little more critical analysis, even though the light currently is green for this approach.—J.A.S., III] ◀

4–17 **Trial Comparing Cefaclor With Co-Trimoxazole in Treatment of Acute Otitis Media.** Acute otitis media is the third most common cause of physician visits in pediatric practice. W. Feldman, H. Richardson, B. Rennie, and P. Dawson (McMaster Univ.) compared cefaclor with co-trimoxazole in the treatment of otitis media in a prospective double-blind trial in patients from private primary-care pediatric practices. Children with acute otitis who were aged 12 or younger and had not received antibiotics in the past week were admitted to the study. None had had more than three episodes of acute otitis in the past 6 months. A total of 223 children received liquid co-trimoxazole or liquid cefaclor in a weight-related dose. Follow-up was complete in 197 cases.

Over 90% of children in both treatment groups who were adequately followed up were improved or cured by visual inspection of the tympanic membrane and, if old enough, by audiography. Among children under age 4 years, 90% of those given co-trimoxazole and 86% of those given cefaclor were improved or cured. Nearly 90% of both groups took at least 70% of the prescribed medication. Side effects were comparable in the two treatment groups.

This double-blind trial showed both co-trimoxazole and cefaclor to be effective and safe in the treatment of acute otitis media in children. Compliance with both treatments was high.

▶ [This article is only one of many from the smorgasbord of studies that have looked at this, that, or the other combination of antibiotics in the management of otitis media. There are lots of problems with this particular study, and you may wonder why it was selected for inclusion in the YEAR BOOK. One of the problems is that we have no idea what organisms were involved in the etiology of otitis media in this series of children. No tympanocenteses were done. Secondly, pure-tone audiograms were performed rather than impedance audiometry that might have found many more cases of residual serous otitis media. Finally, there was no "control" group treated with a more or less standard therapy such as amoxicillin. Because of the last concern, many might wonder why this study was carried out at all. Personally, I do not feel that the principle stating, "Something not worth doing to begin with is not worth doing well anyway," applies to this investigation. What the authors have done here is to simulate a relatively realistic office setting approach. This study is from Canada. There, a few fresh cases of ampicillin resistance were first described in 1974. In 1976, resistant organisms constituted 6.7% of *Hemophilus influenzae* isolates. The percentages were 13% in 1978 and 18.8% in the first half of 1981. When percentages like this begin to appear, you start thinking about whether or not you would like to use amoxicillin as the first-line antibiotic anyway. Not performing tympanocenteses in their patients is, at best, a venial sin in the sense that one would anticipate equal distribution of organisms with or without resistance between the treatment groups without having necessarily to verify it. Furthermore, most pediatricians do not require tympanocentesis to make a diagnosis in the office setting because of the discomfort associated with the procedure. Finally, pure-tone audiograms are sufficient to tell whether or not the child hears even if they do not pick up all cases of effusion. With all these issues now resolved or at least aired (hopefully, not erred), the true value of this study can

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(4–17) Arch. Dis. Child. 57:594–596, August 1982.

be seen; it is the first random double-blinded control trial comparing co-trimoxazole with cefaclor in the treatment of acute otitis media and it shows that both drugs work. It seems reasonable to guess that there were a fairly high number of resistant organisms in both groups, and by inference, if not by proof, both of these drugs would therefore have relatively equal probability of handling that problem as well (the data on ampicillin-resistant *H. influenzae* in Canada may be found in the *Can. Med. Assoc. J.* 127:222, 1982).—J.A.S., III] ◀

4–18 **Choking: The Heimlich Abdominal Thrust vs. Back Blows; An Approach to Measurement of Inertial and Aerodynamic Forces** is presented by Richard L. Day, Edmund S. Crelin, and Arthur B. DuBois (Yale Univ.). The Committee on the Prevention of Accidents and Poisoning of the American Academy of Pediatrics advises against use of the Heimlich abdominal thrust in infants or children and instead suggests four strong back blows followed by "chest thrusts." The forces impinging on a supraglottic foreign body with these procedures were evaluated in young adults and in a half-model of an infant's upper respiratory tract. An accelerometer was used to quantitate the inertial forces produced by back blows in the subjects, and a body plethsymograph was used to measure air pressure in the lungs. The results were demonstrated visually with devices that used moving steel balls.

Back blows produced less pressure than the Heimlich maneuver in seated subjects. Back blows threw the head and neck forward and upward through straightening of the spine. They theoretically could displace supraglottic foreign bodies further downward and backward into the throat or larynx.

The Heimlich maneuver is powerful. The back blow approach is weaker and could propel a supraglottic foreign body toward the glottic aperture. Whether or not this acceleration would defeat the intrathoracic pressure induced by the back blow would depend on the size of the glottic opening and on the size and mass of the foreign body. In the case of a partial obstruction, a back blow might result in complete blockage.

▶ [If you missed the controversy regarding this study and all of the hullabaloo concerning the use of the Heimlich maneuver in young patients during the past 1½ years, you must have been off in the space shuttle most of that time. Everyone seems to be getting into the pro and con act with regard to the Heimlich abdominal thrust procedure. Heimlich staunchly defends the use of his technique in younger persons despite the fact that the Committee on the Prevention of Accidents and Poisoning of the American Academy of Pediatrics advises against the use of abdominal thrust for infants or children because of the risk of possible injury to the abdominal organs. The Committee instead recommends back blows followed by chest thrusts.

It seems to me that there is a little bit of truth in everything that is being said on all sides. The Heimlich procedure itself seems to make sense, but the Academy may be correct in their assumption that it is too vigorous a procedure for younger patients. The latter point, of course, remains to be documented. Those who believe in back blows also have a point. Newton's Third Law of Motion clearly states, "To every action, there is always opposed an equal reaction." If you don't think back blows could possibly work, what do you think you are doing when you turn a bottle of ketchup on its side and give its bottom a swift slap?

Heimlich may have been going a bit too far recently when he recommended that the first step in resuscitating a drowning person should be the Heimlich maneuver, repeated until water ceases to flow from the mouth. His recommendation brought a

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(4–18) Pediatrics 70:113–119, July 1982.

torrent (torment) of protest from many quarters. The Ad Hoc Committee on Treatment of Drowning appointed by the National Research Council to advise the American Red Cross took the position that until data are available, cardiopulmonary resuscitation, followed by appropriate advanced life-support procedures, should be the initial first step, not the Heimlich maneuver. The Heimlich maneuver was not recommended for removal of water from the lungs of a drowning victim largely because of the fear of causing aspiration of the gastric contents (*Ad Hoc Panel on Treatment of Drowning*, National Academy Press, Washington, D.C., 1982).

I have the suspicion that the eponym associated with the abdominal thrust procedure will lose much of its luster in the next few years. There has been just too much controversial press associated with it. The spotlight is fleeting all too often in this regard. It reminds me of the true story of the little boy who came up to President Hoover just after he left the White House and asked for his autograph. When the former President graciously complied, the little fellow said, "Would you mind signing it again further down?"

"All right," said Hoover and did so. Then the President asked, "But why twice?"

"Because," was the young boy's answer, "With two of yours I can get one of Babe Ruth's."

I can see it now—"I will trade you two Heimlichs for 14 Blalocks or one Kasai."—J.A.S., III] ◄

5. The Respiratory Tract

5–1 **Primary Lung Abscess in Childhood: Long-term Outcome of Conservative Management.** M. Innes Asher, Sheldon Spier, Marie Beland, Allan L. Coates, and Pierre H. Beaudry (McGill Univ.) have treated children who have had primary lung abscess with antibiotics alone, without invasive procedures. Review was made of 14 cases of primary lung abscess in children seen between 1961 and 1979. The 7 boys and 7 girls were aged 4 months to 15 years at diagnosis (mean, 8 years). Eleven cases occurred in the winter or spring. Three children had asthma and 2 others had an allergic history.

Eight children received antibiotics before admission. The most common clinical features were fever, cough, chest pain, upper respiratory tract infection, and anorexia. Ten patients had localizing chest signs. Eleven abscesses were in the right lung. Three were multiloculated. Associated pneumonia was not present at admission, but compressive atelectasis was common. The only organism recovered was *Staphylococcus aureus*. All 9 blood cultures grew no pathogens. Antibiotic therapy was given for 10 to 52 days. Agents active against penicillinase-producing *S. aureus* were used in 11 patients. Postural drainage was used in all but 3 patients, with no particular benefit. The children became afebrile after an average of 6 days of antibiotic therapy. The hospital stay averaged 13 days. Only one cavity was identifiable 5 years after acute illness. None of the 11 children followed had had new lower respiratory tract disease or abnormal growth. Lung function was normal except in 1 asthmatic subject.

Antibiotic therapy alone led to rapid recovery of these previously healthy children with primary lung abscess and to return to a normal clinical and functional status. Invasive procedures such as bronchoscopy and lobectomy were not used. There is no advantage to using such methods in children with primary lung abscess.

▶ [This is a nice little study. The pediatric literature provides precious little information on the management of a primary lung abscess that occurs in an otherwise healthy child, in the absence of foreign body aspiration. When you have 14 cases that resolve nicely with antibiotic management alone, that's an excellent track record to do everything possible to keep these children out of the hands of your friendly local surgeon. The latter, based on the experience of this same problem in adults, are accustomed to doing all sorts of nasty things, including drainage procedures and lobectomies. None of that nonsense should be necessary in children.—J.A.S., III] ◀

5–2 **Clinical Predictors of Pneumonia As a Guide to Ordering Chest Roentgenograms.** To develop criteria for a more efficient approach to ordering chest films, John M. Leventhal (Yale Univ.) pro-

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(5–1) Am. J. Dis. Child. 136:491–494, June 1982.
(5–2) Clin. Pediatr. (Phila.) 21:730–734, December 1982.

spectively monitored patients with fever or respiratory symptoms who were being evaluated with this test. During a 6-month period, data were collected on 136 children, aged 3 months to 15 years, seen in a pediatric emergency room.

Pneumonia, defined by appropriate abnormal chest roentgenographic findings, occurred in 26 children (19%). Of the 29 clinical variables studied, 7 were helpful in determining the children most likely to have a positive chest film (Table 1); the variable which was the best predictor of pneumonia was tachypnea. A cluster of pulmonary findings was also a good index for pneumonia (Table 2). The addition of sick appearance and cough to the cluster of pulmonary findings did not improve its predictive accuracy. Most cases of pneumonia occurred in the absence of classic signs (fever, cough, rales). When the patient's age was considered, the presence of pulmonary findings was a more helpful sign in children at least 2 years old (Table 3). The

TABLE 1.—SINGLE CLINICAL FINDINGS AS PREDICTORS OF PNEUMONIA

	Positive Roentgenograms		
Clinical Finding	Finding Absent	Finding Present	p value
Sick appearance	2/19 (11%)	24/117 (21%)	0.24
Cough	2/23 (9%)	24/113 (21%)	0.13
Nasal flaring	17/107 (16%)	9/29 (31%)	0.06
Tachypnea	5/71 (7%)	21/65 (32%)	<0.001
Rales (n = 133)	14/100 (14%)	11/33 (33%)	0.02
Pallor (n = 135)	17/112 (15%)	9/23 (39%)	0.01
Grunting	21/124 (17%)	5/12 (42%)	0.05
TOTAL	26/136 (19%)		

(Courtesy of Leventhal, J. M.: Clin. Pediatr. (Phila.) 21:730–734, December 1982.)

TABLE 2.—CLINICAL CLUSTERS AS PREDICTORS OF PNEUMONIA

	Positive Roentgenograms		
Clinical Clusters	Findings Absent	Findings Present	p Value
Fever, cough, and rales	17/103 (17%)	9/33 (27%)	0.13
Pulmonary findings*	0/41 (0%)	26/95 (27%)	<0.001
Sick appearance, cough, and pulmonary findings*	4/65 (6%)	22/71 (31%)	<0.001
TOTAL	26/136 (19%)		

*Pulmonary findings consist of respiratory distress, tachypnea, rales, or decreased breath sounds.

(Courtesy of Leventhal, J. M.: Clin. Pediatr. (Phila.) 21:730–734, December 1982.)

TABLE 3.—AGE AS A PREDICTOR OF PNEUMONIA IN PATIENTS WITH PULMONARY FINDINGS*

Age (years)	Positive Roentgenograms	
<2	12/57 (21%)	p = 0.09
≥2	14/38 (37%)	
TOTAL	26/95 (27%)	

*Pulmonary findings consist of respiratory distress, tachypnea, rales, or decreased breath sounds.

(Courtesy of Leventhal, J. M.: Clin. Pediatr. (Phila.) 21:730–734, December 1982.)

TABLE 4.—HEIGHT OF FEVER AS A PREDICTOR OF PNEUMONIA IN PATIENTS WITH PULMONARY FINDINGS*

Height of Fever (F)	Positive Roentgenograms	
<101	8/37 (22%)	p = NS†
101–102.9	11/31 (35%)	
≥103	7/27 (26%)	
TOTAL	26/95 (27%)	

*Pulmonary findings consist of respiratory distress, tachypnea, rales, or decreased breath sounds.

†By χ^2.

(Courtesy of Leventhal, J. M.: Clin. Pediatr. (Phila.) 21:731–734, December 1982.)

addition of height of fever to pulmonary findings did not improve the prediction of an abnormal chest film (Table 4).

If the criterion of at least one pulmonary finding had been used to order a chest film, no case of pneumonia would have been missed and the number of roentgenograms would have been reduced by 30%. What was unexpected was that each sign was not more helpful as an indicator of pneumonia. Because certain variables, such as cough and sick appearance, were present in children who were not evaluated with a chest film, the value of these variables as predictors of pneumonia is overestimated in this study.

5-3 **Role of Chest Radiograph in Management of Childhood Asthma.** Alan R. Rushton (Yale Univ.) analyzed retrospectively emergency room records for 1,548 visits involving asthma patients during a 24-month period to determine clinical features that resulted in the ordering of x-ray films and the relevance of results of chest x-rays for management. Degree of asthma was scored by resident physicians according to three conditions: degree of wheezing (0–4), chest retraction (0–3), and cyanosis (0–2); the most severely affected patients had scores of 9. If standard therapy in the emergency room (nebulized isoetharine plus three subcutaneous injections of epinephrine) did not improve the patients' respiratory status, posteroanterior

(5–3) Clin. Pediatr (Phila.) 21:325–328, June 1982.

TABLE 1.—Results of Chest Radiographs

Score	Finding	Per cent of Patients: Emergency Room	Admitted Patients	Total
0	Normal	56	47	53
1	Hyperaeration	15	19	16
2	Peribronchial cuffing	11	11	11
3	Streaky atelectasis	5	4	5
4	Focal atelectasis	3	8	5
5	Pulmonary infiltrate	10	11	10
6	Pneumothorax	0	0	0
7	Pneumomediastinum	1	1	1
	Total x-rays	n = 262	n = 129	n = 391

(Courtesy of Rushton, A. R.: Clin. Pediatr. (Phila.) 21:325–328, June 1982.)

and lateral radiographs were obtained and patients were admitted for continuous infusion of aminophylline. Chest x-ray films were scored from 0 to 7 for normal examination, hyperaeration, peribronchial cuffing, streaky atelectasis, focal atelectasis, infiltrate, pneumothorax, and pneumomediastinum.

Chest x-ray films were obtained during 391 visits. Five percent had focal atelectasis; 10% had a pulmonary infiltrate. The x-ray results of those children successfully treated as outpatients and those requiring hospitalization (Table 1) did not differ. Physicians frequently ordered x-ray films for children younger than 5 years, for those with temperatures greater than 38.3 C, with symptoms lasting longer than 2 days, respiratory rates greater than 40, a more severe attack with an asthma score greater than 3, or with pulmonary rales. Atelectasis or infiltrates were reported in 22% of children younger than age 5 years, but in only 8% of older patients. Although younger children had more pathologic x-ray findings, these results were not useful in predicting clinical response to treatment (Table 2).

Because there are many other causes of wheezing, the chest x-ray film may be useful during an initial episode to exclude nonasthmatic diagnoses. However, when children are already known to have asthma, the information obtained by x-ray study in this investigation did not provide sufficient data to alter the management of acute conditions. Further investigation may determine when the chest x-ray film provides therapeutically useful information for hospitalized asthmatic patients who fail to respond to medical therapy.

▶ [This study and the preceding one deal with the value of chest x-ray films, in previously well children and in children thought to have asthma. This is a very old issue that has been worked over many times before in both cases, and each study has certain design flaws that require interpretation of the data to be done quite carefully. Nonetheless, the questions raised by these studies are ones that we have to deal with just about every day.

It is not surprising to find, as in the Leventhal study, that pulmonary features such as tachypnea, respiratory distress, rales, and decreased breath sounds were useful predictors of a positive chest x-ray film. Textbooks of physical diagnosis, medicine,

TABLE 2.—SUMMARY OF STATISTICAL ANALYSIS

Patient Attributes	X^2_C	P
Chest x-ray score > 3		
and hospital admission	2.73	0.100
Symptoms > 2 days		
and ordering x-ray	25.79*	<0.005
and x-ray score > 3	1.10	>0.250
History of fever		
and ordering x-ray	46.70*	<0.005
and x-ray score > 3	0.00	>0.900
Fever > 38.3 C		
and ordering x-ray	15.64*	<0.005
and x-ray score > 3	0.015	>0.500
Respiratory rate > 40		
and ordering x-ray	70.37*	<0.005
and x-ray score > 3	1.18	>0.100
Asthma score > 3		
and ordering x-ray	14.63*	<0.005
and x-ray score > 3	0.00	>0.900
Rales		
and ordering x-ray	243.26*	<0.005
and x-ray score > 3: all patients	6.61*	0.010
≤5 years	1.10	>0.250
>5 years	4.78*	<0.050
Patient Age ≤5 years		
and asthma score > 3	3.77	>0.050
and hospitalization	21.40*	<0.005
and ordering x-ray	106.12*	<0.005
and x-ray score > 3	12.57*	<0.005
and hospitalization	2.00	>0.250
Physician training		
PL-1 and patient asthma score > 3	6.36*	<0.025
and ordering x-ray	1.10	>0.250

*Statistically significant.
(Courtesy of Rushton, A. R.: Clin. Pediatr. (Phila.) 21:335–338, June 1982.)

and pediatrics all comment on the importance of these findings. What is unexpected, however, is that each individual sign was not more helpful as a diagnostic indicator. For example, only one third of patients with rales turned out to have an abnormal x-ray study. Even more astounding was the fact that rales in the older child were not a better predictor of pneumonia compared to rales in younger children. Another unexpected finding was that the height of fever in addition to abnormal chest findings was not useful in predicting which patients would have an abnormal x-ray study. After reading the Leventhal study, I was about ready to throw up my hands and say that nothing was sacred anymore, when I realized that maybe what this study should teach is that abnormal findings on x-ray films that look like pneumonia are not necessarily pneumonia (atelectasis, for example) and that not all children who have "pneumonia" necessarily have to have an abnormal chest x-ray film. If you accept those two statements, then you would have to accept the statement that x-ray films should be considered complementary to the physical findings rather than as confir-

matory of what you think those findings mean. To put it slightly differently, if a patient looks, sounds, and otherwise acts like he has pneumonia, don't let a chest x-ray film fool you into thinking something else.

The study by Rushton states as clearly as possible that routine chest x-ray films do not appear to provide useful information for the design of treatment plans for children with asthma. Despite this, the relatively high incidence of radiologic abnormalities in patients hospitalized for acute asthma has led most hospitals to recommend that all such patients receive chest x-ray examination on admission. L. J. Brooks (*Chest* 82:315, 1982) examined the records of 128 asthmatics admitted to the hospital for management of status asthmaticus. In only about 2% of cases did the chest x-ray film in any way influence the management of the patients. I don't know how many more studies we are going to have to see like this one to convince everyone of the relatively minor importance of chest x-ray films in the patient who is a known asthmatic. The patient who wheezes who is not known to have asthma may be a different situation. Bronchiolitis, aspiration pneumonia, pulmonary foreign body, cystic fibrosis, congestive heart failure, and compression of the airway due to lymph nodes, vascular structures, or tumor masses all can produce wheezing and may have diagnostic chest x-ray films. This, however, is not the usual case of why x-ray studies are ordered for children who wheeze.

Despite all these investigations, getting emergency room personnel to forego chest x-ray films in asthmatics is about as likely to succeed as getting Charlie Brown to give up his dog.—J.A.S., III] ◀

5–4 **Wheezing, Asthma, and Pulmonary Dysfunction 10 Years After Infection With Respiratory Syncytial Virus in Infancy.** Respiratory syncytial virus is the main cause of bronchiolitis in the first year of life, but data regarding long-term sequelae are inconclusive. C. R. Pullan and E. N. Hey (Newcastle upon Tyne, England) attempted to define the incidences of subsequent atopy, bronchial reactivity, pulmonary dysfunction, recurrent wheeze, and overt asthma in 130 children examined 10 years after admission to the hospital with proved respiratory syncytial viral infection during the first year of life. Average age of the original 180 patients was 14 weeks; no child was admitted more than once. One child died. Among the 130 (72%) who were reexamined, 109 children had originally had diagnoses of bronchiolitis; 10 had bronchitis and 11 had pneumonia.

Skin tests, lung function tests, and histamine-challenge and exercise tests for bronchial lability were done in 107 children in the reexamined group and in a comparable number of controls matched by age, sex, and social class.

A total of 55 (42%) of the 130 reexamined children had had wheezing, whereas only 21 (19% of the 111 controls) had ever wheezed. Few children in either group (6.2% of the infected patients and 4.5% of controls) had troublesome symptoms at age 10. The incidence of bronchial lability in the reexamined children increased threefold but without excess of atopy. Maximal expiratory airflow was reduced throughout the vital capacity maneuver in the reexamined children, even when those with a history of recurrent wheezing were excluded (table). Results of single-breath nitrogen washout tests were normal, however, which suggested that ventilation was not appreciably uneven, although expiratory flow was restricted.

The findings in this study were compatible with the hypothesis that preexisting structural differences in the pulmonary airways at birth

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(5–4) Br. Med. J. 284:1665–1669, June 5, 1982.

FUNCTION OF LUNGS IN CHILDREN WITH NO ADDITIONAL EPISODES OF WHEEZING AFTER ORIGINAL EPISODE OF RESPIRATORY SYNCYTIAL VIRAL INFECTION AND IN CONTROL GROUP OF CHILDREN WITH NO HISTORY OF WHEEZING*

Test	Mean ± SD		% Predicted for height		
	Respiratory syncytial virus infection (n = 52)	Control children (n = 84)	Respiratory syncytial virus infection	Control children	Significance (p)
PEFR (l/min)	312 ± 48	334 ± 43	104·1	110·8	< 0·05
FVC (l)	2·32 ± 0·38	2·36 ± 0·40	97·3	100·0	NS
FEV_1 (l)	1·90 ± 0·28	2·01 ± 0·30	96·2	102·3	< 0·005
FEV_1/FVC (%)	82·1 ± 6·5	85·7 ± 5·8	—	—	< 0·005
MEF_{50} (l/s)	2·39 ± 0·62	2·66 ± 0·52	92·3	101·3	< 0·05
MEF_{75} (l/s)	1·04 ± 0·30	1·27 ± 0·36	93·0	112·3	< 0·001
MEF_{25-75} (l/s)	2·07 ± 0·50	2·34 ± 0·47	94·4	106·1	< 0·005

*NS = Not significant.
(Courtsey of Pullan, C. R., and Hey, E. N.: Br. Med. J. 284:1665–1669, June 5, 1982.)

render some children more susceptible to symptomatic lower respiratory tract infection than most when they are first challenged by respiratory syncytial virus in infancy.

▶ [The medical consequences of bronchiolitis extend beyond the acute viral illness. It is well-known that bronchiolitis is associated with wheezing in subsequent months, although the exact relationship between bronchiolitis and asthma remains unclear. Evidence also is accumulating that it sows the seeds for chronic obstructive lung disease in adult life. This and the preceding article are only two among several studies in the past decade that have come to this same conclusion. Even a single attack may be associated with abnormalities in lung function many years later, leaving open the possibility that clinical illness will develop subsequently. What is interesting in the report by Pullan and Hey is that these authors have broken from the more or less traditional statements that attempt to incriminate an underlying allergy as the cause of the long-term bronchial hyperreactivity seen in some children who have had a preceding episode of bronchiolitis. What they suggest is that patients destined to have future difficulties may, in fact, have been patients who got their clinical picture of bronchiolitis because they had underlying anatomical peculiarities. They also offer the possibility that the inflammatory process associated with bronchiolitis damages the lung structurally forever, causing it to become permanently more hyperreactive. The latter theory is consistent with certain other diseases that do the same thing. Some patients, for example, with cystic fibrosis, a history of surgery for congenital tracheoesophageal fistula, prior bronchopulmonary dysplasia after hyaline membrane disease, or a past history of accidentally inhaling a foreign body or having been near-drowned, have a high incidence of increased bronchial lability on follow-up. It seems fair to say that there are many unanswered questions here. Do some children who wheeze after a bronchiolitis episode wheeze then only because of bronchiolitis, or were they destined on a genetic basis to wheeze anyway? Do some children in whom asthma is destined to develop have more difficulty with their asthma because of an episode of bronchiolitis in infancy? Can bronchiolitis be differentiated from the first asthmatic attack?

To the questions raised in the preceding paragraph should be added the question, "What is bronchiolitis anyway?" Prior to 1940, the word did not even exist in the medical literature. Engle et al. (*Arch. Dis. Child.* 15:219, 1940) simply made up the word by adding "itis" to "bronchiole" because of the pathologic findings in babies who died with wheezing episodes. It has been traditional in medicine to add the suffix "itis" to practically anything that has a few neutrophils in it. It really doesn't explain anything, however. It makes as much sense as generically adding the suffix "ites" following the names of cities in order to describe the occupants of those cities. It works well for towns such as Denver, Portland, and Hartford, but if you try it in Paris, you are liable to get punched in the nose if you use this generic suffix. All this is a

roundabout way of saying we still have much more to learn about bronchiolitis and the respiratory syncytial virus. Fortunately, treatment may be at hand for infants with respiratory syncytial pneumonia. Caroline Hall et al. reported at the spring meetings of the Society for Pediatric Research last year that ribavirin, a synthetic nucleoside, possesses significant antiviral properties against this virus. More importantly, when used clinically, the drug shortened the overall severity of severe bronchiolitis and cut the duration of shedding of the virus in half.—J.A.S., III] ◀

5–5 **Outcome of Acute Lower Respiratory Tract Infection in Infants: Preliminary Report of Seven-Year Follow-up Study.** Jacqueline Y. Q. Mok and Hamish Simpson reviewed findings in 200 children seen 7 years after admission in infancy for acute lower respiratory tract infection to assess respiratory and epidemiologic characteristics. Respiratory syncytial virus infection had been present in 100 children; the 100 controls, matched with study patients for sex, age within 3 months, and, where possible, height, did not have respiratory syncytial virus infection. The mean age of the 200 children at admission was 4.3 months. About half had bronchiolitis, and the rest had pneumonia or bronchitis during the index illness.

The index and control groups did not differ in birth weight or gestational age, but fewer index patients were breast-fed. Social indices were more favorable in the controls. Subsequent respiratory symptoms were more prominent in index patients (Table 1), as were absence from school and physician consultations for respiratory illness. Both bronchitis and asthma were significantly more frequent in the index group. Impaired ventilatory function and bronchial hyperreactivity were more evident in index patients than in controls (Table 2).

TABLE 1.—Respiratory Symptoms, Medication, Absence From School, General Practitioner Consultation, and Established Bronchitis and Asthma in Index and Control Children

	Index (n = 200)	Control (n = 200)	p Value
Tendency to cough:			
At any time	69	26	<0·01*
In past year	34	11	<0·01*
Sputum	10	2	<0·05*
Colds going to chest	105	41	<0·01*
Tendency to wheeze:			
At any time	94	34	<0·01*
In past year	21	2	<0·01*
Recurrent nasal blockage or discharge	70	44	<0·01*
Difficulties in hearing	37	21	=0·05*
Tonsils removed	19	18	NS*
Adenoids removed	35	25	NS*
Medication in past year:	91	35	<0·01*
Antibiotics	83	31	NS
Bronchodilators	22	9	NS*
Absence from school in past year (wks)	1·9 ± SD 3·7	0·8 ± SD 1·3	<0·001†
No of GP consultations for respiratory illnesses in past year	2·1 ± SD 4·8	0·9 ± SD 1·6	<0·005†
Established bronchitis	7	1	NS*
Established asthma	17	5	<0·05*

*McNemar's test.
†Wilcoxon test.
(Courtesy of Mok, J. Y. Q., and Simpson, H.: Br. Med. J. 285:333–337, July 31, 1982.)

(5–5) Br. Med. J. 285:333–337, July 31, 1982.

TABLE 2.—RESULTS OF RESPIRATORY FUNCTION TESTS IN 197 MATCHED PAIRS

	Mean value		Mean difference	Standard error of difference	p Value
	Index	Control			
PEFR (% predicted)	97·3	100·9	−3·64	1·59	<0·05
$FEV_{0·75}$ (% predicted)	88·7	92·8	−4·14	1·31	<0·005
FEV_1 (% predicted)	91·3	95·0	−3·70	1·24	<0·005
FVC (% predicted)	86·3	87·1	−0·73	1·24	NS
$FEF_{25-75\%}$ (predicted)	91·8	102·3	−10·58	3·08	<0·001
FEV_1:FVC	0·88	0·91	−0·03	0·008	<0·001
R_T (kPa/l/s)	0·58	0·60	−0·01	0·016	NS

PEFR = peak expiratory flow rate; $FEV_{0·75}$ = forced expiratory volume in 0.75 seconds; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; $FEF_{25-75\%}$ = forced expiratory flow in middle half of expired volume; R_T = total respiratory resistance.

(Courtesy of Mok, J. Y. Q., and Simpson, H.: Br. Med. J. 285:333–337, July 31, 1982.)

Index children and controls had similar ventilatory function and exercise responses at follow-up evaluation.

Children who require hospital treatment for acute lower respiratory tract infection in infancy have increased respiratory symptoms and more frequent bronchitis and asthma than controls do and have relatively impaired ventilatory function. "Genetic predisposition" might explain their increased susceptibility to both respiratory infection and subsequent respiratory symptoms and illnesses. In this series respiratory syncytial virus probably was responsible for many infections in which it was not isolated. It is not clear whether these children ultimately outgrow their respiratory symptoms and fully recover functionally, or become more vulnerable to such environmental factors as smoking and atmospheric pollution as they grow older.

5–6 **Recurrent Pneumonia in Children and Its Relationship to Bronchial Hyperreactivity.** Howard Eigen, James J. Laughlin, and Jean Homrighausen (James Whitcomb Riley Hosp. for Children, Indianapolis) reviewed the findings in 81 children seen between 1976 and 1979 with persistent or recurrent pneumonia (PRP). The diagnosis was based on recurrent respiratory tract illness with segmental or subsegmental densities or an increase in bronchovascular-associated densities on chest films. Children with "asthma" were excluded, as were those referred for "possible cystic fibrosis." Fifty-six children were referred for recurrent pneumonia and 25 for persistent pneumonia. Mean age was 4.2 years. Over 40% of the children had a history of allergy or a family history of asthma in first-degree relatives. Twenty of the children reportedly had wheezed. Both weight and height were lower than expected. Over two thirds of the children studied had peripheral eosinophilia.

Infiltrates were present at the outset in 74% of patients. Twenty patients had an apparent cause of PRP. Eight had significant neuromuscular dysfunction, mental retardation, or both, with evidence of gastroesophageal reflux or aspiration on swallowing. Three patients

(5–6) Pediatrics 70:698–704, November 1982.

had congenital anomalies of the respiratory system. Others had conditions impairing host defenses. Children with apparently normal pulmonary function had positive methacholine challenge tests indicating bronchial hyperreactivity. Children without an apparent cause of PRP did quite well on chest percussion, postural drainage, and oral or inhaled bronchodilator therapy.

Persistent or recurrent pneumonia causes considerable morbidity and requires prompt and careful evaluation. A preexisting state that might produce the chest x-ray abnormalities should be sought. Bronchoscopy is not likely to be helpful unless a bronchial foreign body is suspected. Lung function testing may show airway obstruction, and testing with methacholine may be diagnostic of bronchial hyperreactivity. A therapeutic trial of bronchodilators may be warranted in young patients who have evidence of allergy or a family history of asthma and no known underlying cause of PRP.

► [The problem of persistent recurrent pneumonia is one that is commonly seen in children. It should come as no surprise that this problem bears some relationship to asthma. Asthma also is one of the most common disorders of childhood. It has been estimated that between 10% and 12% of all children suffer episodes of wheezing severe enough to seek medical attention. The reason why children with persistent or recurrent pneumonia are not thought to have bronchial hyperreactivity is based on the fact that all that is asthma need not wheeze. In fact, so little was the suspicion that these children might have hyperreactive airways that almost all of the patients included in this study underwent extensive evaluations to determine the causes of their pneumonias. When I see a child with recurrent pneumonia, I automatically think of a variety of potential diagnoses (recurrent aspiration, immune deficiencies, cystic fibrosis, anatomical abnormalities, immotile cilia syndrome, etc.). If nothing jumps out in terms of a likely possibility, then a laboratory evaluation along the lines of this preceding differential diagnosis is undertaken. What we too often fail to do is routine pulmonary function testing with a provocation test with methacholine that may be diagnostic of bronchial hyperreactivity. It is sad to admit that frequently the strongly positive family history of allergies that these children have is overlooked. It is also sad that, as the authors of these studies point out, eosinophilia is a rare occurrence in children with recurrent pneumonia who have asthma as an underlying etiology.

There is something in our psyche that makes us extremely reluctant to label young children as asthmatic. A. Speight et al. (*Br. Med. J.* 286:1253, 1983) looked into this problem of underdiagnosis and undertreatment of asthma in children. They found that of 179 children who gave a clear-cut history of wheezing and who had been seen by a physician, only 21 were labeled as having asthma. Two explanations were offered for this reluctance. One was the desire to avoid needless parental anxiety associated with the word "asthma." A second explanation was the belief that wheezy bronchitis is a separate, definable clinical entity and not just a conventional euphemism for childhood asthma. Recent research has undermined this belief, and there seems little clinical value in trying to differentiate between the two conditions when the management itself is identical. All too often, we see children with wheezy (? viral) bronchitis inappropriately treated with antibiotics while the wheeze itself is ignored.

I would have liked to have seen this study by Eigen et al. attempt to look for factors that triggered the bronchial hyperreactivity. Gortmaker, for example, has estimated that between 18% and 34% of the asthma seen up to age 17 can be attributed to maternal smoking (*Am. J. Pub. Health* 72:574, 1982). If you don't think this form of passive smoking on the part of our children is significant, there is an analogous situation that clearly documents that people who don't smoke who are around people who do smoke do inhale some of that smoke. A letter to the editor of the *New England Journal of Medicine* this past year reported a study of nonsmoking flight attendants on the San Francisco to Tokyo commercial airline run. The study examined the quantity of nicotine excreted in these attendants' urine during the course of the flight. It was determined that even though not one attendant picked up a cigarette, each one had inhaled the equivalent of one full cigarette by the time they reached Tokyo.

If that's what it's like in the cabin of a well-ventilated airplane, can you imagine what it's like in a 3-room apartment of a young asthmatic with a smoking parent when the windows are closed in the middle of the winter? Maybe parents have the right to inflict injury on themselves, but even restaurants try to do more to protect their customers. It's time we face up to the fact that parenteral smoking can be one form of passive child abuse.—J.A.S., III] ◀

5–7 **Inhaled Salbutamol (Albuterol) vs. Injected Epinephrine in Treatment of Acute Asthma in Children.** Epinephrine has been the standard treatment for acute asthma, but there is a trend toward use of selective β_2-receptor agonists. Allan B. Becker, Norma A. Nelson, and F. Estelle R. Simons (Univ. of Manitoba) undertook a double-blind, randomized comparison of the efficacies of injected epinephrine and nebulized salbutamol, a β_2 agonist, in 40 children aged 6–17 years seen in an emergency room with acute asthma in a 2-month period. All had documented reversible airways obstruction and had not been treated within 2 hours of presentation. Patients either received 0.01 ml of 1:1000 epinephrine solution per kg subcutaneously or inhaled 0.5% salbutamol solution at a dose of 0.02 ml/kg up to 1 ml. Salbutamol was diluted at least 1:1 and given by face mask and nebulizer with 100% oxygen at a flow rate of 6–10 L per minute over 5–10 minutes. The two treatment groups were clinically comparable. Five patients given salbutamol and 7 given epinephrine received corticosteroids orally at discharge from the emergency room.

Spirometric indices showed highly significant improvement in both treatment groups. There was no significant difference in mean Pa_{O_2} before or after treatment, and Pa_{CO_2} values were also comparable between groups before and after treatment. The heart rate rose only after salbutamol, and the respiratory rate decreased substantially after this treatment. A highly significant fall in diastolic blood pressure occurred in the epinephrine-treated patients. Ten of the 20 patients given epinephrine but none of those given salbutamol had adverse effects. There were no significant group differences in repeat treatment, return to the emergency room, or subsequent admission on return.

Nebulized salbutamol is as effective as injected epinephrine in the treatment of acute asthma in children. No significant differences in efficacy of these treatments were found in this study. In view of its noninvasiveness and lack of adverse effects, nebulized salbutamol, delivered by face mask with oxygen, is recommended as the treatment of choice for children with acute asthma.

▶ [Old habits, like old shoes, tend to stay around a long time. Epinephrine is an old habit and, like an old shoe, it has been around so long that it's starting to get some holes in it. Acute asthma in children in the United States conventionally has been treated initially by subcutaneous injections of epinephrine. In many countries outside the United States, however, long-acting β_2-agonist aerosols have replaced epinephrine for the initial treatment of acute asthma. These aerosols are more specific, require smaller doses, and are considered to have fewer adverse reactions than epinephrine. Theoretically, you might think that parenterally administered agents should be expected to work better or faster than inhaled agents in acute asthma. All theories aside, no one has been able to demonstrate this convincingly. This study indicates that inhaled salbutamol (albuterol) was certainly as effective as subcutaneously ad-

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(5–7) J. Pediatr. 102:465–469, March 1983.

ministered epinephrine. In view of the lack of adverse effects and its noninvasiveness, the clear-cut recommendation came down on the side of the inhaled salbutamol. The exact same findings were reported with another β_2-agonist (fenoterol, a very popular bronchodilator in Europe). Ben-Zvi et al. (*Pediatrics* 70:348, 1982) showed that inhaled fenoterol was just as effective as epinephrine in the emergency room management of acute asthmatic attacks. For the sake of clarity, neither fenoterol nor salbutamol was available in nebulized form in the United States at the time these reports appeared in our American literature. We are the only country in the world that was saddled for such a long time with just one single available nebulized β_2-agonist, metaproterenol (Alupent).

Another old shoe that requires some reexamination is the status of orally administered theophylline versus orally administered β_2-agonists such as metaproterenol in the management of chronic asthma. It has been traditional on this side of the ocean to choose theophylline for the ambulatory treatment of asthma in childhood. The pharmacology of this drug is well documented, sustained-release preparations produce nicely predictable blood levels, and blood levels readily can be obtained now to check our patients. Despite this, complaints of adverse side effects do arise with theophylline preparations. Dusdieker et al. (*J. Pediatr.* 101:281, 1982) have shown us that metaproterenol is essentially comparable to theophylline in the management of chronic asthma. Its side effects are essentially negligible. H. S. Lee (ibid., p. 632) additionally showed us that salbutamol by aerosol was just as effective as orally administered theophylline. If you begin to make the switch to inhalers, you will find that putting a tube spacer on the front of the inhaler will improve drug inhalation in children. This was shown nicely in a report in the *New England Journal of Medicine* (308:1328, 1983). Apparently putting a predictable distance between the inhaler and the mouth makes it easier for a child to self-administer the drug from the handheld aerosol reproducibly.

One last old shoe that requires inspection is the need for repeated injections of epinephrine for the initial treatment of acute asthma. It was about 40 years ago that some investigator suggested that smaller doses of epinephrine given two or three times rather than one large single dose would lessen the side effects and result in greater relief of bronchospasm. This concept gained wide acceptability and, as mentioned previously, currently epinephrine remains the single most widely used agent for the management of acute asthma in offices and emergency rooms. A reexamination of how epinephrine should be given suggests that repeated injections of epinephrine, while necessary to sustain bronchodilation, in fact do not have any cumulative effect. Furthermore, there may not be any significant therapeutic advantage of these repeated injections over a single injection of Sus-Phrine for the initial management of asthma (*Am. Rev. Respir. Dis.* 127:101, 1983).

Well, the above commentary probably has emptied all the shoes out of your closet. Nothing seems to be sacred any longer. I have been taught to use epinephrine in the conventional way and to follow it up with theophylline preparations. Maybe there are better ways of doing things, however, that we all have to adjust to. Nonetheless, I must conclude from all these studies that there are many ways to skin a cat. If something works for you, fine; stick with it. To put it another way, if the shoe fits, holes or no holes, wear it.—J.A.S., III] ◄

5–8 **Double-Blind Evaluation of Methylprednisolone Versus Placebo for Acute Asthma Episodes.** Corticosteroids often are used to treat asthmatic patients, but many courses of corticosteroid therapy are initiated on the basis of limited studies of efficacy. Gail G. Shapiro, Clifton T. Furukawa, William E. Pierson, Rhonda Gardinier, and C. Warren Bierman (Children's Orthopedic Hosp. and Med. Center, Seattle) evaluated methylprednisolone in a placebo-controlled, double-blind trial in 28 children with persistent bronchospasm after outpatient treatment. All had acute asthmatic exacerbations requiring three consecutive β-adrenergic treatments. Treatment began with 32

(5–8) Pediatrics 71:510–514, April 1983.

mg of methylprednisolone and gradually was tapered. Sustained-release theophylline was continued in a dosage maintaining a serum concentration of 10 to 20 μg/ml, and metaproterenol was used in a dosage of 10 to 20 mg three times daily, or more often if needed. Thirteen of the 28 patients received methylprednisolone during the 2-week study.

The corticosteroid-treated and placebo groups were similar with regard to past history and current maintenance therapy. All patients improved initially, and most in both groups had only "mild" involvement within 24 hours. After 2 weeks, 1 corticosteroid-treated patient and 5 placebo patients still wheezed. Both groups showed significant reversibility of airway obstruction. Most respiratory functional measurements were similar in the two groups after 2 weeks. Peak expiratory flow rates showed a general trend toward improvement in both groups. Both groups showed a significant fall in cosyntropin cortisol concentrations after cosyntropin on day 14 compared with day 1.

Methylprednisolone therapy appeared to enhance airway smooth muscle relaxation within 24 hours of treatment in asthmatics in this study. Less residual wheezing was present at the end of the study in corticosteroid-treated than in placebo patients. A short course of treatment with a short-half-life corticosteroid leads to positive physiologic changes in patients with episodes of severe asthma. The authors now use short-term corticosteroid therapy in moderately to severely affected asthmatics who fail to respond optimally to outpatient treatment for major acute asthmatic episodes.

▶ [This report is a classic example of the tail wagging the dog. The Section on Allergy and Immunology of the American Academy of Pediatrics outlined in a position paper on asthma in 1981 the role of steroids in the management of moderate to severe asthmatic episodes. Their recommendations were the same as those of this study, which came down the line 2 years later and, somewhat retrospectively, supports the earlier recommendations. The conclusions of this report only serve to uphold what just about all of us have been doing in the management of our asthmatics. I have been accustomed to using steroids under two conditions. One is when an acute asthmatic episode is only slowly or incompletely relieved by appropriate bronchodilator therapy in an office or emergency room setting, yet the patient is not sick enough to be hospitalized. This is the sort of patient who is sent home with a prescription for theophylline and also one for a steroid preparation. Additionally, I cannot remember the last time a patient with asthma was admitted to our hospital with severe bronchospasm who did not also receive steroids. It is in the former usage that this study by Shapiro et al. provides support. Without question, what most of have been doing on an ambulatory basis has been correct all along.

What is less clear than the above is the role of steroids in the management of acute wheezing in patients younger than age 12 months. For every study suggesting that there may be some clinical benefit to the use of corticosteroids during wheezing episodes in infants, there is another study failing to support that approach. This past year saw a small but well-designed study that compared steroids, salbutamol (as you recall, a β_2-adrenergic drug), both drugs, or none, used in the management of the wheezy baby syndrome. Combined salbutamol-dexamethazone administration resulted in more than twice the rate of improvement of either treatments. Corticosteroids can exert a facilitating effect on the adrenergic nervous system and cause an increase in cyclic AMP levels by decreasing the activity of phosphodiesterase in various tissues. This potentiating effect of corticosteroids on the β-adrenergic responsiveness is a feasible explanation for the advantage of the combination of dexamethazone and salbutamol in the treatment of acute wheezing in young infants. This study was performed in Israel (Tal, A., et al.: *Pediatrics* 71:13, 1983).

You should note that no complications were observed in any of the above reports with the use of short-term oral steroid therapy. The controversy still rages over whether or not beclomethasone spray for asthma suppresses adrenal function. A second major study appeared 1½ years ago indicating that it does (Vas, R., et al.: *J. Pediatr.* 100:660, 1982). Subsequently, two retorts quickly appeared indicating the safety of this drug and the lack of any significant adrenal suppression (Konig, P., et al.: ibid. 101:646, 1983; and Smith, J. M., et al.: *JAMA* 248:1449, 1982). Put your money down and take your choice!—J.A.S., III] ◀

5–9 **Predicting the Course of Asthma in Children.** Ability to predict the course of childhood asthma would be quite useful to practitioners. A. James Martin, Louis I. Landau, and Peter D. Phelan (Royal Children's Hosp., Parkville, Australia) undertook a 14-year prospective study of randomly selected children who began wheezing before age 7 years. A total of 371 children were seen at age 7, and 83 others with severe asthma were selected at age 10 years and, along with 315 of the original children, were followed to age 14. A total of 342 subjects were evaluated at age 21 years. Grade W subjects wheezed in childhood or adolescence but not in the 3 years before follow-up at age 21. Grade X subjects had wheezed within 3 years, but not within 3 months of final follow-up. Grade Y subjects had wheezed in the past 3 months but not very frequently or persistently, while grade Z subjects had wheezed very frequently or persistently in the past year.

Nearly 40% of subjects with an onset of wheezing before age 7 still had significant asthma at age 21 years, but subjects with frequent short episodes of asthma before age 2 or very frequent asthma at ages 2–5 years did not necessarily have significant asthma at age 21 years. Over two thirds of subjects with continuous wheezing in the first 2 years of life and over half of those with eczema at this age were in grades Y and Z at follow-up. Over 80% of subjects with a barrel chest deformity at age 10 years and 73% of those at age 14 were in grades Y and Z at follow-up. More subjects with eczema, especially at age 14, were in grade Z at follow-up. A reduced FEV_1 at ages 10 and 14 years was associated with worse asthma at age 21, as was a high score on allergy skin testing, especially at age 10 years. Height and weight, hay fever, urticaria, and the eosinophil count had no predictive value. The clinical pattern of asthma at ages 10 and 14 did have predictive value. At age 14 years, significantly more subjects who ended up in grade Z at age 21 were undertreated. Subjects who were treated appropriately at ages 10 and 14 did not do better than those who were undertreated with regard to change in asthma grade.

Persons who are likely to have significant wheezing in early adulthood can be identified as early as age 2 years. No long-term benefit from adequate drug treatment of asthma was apparent in this study. The rationale for treating asthma is the maintenance of as normal a life-style as possible.

▶ [Doctor Miles Wienberger, Professor of Pediatrics and Chairman, Pediatric Allergy and Pulmonary Division, State University of New York at Syracuse, comments:

"This is one of a series of excellent articles produced by the Thoracic Department at the Royal Children's Hospital related to the epidemiology and natural history of childhood asthma. As a result of the studies by these authors and others (Blair, H.:

(5–9) Aust. Paediatr. J. 18:84–87, June 1982.

Natural history of wheezing in childhood, *J. R. Soc. Med.* 72:42–59, 1979), some popular myths have been dispelled. Specifically, we know that, contrary to earlier beliefs, asthma not only can begin in infancy, but perhaps it is even appropriate to say that childhood asthma *typically* begins in infancy. We also now know that the common assurance that the child will "outgrow" his asthma is overly optimistic. Certainly, a substantial number of children with symptoms of asthma during the early years cease to have symptoms as they mature. Our ability to prognosticate in the individual patient, however, is limited. Nonetheless, it appears that children who have had only intermittent symptoms in the early years and have not developed large numbers of positive skin tests with a major allergic component to their asthma are much more likely to evidence remission as a young adult. Chronicity, as evidenced by persistent symptoms and signs of airway obstruction, is particularly associated with absence of remission and persistence of continuing chronic disease in adult life.

"The authors did not find that treatment altered the long-term outcome. Nonetheless, they emphasize the goal of utilizing treatment to maintain as normal a life-style as possible. Fortunately, the modern pharmacotherapy of asthma generally allows even those patients with a history of severe asthma to attain this goal of a normal life-style with medical regimens that are reasonably convenient and acceptably safe. Hospitalizations are generally avoidable with appropriate intervention measures, and maintenance medication for those with chronic asthma generally can prevent interference with sleep and activity.

"Identification of symptoms and signs as intermittent or chronic is therefore essential for providing prognostic counseling and recommending therapy (Ekwo, E., and Weinberger, M.: Evaluation of a program for the pharmacologic management of children with asthma, *J. Allergy Clin. Immunol.* 61:240–247, 1978). A careful history of extended symptom-free periods in association with normal physiology (for those old enough to perform spirometry) suggests that no maintenance therapy is needed and predicts a high likelihood of eventual remission. On the other hand, relatively continuous symptoms, even if low grade, and particularly if associated with persistently abnormal pulmonary function, suggest a relatively high likelihood of symptoms continuing into adult life and dictate the need for continuous medication for control in these patients. Waiting for symptoms to go away is a disservice to these children and their families."] ◄

5–10 **Phrenic Nerve Pacing in Infants and Children: Review of Experience and Report on Usefulness of Phrenic Nerve Stimulation Studies.** Since 1964, many adults have received respiratory support with phrenic nerve pacemakers. Robert T. Brouillette, Michel N. Ilbawi, and Carl E. Hunt (Northwestern Univ., Chicago) discuss phrenic nerve pacing in infants and children based on findings in 9 children referred for pacing in whom phrenic nerve conduction times and diaphragmatic action potential amplitudes were measured. Seven had pacemakers inserted and 2 were judged unsuitable for pacing (table).

Phrenic nerve conduction times varied from 2.7 to 7.8 msec (shorter than conduction times in adults), were quite reproducible, and increased with age and with increasing distance between the stimulating electrode and the diaphragm. Diaphragmatic action potential amplitudes were 0.08 to 4.1 mV (roughly equivalent to amplitudes in adults) but varied between patients and within patients on different days. Lower amplitudes were obtained after percutaneous stimulation than after direct phrenic nerve stimulation.

Of 5 patients who underwent preoperative, percutaneous phrenic nerve stimulation, 3 had strong diaphragmatic contractions and pacemakers were inserted, and 2 had weak or absent contractions, con-

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(5–10) J. Pediatr. 102:32–39, January 1983.

DATA ON 9 PATIENTS REFERRED FOR PHRENIC NERVE PACING WHO HAD MEASUREMENTS OF PHRENIC NERVE CONDUCTION TIME AND DIAPHRAGMATIC ACTION POTENTIAL AMPLITUDE

Patient	*Diagnosis*	*Age at referral*	*Outcome*
D. H.	CHS; congenital rubella	9 mo	Died at home at 21 mo; apparent pacemaker transmitter failure
J. K.	Idiopathic CHS	9 mo	Alive; home; pacemakers at night; spontaneous awake breathing
B. R.	Quadriplegic after removal of a posterior fossa meduloblastoma	9 yr	Alive; on IPPV continuously; psychologic problems prevent use of pacemakers
J. S.	Idiopathic CHS	15 mo	Alive; home; pacemakers when awake; IPPV when asleep
J.Y.*	CHS; Arnold-Chiari malformation; meningomyelocele	18 mo	Alive; home; pacemakers when awake; IPPV when asleep
H.S.*	Brain stem and cerebral trauma from auto accident	6 mo	Alive; home; pacemakers when awake; IPPV when asleep
C.B.*	CHS; idiopathic hypothalmic disorder involving regulation of thirst, appetite, and thyroid function	10 yr	Alive; home; pacemakers when awake; IPPV when asleep
E. M.*†	Neurofibromatosis; multiple meningiomas	20 yr	Alive; in hospital; IPPV continuously
A. P.*†	Cervical spine injury; in utero hyperextension breech	5 mo	Died at 6 mo of respiratory failure after IPPV discontinued

CHS = central hypoventilation syndrome; IPPV = intermittent positive-pressure ventilation.
*Preoperative evaluation.
†Not recommended for pacemakers.
(Courtesy of Brouillette, R. T., et al.: J. Pediatr. 102:32–39, January 1983.)

traindicating pacemaker insertion. Postoperatively, noninvasive measurements of oxygen, carbon dioxide, tidal volume, and diaphragmatic action potential amplitudes were used to adjust pacemaker settings. The pacemakers facilitated discharge from the hospital to a home-based ventilation program in 6 of the 7 patients in whom they were inserted.

Phrenic nerve pacing is a practical method of supporting ventilation in carefully selected children. Phrenic nerve stimulation studies are useful in selecting patients for pacing and in adjusting pacemaker settings. Pacing has some limitations. Infants and young children always require tracheostomy to bypass pacing-induced upper airway obstruction. Because children require bilateral pacing and because one phrenic nerve should be paced no longer than 12 to 15 hours per day, another method of maintaining adequate gas exchange must be assured for the other 12 hours each day. In patients who require artificial ventilation continuously, phrenic nerve pacing and intermittent positive-pressure ventilation are complementary techniques, both contributing to the total rehabilitation of the patient. Pacemakers are simple for parents to operate. The most common indications for phrenic nerve pacing are central hypoventilation syndrome and traumatic lesions of the brain stem or upper cervical spinal cord.

5–11 **Pneumothorax in Cystic Fibrosis: Management and Outcome.** F. John McLaughlin, Wallace J. Matthews, Jr., Denise J. Strieder, Kon Taik Khaw, Samuel Schuster, and Harry Shwachman (Boston) evaluated methods of management to formulated therapeutic guidelines in a retrospective study of 150 admissions for pneumothorax and cystic fibrosis (CF) at Children's Hospital Medical Center and of 10 admissions to other hospitals. Pneumothorax was treated by observation, needle aspiration, trocar thoracotomy, pleural sclerosis, or parietal pleurectomy. Results were classified as "resolved" if x-rays after 1 week showed reexpansion or a persistent rim of 1 cm or less; "failed" if the air leak continued or relapse occurred before 1 week; "recurred" if relapse occurred after 1 week; and "successful" when no subsequent relapse occurred.

Among 67 patients, there were a total of 170 pneumothoraces; 93 were first episodes and 77 were recurrences. In 41 patients, pneumothorax was unilateral. Of the 210 trials of methods of management, all methods except needle aspiration resulted in a fair rate of resolution, but recurrence rates were high with use of observation, needle aspiration, trocar thoracotomy, and scleroses by means of tetracycline and silver nitrate. Sclerosis by means of quinacrine and parietal pleurectomy were the most successful methods (table). No morbidity was seen with the use of observation or needle aspiration. Trocar thoracotomy was associated with pain that varied markedly in intensity from patient to patient. Sclerosis by means of quinacrine was well tolerated, whereas both silver nitrate instillation and sclerosis by means of tetracycline caused severe pain (which, with use of tetracycline, subsided in a few hours). Parietal pleurectomy was well tolerated.

Pulmonary function tests made before pneumothorax and after 60% of 12 successful trials of pleural sclerosis and after 75% of 16 attempts of parietal pleurectomy showed no significant difference in function and exchange of gases. Among 69 patients, 42 (60%) died during the 12-year study; 80% of deaths occurred within 3 years of

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(5–11) J. Pediatr. 100:863–869, June 1982.

presentation. Nine patients died during hospitalization for a first pneumothorax. The male-to-female ratio was 1:3.5; mean age was 15 years. Pneumothorax was under control in all but 1 of the patients who died. Patients who died had been admitted initially at a younger age with lower Shwachman scores; women had significantly lower

Results of 211 Trials of Methods of Management

Method	*Trials*	*Failure*	*Resolution*	*Recurrence*	*Long-term success*	*Follow-up (mo)*	*Mean follow-up (mo)*
Observation	46	13 (30%)	33 (70%)	20/33	13/46 (28%)	1-74	16
Needle aspiration	31	17 (55%)	14 (45%)	11/14	3/34 (9%)	1-21	3
Trocar thoracotomy	94	29 (31%)	65 (69%)	41/65	26/94 (28%)	1-140	13
Quinacrine sclerosis	8	1 (12.5%)	7 (87.5%)	0/7	7/8 (87.5%)	13-80	38
Silver nitrate sclerosis	8	1 (12.5%)	7 (87.5%)	3/7	4/8 (50%)	1-13	6
Tetracycline sclerosis	8	1 (12.5%)	7 (87.5%)	6/7	1/8 (12.5%)	1-18	5
Parietal pleurectomy	16	0 (0%)	16 (100%)	0/16	16/16 (100%)	1-30*	9

*Six patients after parietal pleurectomy had follow-up for 3 months or less at end of study; subsequent 12 months showed no recurrences.
(Courtesy of McLaughlin, F. J., et al.: J. Pediatr. 100:863–869, June 1982.)

Shwachman scores. Death in this population seems to be associated not with increasing age, but with severity of disease.

▶ [We have been seeing more and more children with cystic fibrosis in whom pneumothorax develops. This is probably a reflection of the increased length of survivorship in patients treated for cystic fibrosis. The mean survival in 1950 was only about 4 years. Currently, patients can expect to live into the third decade of life and perhaps longer. As you might expect, because a pneumothorax is evidence of a patient who most likely has survived to a relatively advanced age for this disease, the outcome for the patient after the first pneumothorax is not particularly good. Sixty percent of patients in this series died and 80% of these deaths occurred within 3 years of presentation with a first episode of pneumothorax. If there is anything this study teaches us, it is that you cannot just evacuate the air from the chest and hope this problem will disappear. Follow the guidelines these authors suggest and the recurrence rates will be fairly low.—J.A.S., III] ◀

5–12 **Plasma Cell Granuloma of the Lung in Children.** Plasma cell granuloma is an uncommon benign lesion of unknown cause. In children, it occurs principally as an intrapulmonary mass, ranging in size from a coin-sized lesion to a large mass. On chest films, a distinction between a benign unresolving process and a malignant lesion often cannot be made. The granuloma is characterized by proliferation of plasma cells, along with other mesenchymal elements. Patients may be asymptomatic; in symptomatic patients, cough (sometimes productive) and fever are the most frequent symptoms, but in more chronic situations, symptoms may include weight loss, hemoptysis, chest pain, pneumonia, and upper respiratory tract infections. Often, there is a disproportion between the size of the tumor and presenting symptoms.

Carlos M. Monzon, Gerald S. Gilchrist, E. Omer Burgert, Jr., Edward J. O'Connell, Robert L. Telander, Alan D. Hoffman, and Chin-Yang Li (Mayo Clinic and Found.) present data on 3 children with plasma cell granuloma of the lung who had a syndrome characterized by digital clubbing, roentgenographic evidence of an intrapulmonary lesion with diverse configuration (Fig 5–1), elevated erythrocyte sedimentation rate, elevated serum immunoglobulin levels, and thrombocytosis. Immunoperoxidase staining of specimens revealed plasma cells positive for κ- and λ-light chains in normal proportions, indicating polyclonal plasma cell proliferation, which implies a reactive inflammatory process. Most abnormalities tended to become normal after removal of the lesion. Clubbing resolved completely after surgical removal in 2 patients and partially in 1 patient who had 1 month of follow-up.

Surgical removal of the mass appears to be the treatment of choice, although radiation therapy has been employed for recurrences. In general, the prognosis is excellent.

▶ [While I wouldn't stay up nights waiting to see the next case that comes into the office of a plasma cell granuloma of the lung in a child, we should nonetheless still be remotely familiar with this problem. It must be included in the differential diagnosis whenever we see an isolated pulmonary nodule on a chest x-ray film. The mass itself may not even be a tumor and, for this reason, this article appears in this chapter, "The Respiratory Tract," rather than Chapter 10, "Oncology." Plasma cell gran-

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(5–12) Pediatrics 70:268–274, August 1982.

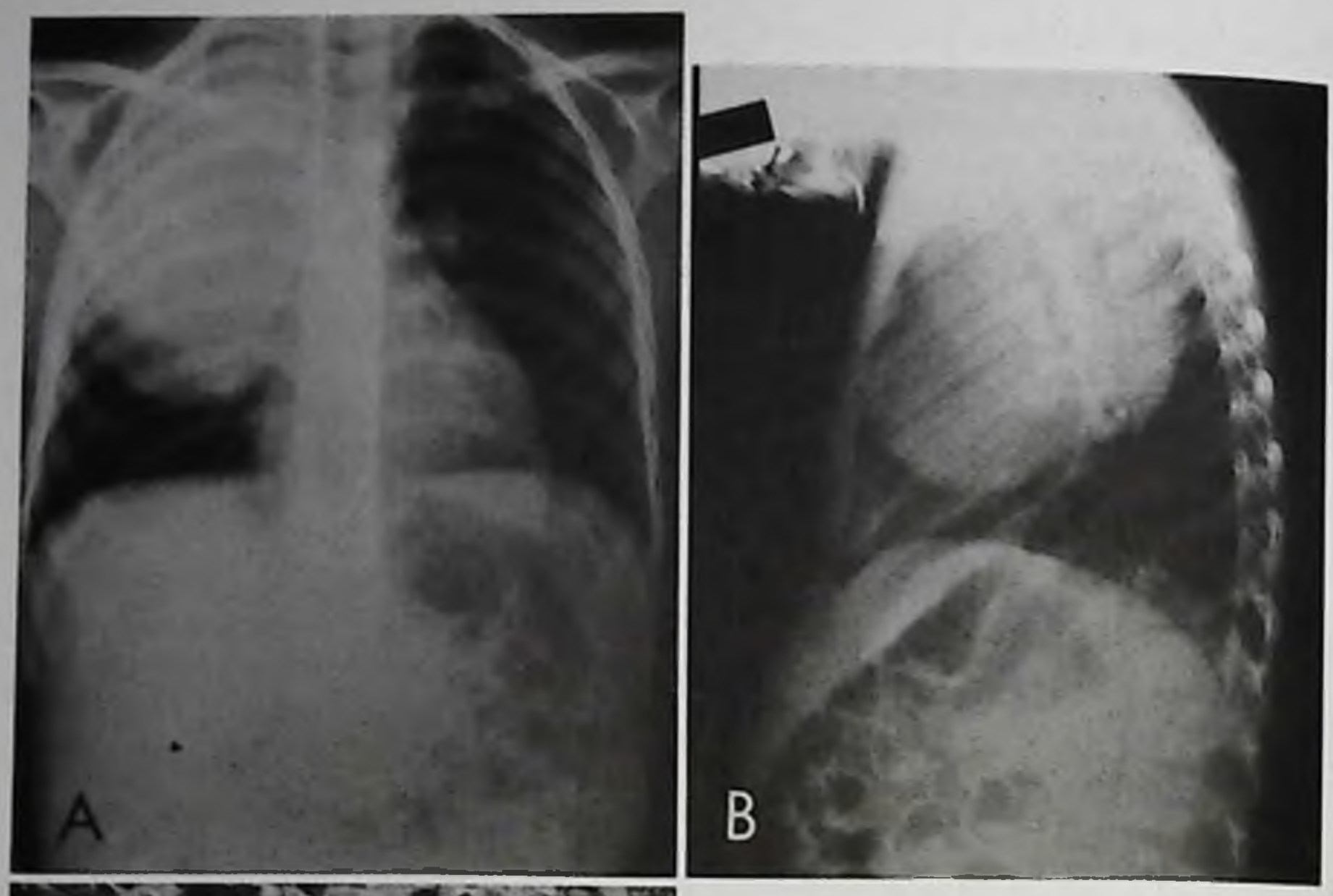

Fig 5–1.—Plasma cell granuloma in boy aged 5 years. A, posteroanterior and B, lateral views reveal well-defined mass occupying entire left upper lobe and bulging inferiorly. C, histologic section reveals proliferation of fibroblasts, vessels, and abundant infiltrate of plasma cells with scattered eosinophils. Hematoxylin-eosin; ×400. (Courtesy of Monzon, C. M., et al.: Pediatrics 70:268–274, August 1982. Copyright American Academy of Pediatrics, 1982.)

ulomas have been named as such only for the past 11 years. They used to go by various names, including "xanthoma," "xanthofibroma," "xanthogranuloma," "sclerosing hemangioma," "histiocytoma," "fibroxanthoma," and "postinflammatory pseudotumor." Inasmuch as the mass itself consists of a variety of inflammatory cells that seem to elaborate immunoglobulins, the last in this series of pseudonyms appears to be the most accurate term. A differential diagnosis of these chest lesions should include infectious processes, neoplasms, either malignant or benign (hamartomas or teratomas), and congenital lesions such as sequestration or duplication of the lung. If you find a coin-sized lesion, or even something larger, such as in Figure

5–1, in the presence of hypergammaglobulinemia, chances are excellent that you are dealing with a plasma cell granuloma. The prognosis with this mass is excellent. Such conglomerations of plasma cells producing monoclonal immunoglobulins are suggestive of multiple myeloma. None of the patients, however, with isolated granulomas of lung has gone on to have this much more complex disease.—J.A.S., III] ◀

6. The Gastrointestinal Tract

6–1 **Cystic Fibrosis Screening by Dried Blood Spot Trypsin Assay: Results in 75,000 Newborn Infants.** Screening of newborn infants for cystic fibrosis has been controversial because of high false positive and false negative rates for methods that use meconium or feces and lack of agreement about the benefit accruing from an extremely early diagnosis. Bridget Wilcken, A. R. D. Brown, Ruth Urwin, and D. A. Brown (Sydney) reviewed the results of screening 75,000 infants aged 5 days in Australia for cystic fibrosis by the blood spot immunoreactive trypsin (IRT) assay. The assay was performed on dried blood specimens. The IRT value was elevated in 433 infants, and retesting showed a persistent elevation in 38. Sweat testing confirmed cystic fibrosis in 35 infants. One mother refused sweat testing. Cystic fibrosis was clinically unsuspected in 22 infants, although all but 4 had suggestive symptoms. Stool trypsin activity was normal in 9 of 16 cases at the time of screening. One case of cystic fibrosis was missed by screening because of a normal IRT test. In a review of samples from 36 newborn infants who later had a diagnosis of cystic fibrosis, all were found to have IRT values greater than those in matched control infants.

An elevated IRT value is characteristic of newborn infants with cystic fibrosis. The test is highly specific and sensitive when used as a newborn screening measure. The cost of screening has been about $0.70 per infant. The authors believe that large-scale, long-term trials of screening should now be conducted at several centers. Although neonatal screening may be somewhat helpful in relation to genetic counseling, full benefit will not be obtained without a reliable method of prenatal diagnosis.

▶ [Phillip T. Swender, Department of Pediatrics, State University of New York at Syracuse, comments:

"This interesting article again raises several questions about the value of neonatal screening for cystic fibrosis. The authors point out that of the 35 babies with an elevated IRT test, only 4 were without some symptoms suggestive of cystic fibrosis. Presumably, an astute clinician would have considered cystic fibrosis in the differential diagnosis within a reasonable period of time. In addition, we are not told what symptoms were present in the 18 infants who had symptoms but did not have either meconium ileus or an affected sibling. If these infants had primarily gastrointestinal symptoms, then Reid's observation on lung remodeling in cystic fibrosis is a less compelling argument for early diagnosis (*Am. Rev. Respir. Dis.* 119:531, 1979). In addition, one must consider the emotional impact on the 395 families who thought their babies might have cystic fibrosis for the 4 to 7 weeks before retesting was performed. This study clearly confirms previous studies and demonstrates that newborn screening for cystic fibrosis can be successfully accomplished. However, until such time as the value of early diagnosis is firmly established, one must raise the question about whether it is better for a child to be thought of as normal for whatever brief

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(6–1) J. Pediatr. 102:383–387, March 1983.

period of time, or to be labeled from the beginning as having a chronic and eventually fatal disease. One must at least pause briefly before launching into a massive screening program and ask an intriguing ethical question. 'Are there things that we should not know?'"] ◄

6–2 **Incidence of Anemia, Hypoproteinemia, and Edema in Infants as Presenting Symptoms of Cystic Fibrosis: Retrospective Survey of Frequency of This Symptom Complex in 130 Patients With Cystic Fibrosis.** Ole Haagen Nielsen and Birthe Furlie Larsen (Univ. of Copenhagen) determined the occurrence of anemia, hypoproteinemia, and edema in 130 children with cystic fibrosis (CF) who were alive a month after birth and were seen before age 6 months in 1949–1980. In 7 patients (5.4%) the complete symptom complex developed within the first 5 months of life; all 7 survived for more than a year after onset of the symptom complex. Six of the 7 infants were fed mother's milk only. The mean duration of edema was about 3 weeks, during which time sweat testing was unreliable. The 7 study patients remain alive at ages 20 months to 15 years; 5 are aged 5 or older.

Thus, in about 5% of infants with CF in this series, the triad of anemia, hypoproteinemia, and edema developed in the first 6 months of life. Poor weight gain before the onset of edema was a characteristic finding. Most infants were exclusively breast-fed, and breast-feeding may result in protein deficiency in some CF patients. Hypoproteinemia also may be caused by hepatic dysfunction, but this was not evident in the present series. The symptom complex should always suggest CF. Although previous studies indicate a poor prognosis for these patients, no child in the present series has died. Breast-feeding is not contraindicated in families with a history of CF, but a sweat test and regular hemoglobin and protein measurements should be obtained in the first 6 months of life. If low values develop, dietary protein supplementation is indicated.

► [The symptom complex of anemia, hypoproteinemia, and edema in infants with cystic fibrosis has been known now for about 20 years. This triad may occur before the diagnosis is suggested by other symptoms. It also may occur in children with cystic fibrosis who already have been diagnosed and who are ingesting less than optimal quantities of protein. This report from Denmark is useful for two purposes. First, it tells us how frequently these problems occur. Second, it describes the circumstances under which they occur. About 5% of infants with cystic fibrosis either will present with anemia, hypoproteinemia, and edema or will develop these findings within the first few months of life after diagnosis. In the Denmark study, the overwhelming culprit was breast milk. Breast milk, of course, contains less protein than most of the proprietary formulas or evaporated milk preparations. If protein absorption is marginal, the difference in the quantity of protein in breast milk may make enough difference to cause this problem. The curious thing about these babies is that they rarely demonstrate obvious malabsorption historically; nonetheless, they may well demonstrate evidence of this on careful stool examination or by measurement of the levels of fat-soluble vitamins. It is important to get these infants back on track as rapidly as possible because death has been reported as a complication of the symptom triad. Just as important, if these babies remain vitamin E deficient long enough, they might be candidates for the neurologic complications of vitamin E deficiency that may be irreversible. Degenerative neuromuscular disease secondary to vitamin E deficiency sometimes complicates cholestatic liver disease in children

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(6–2) J. Pediatr. Gastroenterol. Nutr. 1:355–359, 1982.

(*Ann. Neurol.* 13:291, 1983). Older children may have ataxia and dysarthria (Lloyd, B. W., et al.: *Neuropediatrics* 13:155, 1982).

If you haven't switched to enteric-coated forms of pancreatic enzyme preparations for your patients, you are now probably behind the times. Gastric acid and pepsin partially inactivate enzyme supplements, and the effectiveness of such treatment varies in different patients. Lipase is particularly sensitive to acid degradation, with as much as 90% of this enzyme being destroyed in the stomach. This is much less true of trypsin. A form of pancrelipase, containing lipase, amylase, and protease, consisting of enteric-coated pH-sensitive microspheres packaged in capsule form, has now been on the market for the past few years. Studies done to date clearly indicate that there may be a distinct advantage in favor of these new preparations (Pancrease, Cotazym-S). Significant improvement in fat absorption follows use of these preparations. There isn't much change in protein absorption because this wasn't much of a problem to begin with with the old style pancreatic enzyme preparations. The other distinct advantage of these products is that they allow you to stop using cimetidine, which had been touted for a long time as improving absorption in patients with cystic fibrosis by shutting down the stomach acid that inactivated the enzyme preparations. Patients with cystic fibrosis have enough problems of their own without being subjected to the risks of cimetidine.—J.A.S., III] ◀

6–3 **Biliary Atresia and Reovirus Type 3 Infection.** Neonatal biliary atresia may result from an ongoing postnatal process such as infection rather than being caused by developmental malformations as previously thought. Although microscopic lesions of the bile duct suggest such a process, viral isolation and serologic studies usually have been negative. Similarities have been found between reovirus type 3-induced hepatobiliary injury in mice and biliary atresia in human beings, but measurements of neutralizing antibodies proved inconclusive. Rachel Morecki, Joy H. Glaser, Sangho Cho, William F. Balistreri, and Marshall S. Horwitz examined the hypothesis that the neutralization test might be inadequate to detect reovirus type 3 (reo-3) antibodies in infants with hepatobiliary disease.

Serum from 25 babies with morphologically confirmed biliary atresia and from their mothers was examined. Paired samples were available in 14. Control samples were taken from 37 other children, with maternal samples in 8. Reo-3 was used to infect L cells (murine fibroblasts tissue culture line). These were then centrifuged, sectioned, and fixed before incubating with human serum at various dilutions. Second incubation was with fluorescein-conjugated goat antihuman immunoglobulin.

Initial determinations of indirect fluorescent antibody were performed at serum dilution of 1:10 (table). Among those younger than age 4 months, 9 of 15 patients and none of 15 controls had reo-3 indirect fluorescent antibody ($P = .001$). Of 6 babies whose convalescent-phase serum was obtained at age 5–12 months, 5 showed antibody, whereas only 3 of 18 controls showed antibody. Of all 25 patients, a total of 17 (68%) were positive for reo-3 antibody; of 37 controls, only 3 (8%) were positive ($P < .0001$). Five of the 14 patients with sequential samples showed a fourfold rise in titer of reo-3 antibody. Seven had titers fourfold higher than those of their mothers, indicating that the antigen had affected the baby directly rather than being introduced transplacentally. Confirmation of the putative role

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(6–3) N. Engl. J. Med. 307:481–484, Aug. 19, 1982.

INDIRECT FLUORESCENT ANTIBODY TO REOVIRUS TYPE 3 (REO-3 IFA) IN PATIENTS WITH BILIARY ATRESIA AND IN CONTROLS*

AGE ‡	PATIENTS WITH BILIARY ATRESIA		CONTROLS		P VALUE †
	NO. OF PATIENTS	NO. REO-3 IFA-POSITIVE	NO. OF SUBJECTS	NO. REO-3 IFA-POSITIVE	
mo					
0–4	15	9	15	0	0.001
5–8	6	5	1	0	—
9–12	0	0	17	3	—
13–18	1	1	0	0	—
19–36	3	2	4	0	—
Totals	25	17	37	3	<0.0001

*Reo-3 IFA was determined at a 1:10 serum dilution in phosphate-buffered saline.

†*P* values were calculated by the χ^2 method with the Yates correction.

‡Age when the convalescent-phase serum sample was obtained. Most clinical signs of illness began at about 4 weeks in all age groups.

(Courtesy of Morecki, R., et al.: N. Engl. J. Med. 307:481–484, Aug. 19, 1982.)

for reo-3 as a cause of biliary atresia would be furthered by isolation of the infectious agent from patients, but the current demonstration should serve to stimulate prospective epidemiologic and virologic investigations.

► [I would agree with the authors of this study that confirmation of the putative role for reo-3 as a cause of biliary atresia would be furthered by isolation of the infectious agent from patients. We are not even sure that such isolation could be done, however. Shedding of this virus is extremely brief, at least in the animal model, where virus shedding occurs early and lasts only about 8 days. Obviously, if this is true in human beings, by the time a child is born we will have missed the opportunity to culture the virus directly. Why continuing hepatobiliary degeneration occurs after the virus is gone remains an even more problematic question. If the reo-3 theory is correct, perhaps the reason for progression of disease is ongoing immunologic tissue damage initiated by the virus. The investigative efforts with regard to reo-3 are highly speculative at best. I don't know how worthwhile it is to spend a lot of police effort chasing after one organism when it seems likely that there may be multiple etiologies for this serious disease. The cutting edge of police work of the type done by Dick Tracy should be found in the funny papers, not in our scientific journals, until better substantiated.—J.A.S., III] ◄

6–4 **Portal Hypertension: American Academy of Pediatrics Surgical Section Survey—1981.** R. Peter Altman and Joseph Krug (Columbia Univ.) reviewed 76 cases of portal hypertension. In 38 patients, the etiology was hepatic (cirrhosis); 36 has portal hypertension resulting from extrahepatic portal vein obstruction, 1 had suprahepatic portal hypertension (Budd-Chiari syndrome) of unknown cause, and 1 had portal hypertension also of unknown cause. A history of umbilical vein catheterization was found in 9 of 27 patients surveyed who had portal vein obstruction. Biliary atresia was the most common diagnosis among patients with portal hypertension arising from hepatic parenchymal disease (table).

Patients with portal hypertension on the basis of cirrhosis constituted a much less favorable clinical group than those with extrahe-

(6–4) J. Pediatr. Surg. 17:567–570, October 1982.

PORTAL HYPERTENSION: CAUSES OF CIRRHOSIS

	Number of Patients
Biliary atresia	10
Congenital hepatic fibrosis	8
Cystic fibrosis, focal biliary cirrhosis	6
Alpha, antitrypsin deficiency	3
Postradiation/chemotherapy	3
Chronic active hepatitis	3
Sclerosing cholangitis	1
Histiocytosis X	1
Galactosemia	1
Congenital biliary cirrhosis	1
Etiology ?	1
Total	38

(Courtesy of Altman, R. P., and Krug, J.: J. Pediatr. Surg. 17:567–570, October 1982.)

patic portal hypertension. Balloon tamponade was more successful in controlling bleeding in the group with extrahepatic portal hypertension than in those with cirrhosis. Vasopressin infusion was generally successful in controlling hemorrhage in both groups.

In patients with extrahepatic portal hypertension, results of devascularization procedures were excellent in 2 and poor in 1 patient. Splenectomy, when utilized, was successful, as was sclerotherapy, transthoracic ligation of varices, and colon interposition. In cirrhotic patients, results of nonshunt therapy were less favorable. Among 8 patients treated without surgical intervention, only 1 did well (in contrast to 4 with a good outcome of 4 patients treated conservatively in the extrahepatic portal hypertension group).

Central splenorenal shunt was most commonly used (both groups). The selective splenorenal (Warren) shunt is gaining in popularity. No clear advantages of any particular method of portosystemic shunting were found in either group. In the extrahepatic portal hypertension group, results in 13 patients who had central splenorenal shunts were considered excellent in 11, good in 1, and poor in 1. All 4 patients who had Warren shunts had good or excellent results.

In the hepatic (cirrhosis) group, of 7 patients having central splenorenal shunts, only 1 had an excellent result; 3 results were good, 2 were poor, and 1 patient died. From the group of 3 patients having Warren shunts, 1 result was excellent, 1 was poor, and 1 patient died.

▶ [Dr. Judith M. Sondheimer, Associate Professor, Department of Pediatrics, State University of New York at Syracuse, comments:

"The population receiving surgery for bleeding secondary to portal hypertension is changing. In the past, by and large it was patients with extrahepatic portal hypertension who were both big enough and healthy enough to undergo surgery (see *J. Pediatr. Surg.* 8:467, 1973). In this review, however, fully 50% of the population consists of biliary atresia patients with portoenterostomies who have intact liver function but need shunting for the progressive hepatic fibrosis and portal hypertension that seem almost inevitable occurrences. The old 10-mm diameter size limit on vessels used for shunts seems to be changing too, as a result of better materials for vascular interposition. Nineteen of the 38 reported shunts here utilized vessels 10 mm or less

in diameter, thus opening up these procedures to a much younger group of infants. Some dicta from the adult world appear confirmed for pediatric patients. Peripheral pitressin works as well as tamponade or selective arterial pitressin in temporarily stopping variceal bleeding. Nonshunt procedures don't work well in patients with liver disease, and anything works better in patients with healthy livers."] ◀

6–5 **Hydrops of the Gallbladder in Children.** Acute hydrops of the gallbladder is an uncommon entity that seems to occur only in children. It is characterized by massive distention of the gallbladder without congenital malformation, stones, or bacteria. Thomas O. Rumley, and Bradley M. Rodgers (Univ. of Florida) report a case.

Boy, 3, had had abdominal pain, vomiting, fever, and earache for 2 weeks and had received ampicillin for 1 week for diagnosed otitis media. The drowsy child had a temperature of 39 C and exhibited marked tenderness and guarding in the right upper quadrant, with a mass palpable in the right subcostal region. The white blood cell count was 15,000/cu mm with a left shift. The bilirubin concentration was 6.8 mg/dl, with a direct fraction of 3.0 mg/dl, and the alkaline phosphatase value was 233 IU. Roentgenography and ultrasonography indicated a large, cystic mass below the liver, with no apparent calculi, and exploration showed a markedly distended gallbladder with only mild surrounding inflammation. Aspiration yielded thick, dark green bile under pressure. An operative cholangiogram showed retrograde filling of the bile ducts and no duct obstruction. Cholecystectomy was carried out. Cultures were negative. Examination of the specimen showed mild edema and minimal inflammation. The patient recovered promptly, with return of the serum bilirubin value to normal within 5 days of operation.

The most common preoperative diagnosis in these cases is appendicitis with periappendiceal abscess. The differential diagnosis also includes intussusception, volvulus, peritonitis, and pyelonephritis. Contrast roentgenography and abdominal ultrasonography may be diagnostically helpful. The cause of acute hydrops of the gallbladder in children is unknown, but bile stasis and mesenteric lymphadenitis appear to be important factors. Most children have been managed by exploration and simple aspiration or cholecystectomy.

6–6 **Cholelithiasis in Infants: Role of Total Parenteral Nutrition and Gastrointestinal Dysfunction.** Total parenteral nutrition (TPN) has become a common treatment for infants with severe gastrointestinal dysfunction. Denis R. Benjamin (Univ. of Washington) reports its use in 3 infants in whom gallstones were found at autopsy.

Female infant, aged 2 months, was seen 4 days after resection of most of the small bowel for midgut volvulus, and TPN was begun via a right internal jugular vein catheter. Persistent small bowel obstruction necessitated reexploration 3 weeks later. Peritoneal adhesions were lysed, the anastomoses were reconstructed, a Silastic catheter was placed through the gastrostomy, and vagotomy and pyloroplasty were done. Gastrostomy and oral feedings supplemented the parenteral nutrition, and the infant gradually gained weight. An episode of septicemia occurred at 2 months. Subsequently, *Salmonella* gastroenteritis occurred, and parenteral nutrition was restarted. The infant improved gradually until another episode of sepsis necessitated removal of the catheter. Parenteral nutrition was resumed after *Candida* septicemia developed. A fatal episode of *Klebsiella* sepsis ensued. The infant died

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(6–5) J. Pediatr. Surg. 18:138–140, April 1983.
(6–6) Ibid. 17:386–389, August 1982.

a year after presentation, having received parenteral nutrition for about 6 months.

Autopsy showed recent thrombus in the internal jugular vein, gram-negative sepsis, and bilateral adrenal hemorrhages. An old thrombus occluded the right internal jugular vein. Pulmonary emboli and a small infarct were seen. The kidneys showed acute tubular necrosis. The gallbladder contained numerous small, black calculi, and stones were impacted in the distal part of the common bile duct and in the cystic duct. Mild periportal fibrosis and chronic inflammation were found in the liver.

The pathogenesis of cholestasis in these patients is unclear, but the hepatobiliary abnormalities resolve soon after parenteral nutrition is discontinued and normal feeding is resumed. Gallstones are more frequent after massive ileal resection or in patients with severe small bowel disease. All the author's 3 patients had severe gastrointestinal dysfunction, 2 after massive bowel resections. Even older infants can develop this complication. Parenteral nutrition may act merely by allowing these infants to live long enough to develop cholelithiasis as a complication of gastrointestinal dysfunction.

▶ [This article and the preceding one, both dealing with gallbladder disease, highlight other studies commenting on the same issues. The first pediatric cases of hydrops of the gallbladder were reported more than 50 years ago. The pediatric disorder is distinguished by the presence of a massively distended gallbladder in the absence of stones, congenital ductal malformations, infection, or major inflammation. It has been reported from the nursery period right on up, although the average age of patients presenting with this disorder is 5 years. Most children have some preceding illness such as otitis media, upper respiratory tract infections, or gastroenteritis. This is followed by fever, nausea, vomiting, and abdominal pain that is usually in the right upper quadrant where the gallbladder should be. A right upper quadrant mass frequently can be felt in the abdomen. Because of the uncommon frequency of hydrops of the gallbladder, pediatricians and surgeons alike generally think they are dealing with atypical appendicitis. What this study from the *Journal of Pediatric Surgery* convinces me of is the fact that ultrasound should be the first and most important diagnostic test to perform after the history and physical examination. It easily will show a massively enlarged gallbladder. If the patient doesn't have hydrops but does have run-of-the-mill cholecystitis or cholelithiasis, it should be diagnostic here, too. Once you make a diagnosis of hydrops of the gallbladder, you have an important decision to make. Should the patient be operated on or not? Unfortunately, the literature won't help you much in this regard. Most patients have been operated on, but such a history need not be the correct precedent for the future. Hydrops of the gallbladder is now a recognized complication of mucocutaneous lymph node syndrome. Hydrops in association with this disorder probably does not need to be operated on because each of the described patients had a return of the gallbladder to normal size within 15 days of the diagnosis.

Total parenteral nutrition must be added to the long list of things that can cause gallstones in infancy and childhood. This list seems to be getting longer every year and now includes, in addition to total parenteral nutrition, hemolytic diseases, cystic fibrosis, malformations of the biliary tract, chronic enteric infection, Wilson's disease, metachromatic leukodystrophy, obesity, and small bowel dysfunction. There have been enough reports of gallbladder disease in patients on long-term parenteral nutrition to incriminate the latter unequivocally as an etiologic agent in the pathophysiology of this problem. Some, however, feel that parenteral nutrition is not the culprit but, rather, keeps patients with other illnesses alive sufficiently long that gallbladder disease develops as a consequence of the primary illness. The fact that this form of nutritional administration is so extraordinarily associated with gallbladder disease strikes me that there is a true cause-and-effect relationship operating here. In adults receiving total parenteral nutrition, the incidence of gallbladder disease ranges between 23% and 40%, as just one example of this relationship (Roslyn, J. J., et al.: *Gastroenterology* 84:148, 1983). Three premature babies have been described in

whom gallstones developed in association with total parenteral nutrition and the use of furosemide. The relationship between furosemide and gallstones may be merely fortuitous, but the drug is known to enhance excretion of calcium into the urine. As discussed in Chapter 7, "The Genitourinary Tract," the latter property of the drug is well-known to cause renal stones in preterm neonates. Frankly, the association between gallstones and furosemide is probably speculative, at best, at this time.—J.A.S., III] ◄

6–7 **Sonographic Findings of Pancreatitis in Children.** Arthur C. Fleischer, Paul Parker, Sandra G. Kirchner, and A. Everette James, Jr. (Vanderbilt Univ., Nashville) evaluated the size and echogenicity of the pancreas with real-time and static sonography and correlated the results retrospectively with amylase values in 17 asymptomatic children, 19 children with acute pancreatitis, and 2 with chronic pancreatitis.

A ratio of the greatest anteroposterior dimension of the body of the pancreas relative to the transverse lumbar vertebral body measurement (P/V ratio) greater than 0.3, when associated with a hypoechoic pancreatic parenchyma, was indicative of acute pancreatitis. Four patients were considered to have a false negative sonogram; 1, with a dumbbell-shaped pancreas, had a false positive sonogram.

The sensitivity of sonography in the detection of pancreatitis in children was 0.71; the specificity was 0.95. The predictive value of a positive sonogram was 0.93, whereas the predictive value of a negative sonogram was 0.78.

Although the number of patients with a dilated pancreatic duct in this study was small, an abnormally dilated main pancreatic duct may also indicate pancreatitis. The diagnostic utility of decreased pancreatic echogenicity may be limited, since in a small percentage of normal children the pancreas may be slightly less echogenic than the liver. It appears that the pancreas in chronic pancreatitis is usually small and echogenic relative to the liver. The study showed that the pancreas in children with acute pancreatitis may remain enlarged several months after the initial episode; this phenomenon would limit the use of sonography in detecting recurrent pancreatitis in children with a previous episode of pancreatitis.

The data indicate that sonography is a useful adjunct to laboratory and clinical evaluation in the detection of pancreatitis in children.

► [There are various diagnostic steps that can be undertaken if one wishes to establish the presence or absence of pancreatitis. Unfortunately, no one step will be without its false negative and false positive results and, for this reason, it is usually necessary to institute a series of investigations. Determination of the serum amylase level is usually first on the list. An elevated level is not diagnostic of pancreatitis, because a number of other things will increase it as well. Viral infections, vasculitis, hepatitis, trauma, drug reactions, renal disease, parotitis, acute salpingitis, ruptured ectopic pregnancy, macroamylasemia, opiate administration, and intestinal infarction all potentially can raise the serum amylase level. In addition to these, psychogenic self-induced hypersalivation can produce elevated serum amylase levels (Belik, J., et al.: *Pediatrics* 71:585, 1983). The ratio of renal clearance of amylase to clearance of creatinine by the kidney has been reported to be more accurate than the serum amylase level alone in the diagnosis of acute pancreatitis in adults. If you have forgotten how to make these calculations, see the report by M. R. Eichelberger et al. (*J. Pediatr. Surg.* 17:244, 1982).

(6–7) Radiology 146:151–155, January 1983.

A normal serum amylase level in no way excludes the diagnosis of pancreatitis. Sonography of the pancreas also suffers from this problem of sensitivity. However, the test does pick up most cases of pancreatitis and if the sonogram is abnormal, specificity is very high in the sense that the patient is exceptionally likely to have inflammation of the pancreas. The same can probably be said of computed tomography scanning in this regard. This, however, is an expensive way to get the same information. Endoscopic retrograde cholangiopancreatography which involves direct visualization and cannulation of the pancreatic duct is also helpful in complex cases, but is contraindicated in the acute phase of pancreatitis. In addition to all these diagnostic procedures, peritoneal lavage with biochemical studies of peritoneal fluid occasionally will establish a diagnosis of pancreatitis when all else fails.

There must be a reason behind all of the difficulty that exists in making the diagnosis of pancreatic disease. The pancreas is one of the few organs of the body that is relatively unforgiving once it is mucked up by a surgeon. It doesn't like to be operated on. I think that is the reason why God made this organ so difficult to evaluate. I think it is also the reason why he tucked it way back up against our abdominal walls.—J.A.S., III] ◄

6–8 **Vertebral Anomalies and Duodenal Atresia.** Although duodenal atresia has been associated with other alimentary and cardiovascular anomalies and with Down's syndrome, previous studies have shown a relatively low incidence of skeletal anomalies. J. D. Atwell and A. M. Klidjian (Southhampton, England) describe 35 patients with duodenal atresia seen between 1963 and 1976 who were examined to determine the incidence of musculoskeletal anomalies. "Intrinsic" duodenal atresia, with normally rotated and fixed intestines, was found in 29 patients. Six patients had "extrinsic" atresia, characterized by disturbance in intestinal rotation. Vertebral anomalies were apparent on most routine radiographs taken before or after operation. Eight infants were classified as group A with birth weight of more than 2.5 kg; 15 as group B with birth weight of 1.8–2.5 kg, or with higher weight plus a second moderately severe congenital anomaly; and 12 as group C with birth weight less than 1.8 kg, or with higher weight and a second severe anomaly. Gestation ranged from 29 weeks to full-term; birth weight ranged from 1.25 to 4.53 kg.

Thirteen patients (37%) had 16 musculoskeletal anomalies. One was in the extrinsic atresia group. Two patients had cervical lesions: 1 with fusion of the spinous processes of C2 and C3 and 1 with bilateral cervical ribs. Four had altered numbers of thoracic vertebrae and

CONGENITAL ANOMALIES ASSOCIATED WITH DUODENAL ATRESIA

Type of Congenital Anomaly	No. Patients	%
Down's syndrome	13	37%
Vertebral and musculo-skeletal	13	37%
Gastro-intestinal	9	24%
Renal	3	8.5%
Cardiovascular	3	8.5%

(Courtesy of Atwell, J. D., and Klidjian, A. M.: J. Pediatr. Surg. 117:237-240, June 1982.)

(6–8) J. Pediatr. Surg. 117:237–240, June 1982.

paired ribs: 2 with 13 and 2 with 11 thoracic vertebrae and ribs. Five had 6 lumbar vertebrae (including the patient in the extrinsic group). Three patients had sacral defects. Other musculoskeletal defects included bilateral absence of thumbs and bilateral talipes equinovarus. Other anomalies are listed in the table.

The 37% incidence reported for vertebral anomalies is similar to that found for esophageal atresia and tracheoesophageal fistula. Evidence for an early defect in embryologic development is the finding of chromosomal defects such as Down's syndrome. Thalidomide taken by the mother between the 30th and 40th days after ovulation produced duodenal atresia in the infant. The vertebral column is developing at a similar time, which suggests that factors leading to segmentation or disturbances of segmentation may be responsible for producing atresias of the alimentary tract.

► [I was not aware that there was a high association between musculoskeletal abnormalities and duodenal atresia. Most of the previously reported associations of various anomalies with duodenal atresia have not commented on this. One cannot ignore a 37% incidence, and now we will have to keep a watchful eye for vertebral abnormalities every time we see a baby with duodenal atresia.—J.A.S., III] ◄

6–9 **Abdominal Technetium Scan (A Decade of Experience).** Donald R. Cooney, Diane O. Duszynski, Edgar Camboa, Melvyn P. Karp, and Theodore C. Jewett, Jr. (Children's Hosp. of Buffalo) report that in 270 children with gastrointestinal (GI) symptoms, the indications for technetium (Tc) scanning were GI tract bleeding (165 patients), abdominal pain (99), or a history of intussusception (6). Thirty children had abnormal findings, but the remaining 240 had "normal" scans. Four of the 30 children with positive scans were not explored; the others underwent laparotomy.

Of the 26 patients who were operated on, 12 (46%) had Meckel's diverticulum; 9 had other pathologic lesions detected by the scan. Five (19%) had true "false positives," as no pathologic lesions were found. Of the 240 children with negative scans, 19 were eventually explored because of persistent symptoms or clinical findings. Two (representing <1% false negative scan results) had Meckel's diverticulum. Eleven had a negative exploration, and 6 had other lesions.

It has been observed that ^{99m}Tc-sulfur colloid has resulted in a better emission image than ^{99m}Tc-pertechnetate in actively bleeding patients, as active bleeding may cause a "washout" phenomenon. The scan does not appear to be a sensitive test in the diagnosis of all inflammatory and obstructive lesions of the GI tract. The relatively low yield of positive results in this study would suggest that more careful patient selection is needed for children undergoing abdominal technetium scanning.

Technetium scan should reliably detect about 80–90% of Meckel's diverticula; it accurately will exclude the diagnosis in more than 90% of patients. The 19% negative exploration rate of this study associated with a positive scan points out the need for cautious interpretation of positive scan results. Studies such as GI contrast radiography,

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(6–9) J. Pediatr. Surg. 17:611–619, October 1982.

endoscopy, intravenous pyelography, and computed tomography would have eliminated a number of unnecessary operations. If the patient is only mildly symptomatic and there is not a definite area of uptake, it may be wise to repeat the technetium scan before operation is performed. The main indication for operation should be the patient's clinical findings.

► [This review of abdominal technetium scans for Meckel's diverticulum is one of the largest in the medical literature and comes from the institution that first described this scanning technique 15 years ago. As you might suspect, the results of this report are favorable to the use of the scan when directed for this purpose. The experience of other institutions has not been quite as favorable. A number of false negative and false positive scan results have appeared in the literature. Indeed, this fact has resulted in concern regarding the reliability and clinical applicability of the technetium scan. The YEAR BOOK has followed the changing story of technetium scans in the diagnosis of Meckel's diverticulum for some years now. This report from Buffalo, if nothing else, serves as a defense of the technique and points out many of the reasons why the scans may have been misapplied or misinterpreted in other institutions (as well as their own). Not all Meckel's diverticula can be detected utilizing the abdominal technetium scan. It just depends on how much gastric tissue is in the Meckel's diverticulum. These authors present a few tips on how to maximize the efficiency of the procedure. They suggest making sure the patient was kept NPO (receiving nothing by mouth after midnight of the day before the procedure). This will result in a decreased size of the stomach, which is also imaged with this scan. The bladder also should be empty at the time of the scan, because the bladder also will be imaged and most Meckel's diverticula are near the bladder. All barium should be out of the bowel because this can interfere with the recording of the image. One other reason for a false scan has been referred to as the "washout" phenomenon. In situations in which the intestinal transit may be relatively rapid, the technetium excreted by the surface cells of the Meckel's diverticulum may be diluted and washed out so rapidly that a definitive positive image is not seen. Active intestinal bleeding can increase gastrointestinal motility and produce this "washout" phenomenon. Finally, the most serious concern with technetium scanning arises from overinterpretation. Even in Buffalo, 5 children were subjected to laparotomy on the basis of the scan results and mild symptomatology, yet no Meckel's diverticulum was seen. I agree that any child with gastrointestinal bleeding and abdominal pain should have a technetium scan. I have not been overly convinced from my own experience that the scans are, however, as helpful as the report above suggests. On my side are the numerous reports to the contrary, as alluded to above.

Watching the literature on abdominal technetium scanning for Meckel's diverticula is a little like watching a circus wrestling match. There generally is a lot to see, but in the end it's difficult to figure out who the winners were.—J.A.S., III] ◄

6–10 **Eosinophilic Gastroenteritis in the Pediatric Patient.** Lillian P. Kravis, Mary Ann South, and Mary Loretta Rosenlund (Univ. of Pennsylvania, Philadelphia) report that eosinophilic gastroenteritis is a diagnosis to be considered when a patient has abdominal complaints accompanied by striking peripheral eosinophilia. Two major classes have been defined: class I, in which the gut wall is infiltrated diffusely by eosinophils and in which peripheral eosinophilia is prominent, and class II, in which a circumscribed granuloma takes the form of a pseudotumor or a polyp massively infiltrated by eosinophils but unassociated with peripheral eosinophilia. A definitive diagnosis is important in this illness, because a needless exploratory operation is often performed in undiagnosed cases.

(6–10) Clin. Pediatr. (Phila.) 21:713–717, December 1982.

Black female infant, aged 2 years 10 months, with crampy intermittent abdominal pain, abdominal distention, and vomiting, had a white blood cell count of 50,000/cu mm with 54% eosinophils and eosinophilic ascites. After many studies had been made to exclude other diagnoses, including two exploratory laparotomies, a diagnosis of eosinophilic gastroenteritis was made on an antral biopsy specimen. Involved tissue did not contain unusual numbers of mast cells. Peripheral eosinophils were normal morphologically when studied by light and electron microscopy.

Intermittent courses of prednisone kept the patient relatively asymptomatic for the next 20 years, but cromolyn sodium was not effective. Immunologic studies shed no light on the etiology of the disorder. Striking elevations of IgE levels gradually decreased to normal. Of 5 offspring, only the patient was homozygous for HLA B8.

In this disorder, tissue eosinophilia may be spotty in distribution and may wax and wane, necessitating repeat biopsies for confirmation of a suspected diagnosis; the stomach seems to be the best gastrointestinal organ for diagnostic biopsy. Cromolyn sodium has been used in a small number of patients with eosinophilic gastroenteritis. Corticosteroid therapy has resulted in symptomatic relief in all but 1 reported case. The possible relationship of this disorder to atopic illness is tantalizing in that over half the patients described have one or more hallmarks of immediate hypersensitivity; however, gastrointestinal symptoms seldom are related to exacerbations of asthma, eczema, urticaria, or rhinitis.

▶ [Because reports of eosinophilic gastroenteritis in children are particularly rare, little is known of the natural history of the disorder. As far as I am aware, the case report presented in this article has the longest follow-up of a patient and tells us that this disorder is one that waxes and wanes but is not necessarily associated with a poor outcome. Eosinophilic gastroenteritis should be thought of whenever you see an individual who presents with recurrent bouts of abdominal pain, nausea, vomiting, and diarrhea and who has an elevated peripheral eosinophil count for which there is no other explanation. The gut wall may be infiltrated by eosinophils and there may be ascites with eosinophils in the ascitic fluid. If you've read Chapter 13, "The Musculoskeletal System," by now in this edition of the YEAR BOOK, you will see that eosinophilic gastroenteritis seems to bear some resemblance to eosinophilic fasciitis and eosinophilic cellulitis. Do not expect to learn any more about the etiology of these eosinophilia syndromes from the information provided in that chapter, however. Nobody seems to know exactly what is going on with these disorders.

The eosinophil seems to be insinuating itself into everything these days. Intraepithelial eosinophils may be a marker of gastroesophageal reflux because they commonly are seen in esophageal biopsies in this disorder (Winter, H. S., et al.: *Gastroenterology* 83:818, 1982). The nice part about this approach to making a diagnosis of esophageal reflux is that it is highly sensitive in the sense that approximately 95% of children who have gastroesophageal reflux will show these changes on biopsy. Also, the patient does not have to be refluxing actively at the time the studies are done as distinguished from every other test of esophageal reflux. The only other disorder associated with increased numbers of intraepithelial eosinophils is the very rare syndrome of allergic gastroenteropathy that is marked by peripheral eosinophilia, hypoalbuminemia, and a diffuse eosinophilic infiltrate of the intestine. The latter disease has many features in common with the entity eosinophilic gastroenteritis discussed above. However, allergic gastroenteropathy is a much more fulminant process that brings the patient quickly to a doctor because of the profound edema that results from the hypoalbuminemia and hypogammaglobulinemia.

We tend to think of eosinophils as just being indicative of some kind of simple allergy. That concept is now classifiable as a myth, just a bit of medical gossip grown old. The story just isn't that simple.—J.A.S., III] ◀

6–11 **Management of Perforated Appendicitis in Children: The Controversy Continues.** Appendiceal perforation still occurs in up to 45% of cases of appendicitis; its proper management remains controversial. Marshall Z. Schwartz, David Tapper, and Robert I. Solenberger devised a specific treatment plan for perforated appendix in children (table) and applied it to 143 patients at two centers between 1976 and 1979. Appendectomy is done in all cases, and if perforation is found at operation, parenteral antibiotic therapy is begun in the operating room. Gentamicin, ampicillin, and clindamycin are administered. Limited debridement of the area surrounding the perforation is done before the peritoneal cavity is copiously irrigated with cephalothin in saline. Parenteral antibiotic therapy is continued for at least 9 days regardless of the patient's course.

None of the 143 patients managed in this way died. The rate of significant complications was 7.7%. Six complications were attributable to infection. Four patients with pelvic phlegmons were adequately managed with antibiotics. There were no intraperitoneal abscesses. Two patients developed wound infection after discharge.

Morbidity has been less with this management than in other series of cases of perforated appendicitis in children. Many residents and faculty surgeons participated in the trial. The rate of infectious complications was less than 5%. It appears that intensive primary treatment can reduce common adverse sequelae of perforated appendix in children significantly.

6–12 **Rational Use of Antibiotics for Perforated Appendicitis in Childhood.** Medical records of all patients at one pediatric hospital who underwent appendectomy for gangrenous or perforated appendicitis from January 1975 to September 1980 were reviewed by Irving

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PROTOCOL FOR MANAGEMENT OF PERFORATED APPENDIX IN CHILDREN

1. Administer fluids, control hyperthermia, and administer antibiotics (gentamicin 5 mg/kg/24 h, ampicillin 100 mg/kg/24 h, clindamycin 40 mg/kg/24 h) on admission.
2. Explore peritoneal cavity via right lower quadrant incision.
3. Perform appendectomy in all cases.
4. Perform limited peritoneal debridement.
5. Irrigate peritoneal cavity with cephalothin solution (4 g/l).
6. Place penrose drains in pelvis and right pericolic space, which exit through the lateral margin of the wound.
7. Close the muscle layers, Scarpa's fascia, and skin around the drains with absorbable suture.
8. Encourage postoperative activity and position at will.
9. Continue parenteral antibiotics for nine days.
10. Remove transperitoneal drains from the 7th to the 9th postoperative days.
11. Discharge patient generally on 10th postoperative day.

(Courtesy of Schwartz, M. Z., et al.: Ann. Surg. 197:407–411, April 1983.)

(6–11) Ann. Surg. 197:407–411, April 1983.
(6–12) J. Pediatr. Surg. 17:494–500, October 1982.

B. David, James R. Buck, and Robert M. Filler (Hosp. for Sick Children, Toronto). Excluded from the study for various reasons were 21 patients. Data obtained for the remaining 300 patients included age, sex, pathology, surgical technique, antibiotic regimen, duration of ileus, postoperative complications, and length of hospitalization.

The mean age of the 176 boys and 124 girls was 8.9 years. Of the 300 patients, 30 had gangrene of the appendix (stage I), 143 had local perforation (stage II), and 127 had generalized peritonitis (stage III). Patients were grouped according to their antibiotic regimen. Group A (86 patients) was given ampicillin, gentamicin, and clindamycin; ampicillin or gentamicin, or both, was given to 46 children (group B); 168 patients received no antibiotics (group C). Intraoperative peritoneal specimens for cultures were taken immediately upon entering the abdomen in 282 cases and the results of bacteriologic studies and wound infection cultures are shown in the table.

Wound infection was reduced significantly in group A (10%) and group B (24%) of stage II patients, compared with group C (43%). In stage III patients, infective complications were reduced markedly for group A (2%), compared with group B (36%) and group C (58%). Significantly, intraperitoneal abscesses occurred in 5%, 18%, and 33%, respectively. Of the 270 stage II and stage III patients, 191 had a peritoneal drain. The presence of intra-abdominal drains was not significantly associated with abscesses except in group A patients, where the drain increased the risk of abscess. The presence of a drain (subcutaneous in 56 patients, peritoneal in 191) did not influence the incidence of wound infection.

An appropriate antibiotic program includes drugs active against gram-negative and gram-positive organisms, aerobes, and anaerobes. The presence of gram-positive aerobes (enteric streptococci sensitive to ampicillin), gram-negative aerobes (sensitive to gentamicin), and anaerobes (sensitive to clindamycin) in combination recommends the choice of these three antibiotics. Full-dose therapy for 5–7 days ap-

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BACTERIOLOGY OF PERITONEAL AND WOUND INFECTION CULTURES

Bacteriology	Peritoneal Cultures 282 of 300		Wound Infection Cultures 73 of 94	
	No. of Isolates	% of Patients Cultured	No. of Isolates	% of Patients Cultured
E. coli	191	67	52	71
Streptococci	142	50	30	41
Bacteroides	67	24	23	32
Clostridia	49	17	11	15
Pseudomonas	45	16	12	16
Klebsiella	12	4	5	7
Staphylococci	11	4	11	15
Other aerobes	29	10	4	6
Other anaerobes	11	4	3	4
No growth	45	16	1	1
No. of organisms/patient	2 (0-6)		2 (0-4)	

(Courtesy of David, I. B., et al: J. Pediatr. Surg. 17:494–500, October, 1982.)

pears safe and effective. Patients with local perforation or generalized peritonitis (stages II and III) who were treated with these three antibiotics had a 6% wound infection rate and 5% incidence of abscess.

▶ [This article and the preceding one really seem to make some sense out of the issues involved with the management of perforated appendix in children. The surgical literature has waffled back and forth with respect to when to operate, to take out the appendix immediately or simply drain the abdominal cavity, to irrigate or not to irrigate, and on and on. I normally don't like rigid protocols for the management of anything. They always seemed as stiff as something that fell off Edgar Bergen's lap. With respect to the report of Schwartz et al., however, I think their protocol for the management of perforated appendix is about as good as any that can be constructed. Basically, they suggest operating on everyone, putting drains in everyone, irrigating the abdominal cavity in everyone, and using antibiotics in everyone as well. The fact that they had very low morbidity and no mortality in their series attests to the usefulness of this approach. Whether they could have gotten by with a lesser approach cannot be answered because they did not perform any randomized trials in this report. The study of David et al. and the table presented above tell us what organisms we are likely to find once the appendix is perforated. Any one of a number of different combinations of antibiotics should be effective if you remember to cover anaerobes as well as the usual other group of gram-negative organisms.

With respect to other surgical issues, R. W. S. Yeung et al. (*J. Pediatr. Surg.* 17:347, 1982) tell us not to get too excited by postoperative fevers. The "adult" approach to a postoperative fever includes doing a battery of tests including a complete blood count, blood culture, urinalysis, and chest x-ray study. Many times, this gets carried over into the surgical practice of pediatrics when surgical house officers fresh off the adult services start to care for children. Yeung found that only 5% of all postoperative fevers in children had a documented infectious cause. In all the cases, physical examination suggested the actual cause for the complication. The message in this report was to put a little reason into practice and not just automatically order tests. With respect to other tests and the actual diagnosis of acute appendicitis, an increasing number of stones are being thrown at the utility of the white blood cell count. Daehlin (*Acta Chir. Scand.* 148:291, 1982) found that the white blood cell count helped very little in the first 3 years of life in deciding if a child with abdominal pain had acute appendicitis. In a review of a large number of patients going to the operating room for acute appendicitis, Miskowiak et al. (*Dan. Med. Bull.* 29:210, 1982) found that the predictive value of an elevated white blood cell count in adults was only 55% predictive. Its predictability in children was even less at 33%. On the other hand, a normal white blood cell count excluded appendicitis in 89% of cases. In children, this number fell to only 70%. No matter what way you look at all these numbers, I think you would come to the conclusion that you wouldn't hang your hat on the white blood cell count to make up your mind whether or not a patient ought to go to the operating room.—J.A.S., III] ◀

6–13 **Acute Intussusception: A Classic Clinical Picture?** S. Fanconi, D. Berger, and P. P. Rickham (Univ. of Zurich) retrospectively reviewed the cases of 57 patients with acute intussusception treated surgically between 1972 and 1979.

The classic symptomatology, which may appear during the course of the illness or may not occur at all, is as follows: a previously healthy boy (60%) younger than age 3 years (91%) has intermittent colicky pain (81%), vomiting (93%), a palpable abdominal mass (72%), and rectal bleeding (72%). However, 20–30 hours after onset of the illness, only 23 patients had such typical signs. Blood per rectum was present in the first hours of illness in only 5%, vomiting in 44%, and colicky pain in 33.5% of the patients (Table 1). Changes in bowel action were present in 46 patients: 15 had passed no feces, 14

(6–13) Helv. Paediatr. Acta 37:345–352, 1982.

had diarrhea, and 17 had passed mucus. During the course of the intussusception, 24.5% of the patients had diarrhea.

Only a few children drew up their legs with obvious pain during examination. The abdomen was usually soft (80.5%) but somewhat tender (63%). There was little muscular resistance over the area of the intussusception in 35% of the patients; 72% had pathologic bowel sounds. Rectal examination showed blood on the finger in 34 cases (Table 2).

Radiologic examination was performed on 42 patients. In 23, the plain film showed a nonspecific picture of intestinal obstruction; in 3 an abdominal mass was suggested. A barium enema, performed in 17 atypical cases, showed an intussusception in 15.

One patient died, and 7 needed a bowel resection; 9 intussusceptions were difficult to reduce, 32 were easy to reduce, and 9 had spontaneous reduction. The doctor's delay was about 15 hours in the difficult reduction group and 35 hours for patients who needed a bowel resection. The severity of the intussusception could not be predicted

TABLE 1.—SYMPTOMS AT ONSET OF ACUTE INTUSSUSCEPTION

	No.	%
Vomiting	25	44
Colicky pain	19	33.5
Refusal of food	4	9
Increased crying	4	7
Bloody stool	3	5
Fever	1	1.5
Total	57	100

(Courtesy of Fanconi, S., et al.: Helv. Paediatr. Acta 37:345–352, 1982.)

TABLE 2.—SYMPTOMS ON ADMISSION

	No.	%
Reduced general condition	47	82.5
Apathy	42	73.5
Palpable abdominal mass	41	72
Pathologic auscultation	41	72
Dehydration	37	65
Abdominal tenderness	36	63
Blood on examining finger	34	59.5
Pallor	30	53
Muscular resistance	20	35
Abdominal distension	12	21
Normal abdomen	16	18
Upper respiratory tract infection	5	9

(Courtesy of Fanconi, S., et al.: Paediatr. Acta 37:345–352, 1982.)

from the clinical picture. An initial error on the patient's first visit to the physician affected treatment in 59.5%.

A high degree of awareness is needed to diagnose intussusception during the first hours of illness. The accuracy of the diagnosis is particularly important because reducibility and resection rate depend directly on the duration of symptoms.

▶ [I once knew someone who drank wine to sober up. He should have read this report. It's enough to sober anyone up. What it says is that there really is no classic picture for intussusception and the only way to diagnose this potentially lethal problem is just to have a heightened awareness of all of its modes of presentation. It wouldn't hurt to think of this diagnosis every time you saw a child with any symptom referable to the abdomen.—J.A.S., III] ◀

6–14 **Continuous Elemental Enteral Alimentation in Treatment of Children and Adolescents With Crohn's Disease.** Claude L. Morin, Michel Roulet, Claude C. Roy, Andrée Weber, and Normand Lapointe (Univ. of Montréal) treated 10 consecutive patients aged 8½–19 years who had active, symptomatic Crohn's disease; continuous elemental enteral alimentation (CEEA) was administered for 3 weeks, and for 1 year thereafter the patients received low doses of prednisone. Uncomplicated Crohn's disease was newly diagnosed in all patients. Alimentation consisted of intragastric infusion of Standard Vivonex, given 22 hours a day using a peristaltic pump. At least 50 kcal/kg were given, the average amount being 80.5 kcal/kg. Vitamin K, folic acid, elemental iron, and Intralipid also were given, as was vitamin B_{12}.

Treatment was well tolerated by all patients. No renal, hepatic, or metabolic complications developed. Clinical remission occurred in all patients. Symptoms resolved within 7–12 days of the start of CEEA. In 1 child a fistula healed during CEEA therapy, but subsequently reopened. All patients had significant weight gain during treatment, and all but 1 of the 9 followed up continued to gain weight in the first 3 months after CEEA. An increase in arm muscle circumference and in triceps skinfold measurements also was noted. The hemoglobin level and serum albumin concentration rose substantially in the months after CEEA therapy began. A significant increase in the T lymphocyte percentage occurred also. There were no significant changes in fecal bile acid values or in the fecal microflora.

Three weeks of CEEA therapy induced clinical remission in these children and adolescents with active Crohn's disease. No other treatment was necessary. The nutritional status improved significantly during and after treatment. This alternative approach to the treatment of Crohn's disease is especially important for adolescents, whose body image may be disturbed by side effects of corticoid therapy.

▶ [Dr. David Hitch, Associate Professor of Surgery and Pediatrics, State University of New York at Syracuse, comments on this and the following article:

"These studies emphasize (1) the vagaries of Crohn's disease and (2) the importance of adequate nutrition. Specifically enteral and parenteral nutrition should be considered active therapy. The standard against which this study must be compared is the placebo group of the National Cooperative Crohn's Disease Study (Mekhjian, H. S., et al.: *Gastroenterology* 77:898–906, 1979). Thirty percent of the patients in the

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(6–14) J. Parent. External Nutr. 6:194–199, June 1982.

latter group attained and maintained disease quiescence at least once during the same period. Chi-square analysis of these groups supports the efficacy of continuous enteral alimentation to achieve and maintain remission when compared to either placebo or steroid therapy as reported in the Cooperative Study. Unfortunately, no study has shown that remission can be maintained."] ◄

6–15 **Course and Prognosis After Colectomy and Ileostomy for Inflammatory Bowel Disease in Childhood and Adolescence.** Jeffrey S. Hyams, Richard J. Grand, Arnold H. Colodny, Samuel R. Schuster, and Angelo Eraklis (Harvard Med. School) reviewed the course of 32 young patients with inflammatory bowel disease after bowel resection between 1963 and 1978. Eighteen had ulcerative colitis and 14, Crohn's disease. Age range at operation was 9 to 21 years. Indications for operation included severe ulcerative colitis or fistulas, severe colitis, hemorrhage, and growth failure related to Crohn's disease. The patients represented about 13% of all those seen at the authors' institution in the review period with inflammatory bowel disease. Treatment before operation included prednisone and usually sulfasalazine. Patients with severe colitis received parenteral corticosteroid treatment and broad-spectrum antibiotics and often parenteral nutritional support.

Proctectomy was done at colectomy in 72% of patients with ulcerative colitis and 64% of those with Crohn's disease. Significant complications occurred in about 60% of cases. Recurrences were found in 42% of patients with Crohn's disease but not in patients with ulcerative colitis. Mean follow-up in both groups was 5 years. Sexual activity was unchanged or improved in sexually active patients after operation. None of the males became impotent. Three fourths of the patients felt that the operation had improved the quality of their lives. All 7 patients with bowel disease for longer than 5 years preoperatively felt that they had improved.

Pediatric patients have complications after operation for inflammatory bowel disease about as often as adults do, and the high recurrence rate of Crohn's disease is similar to that in some adult series. Despite these negative factors, most young patients in this study felt that their lives had been improved by colectomy and ileostomy.

► [Doctor Hitch continues to comment:
"The authors have used stringent criteria for colectomy and ileostomy in 32 patients with colonic inflammatory bowel disease. They confirm that surgical therapy is associated with significant complications as well as improvement in the quality of life. These data are in accord with other reports (Meyers, S., et al.: *Gastroenterology* 78:1–6, 1980; and Sales, D. J., and Kirsner, J. B.: *Arch. Intern. Med.* 143:294–299, 1983). Patients with ulcerative colitis should be cured by proctocolectomy, whereas patients with Crohn's disease will have recurrence. Additionally, patients with inflammatory bowel disease are at risk for bowel carcinoma. Those patients with ulcerative colitis have a 65% 40-year cumulative incidence, while those with Crohn's disease have a 33% risk. Balancing the risks associated with surgery and those associated with nonsurgical therapy, surgery looks good."] ◄

6–16 **Oral Rehydration Therapy of Infantile Diarrhea: Controlled Study of Well-Nourished Children Hospitalized in the United States and Panama.** Since its use in cholera, oral rehydration ther-

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(6–15) J. Pediatr. Surg. 17:400–405, August 1982.
(6–16) N. Engl. J. Med. 306:1070–1076, May 6, 1982.

apy has been widely employed in the treatment of other types of acute diarrhea, including those due to enterotoxigenic *Escherichia coli* and rotavirus. Mathuram Santosham, Robert S. Daum, Ludwig Dillman, Jose L. Rodriguez, Sarah Luque, Rebecca Russell, Miguel Kourany, Robert W. Ryder, Alfred V. Bartlett, Allan Rosenberg, Abram S. Benenson, and R. Bradley Sack undertook a randomized study of oral glucose-electrolyte solution administration in well-nourished children aged 3 months to 2 years who were hospitalized with acute diarrhea. Fifty-two infants in the United States and 94 in Panama received a solution containing 90 mmole of sodium per L, one containing 50 mmole/L, or standard intravenous therapy.

All children but 1 were treated successfully. No intravenous treatment was necessary in 89% of children treated by oral rehydration. All 6 children with hypernatremia at admission were managed successfully with oral therapy alone. The 1 treatment failure was in a child with severe hyponatremic dehydration who received oral therapy initially. Periorbital edema developed in 2 children given oral therapy in considerable excess of the diarrheal output. Three children had complications from intravenous hydration.

Oral administration of glucose-electrolyte solutions containing 50 or 90 mmole of sodium per L is an effective and safe means of treating well-nourished children hospitalized with acute diarrhea. This approach can replace intravenous hydration in most such children. The cost of oral treatment is lower than that of intravenous hydration. Much of the treatment can be given by the mother without interrupting feeding, and the discomfort of intravenous treatment is avoided.

▶ [Dr. Laurence Finberg, Professor and Chairman, Department of Pediatrics, State University of New York, Downstate Medical Center, comments:

"The use of oral electrolyte-glucose solutions in managing patients with diarrheal disease is a technique that has become prominent in certain of the developing countries over the past 10 years, thanks to energetic efforts from the World Health Organization (WHO). Whereas this is not truly new, the application is, and newer knowledge about coupled transport of glucose and sodium in the intestine has been incorporated. It has been highly effective in controlling one of the most serious problems of developing countries. The article by Santosham and associates is another study designed in part to allay the concerns of the United States pediatricians concerned about the development of hypernatremia from the high-sodium solutions (90 meq/L) recommended by the WHO.

"One of the problems with the literature on the subject is that a number of the authors have not been careful to distinguish between *rehydration* and *maintenance* of hydration. The high-sodium solution (90 meq/L) has had wide use as a rehydration solution, for which it is eminently suited and highly successful. When it has been used properly as a maintenance solution (or preventative), it has been used in association with other fluid intake, thus effectively diluting the sodium to somewhere between 50 and 60 meq/L of total administered fluid.

"The study reported in this paper purports to compare a high-sodium (90 meq/L) with a low-sodium (50 meq/L) solution for *rehydration*. In fact, both rehydration and maintenance phases are incorporated in the design, and the study does not really warrant the conclusion stated in the abstract. Careful reading of the methods and results show that the authors did something different from comparing these two solutions by themselves; there were only mixed regimens. Further weakness in this particular study is that the patients who received only oral rehydration were not really very sick, particularly those in the United States. These patients might have done well on virtually any glucose-electrolyte solution. What is wanting is a solution or solutions or alternative methods of administration that protect the most vulnerable infant, not just the mildly ill.

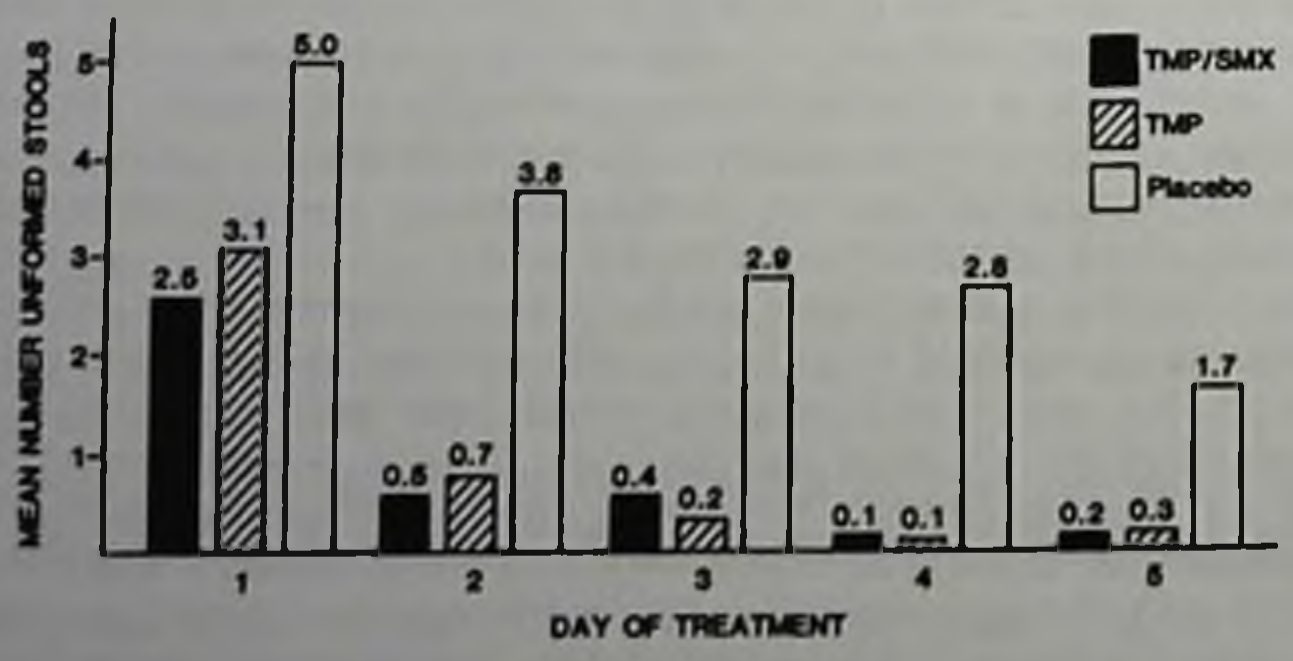
"We are, I believe, rapidly approaching that state of affairs. The more recent literature continues to clarify these issues. Oral therapy should be an important part of the armamentarium of every pediatrician. It is to be expected that pediatricians will have a full understanding of what they are doing as they use it. Most will then either choose two or more solutions for specific uses or know how to modify the administration of a single solution where economic reasons so dictate."] ◀

6–17 **Treatment of Traveler's Diarrhea With Trimethoprim-Sulfamethoxazole and With Trimethoprim Alone.** Traveler's diarrhea, usually associated with *Escherichia coli* and other enteropathogens, can be severe and may be accompanied by such complications as dehydration and dysentery. Herbert L. DuPont, Randall R. Reves, Emma Galindo, Peggy S. Sullivan, Lindsey V. Wood, and Jaime G. Mendiola compared the effect of trimethoprim (TMP) alone and combined with sulfamethoxazole (SMX) in the treatment of acute diarrhea in 110 young adults from the United States studying in Mexico. The students, who were enrolled within 48 hours of onset of illness, were given 160 mg TMP with 800 mg SMX, 200 mg TMP alone, or placebo twice daily for 5 days, in a double-blind manner. Either *E. coli* or *Shigella* or no identifiable agent was isolated.

The frequency of unformed stools passed during treatment is shown in Figure 6–1. Both active treatments appeared to be effective, reducing diarrhea, abdominal cramps or pain, and nausea. In patients with *E. coli*-induced illness, recovery within 72 hours occurred more often with TMP alone than with TMP/SMX therapy. Both active treatments reduced the duration of diarrhea in all categories of illness (table). About half of the placebo patients continued to have diarrhea after 5 days or deteriorated clinically during the trial. Only 3 treatment failures occurred in the TMP group and 2 in the TMP/SMX group. The drugs were well tolerated. Trimethoprim therapy was discontinued in 1 patient because a rash developed.

Both TMP/SMX and TMP alone were effective in treating traveler's diarrhea resulting from a variety of causes. Bismuth subsalicylate may be adequate for mild diarrhea without fever. Single-dose tetracycline probably will not prove to be as effective as TMP or TMP/

Fig 6–1.—Mean number of unformed stools passed during 5 days of treatment for traveler's diarrhea in 110 patients. (Courtesy of DuPont, H. L., et al.: N. Engl. J. Med. 307:841–844, Sept. 30, 1982.)



(6–17) N. Engl. J. Med. 307:841–844, Sept. 30, 1982.

MEAN NUMBER OF HOURS FROM INITIATION OF TREATMENT TO PASSAGE OF LAST UNFORMED STOOL, ACCORDING TO GROUP AND CAUSE OF DIARRHEA

TREATMENT GROUP	ALL CAUSES		*E. coli* STRAIN						SHIGELLA		UNKNOWN	
			HEAT-STABLE/ HEAT-LABILE		HEAT-STABLE		ALL STRAINS					
	students *	*hours* †	*students* *	*hours* †	*students* *	*hours* †	*students* *	*hours* †	*students* *	*hours* †	*students* *	*hours* †
TMP/SMX	37	29.2	6	31.2	8	37.6	18	40.1	9	15.7	8	22.5
TMP	38	30.7	9	24.3	8	39.6	19	31.2	9	32.6	9	17.9
Placebo	35	92.8	8	99.2	8	97.1	17	93.6	5	109.6	10	76.6

*Number of students in each group.
†Mean number of hours from beginning of treatment to passage of last unformed stool.
(Courtesy of DuPont, H. L., et al.: N. Engl. J. Med. 307:841–844, Sept. 30, 1982.)

SMX. Diarrhea not responding to these drugs may be caused by *Campylobacter* or an intestinal parasite.

▼ [This is the best thing that has come along for the prevention and treatment of traveler's diarrhea since Pepto-Bismol. Please refer to Chapter 4, "Dentistry and Otolaryngology," in this YEAR BOOK, for an update on trimethoprim-sulfamethoxazole.]

am not sure whether this drug combination or Pepto-Bismol is the best route to go for children. Each has their own set of problems, which should be relatively minor when the drugs are used in the appropriate amounts. Pepto-Bismol does contain an absorbable salicylate. Children have been found to absorb over 90% of the calculated amount of salicylate in the Pepto-Bismol. If you take large doses of Pepto-Bismol, you can run into problems with salicylate toxicity. Obviously, anyone who is allergic to salicylate should avoid this like the plague. The article on traveler's diarrhea abstracted above was accompanied by an excellent editorial that is well worth reading (Gorbach, S. L., et al.: *N. Engl. J. Med.* 307:881, 1982).—J.A.S., III] ◀

6–18 **Lubricant Versus Laxative in the Treatment of Chronic Functional Constipation of Children: A Comparative Study.** Treatment failures are frequent in children with chronic functional constipation (CFC), but failures usually are attributed to poor patient compliance. J. M. Sondheimer and E. P. Gervaise (SUNY, Upstate Med. Center, Syracuse) evaluated treatment of CFC in a highly supportive environment with either mineral oil, which is a stool lubricant, or Senokot, which is an anthraquinone cathartic, in 37 patients aged 3–12 years. Nineteen patients with a mean age of 6.3 years were treated with mineral oil by mouth twice daily in doses adequate to induce loose stools and leakage of oil per rectum. After the first week the dose was reduced until oil leakage ceased. This dosage was continued for at least 3 months. Eighteen patients with a mean age of 8.1 years received Senokot tablets or syrup in doses sufficient to induce at least one bowel movement a day for 2 weeks, and this dose was maintained for 3 months before tapering.

Compliance was similar in the two treatment groups. Neither group had significantly increased the mean fiber intake at follow-up. All patients treated with mineral oil and all but 2 in the Senokot group had at least one daily bowel movement at 1 month, and all patients treated with mineral oil and all but 5 in the Senokot group had daily movements at 3 months. More Senokot-treated patients had daily involuntary fecal soiling. At the latest follow-up, 55% of patients treated with mineral oil and 22% of those given Senokot had discontinued regular medication successfully. Another 33% of the Senokot-treated patients had discontinued regular treatment because of unacceptable symptom control.

Mineral oil has several advantages over senna in the treatment of CFC using a supportive, symptom-oriented approach. Better symptom control is obtained with fewer and later relapses. Weaning from treatment is easier with mineral oil. Further prospective studies are needed to evaluate the importance of other medications and elements commonly included in multifaceted programs for CFC.

▶ [This study legitimizes the approach involving the use of mineral oil which most of us have employed in preference to laxatives. I have always viewed laxatives as sort of forcing children to have BMs while mineral oil let them have their number 2's. The latter seemed more closely aligned by nature's way. Although mineral oil is perhaps messier, it sure works for functional constipation.

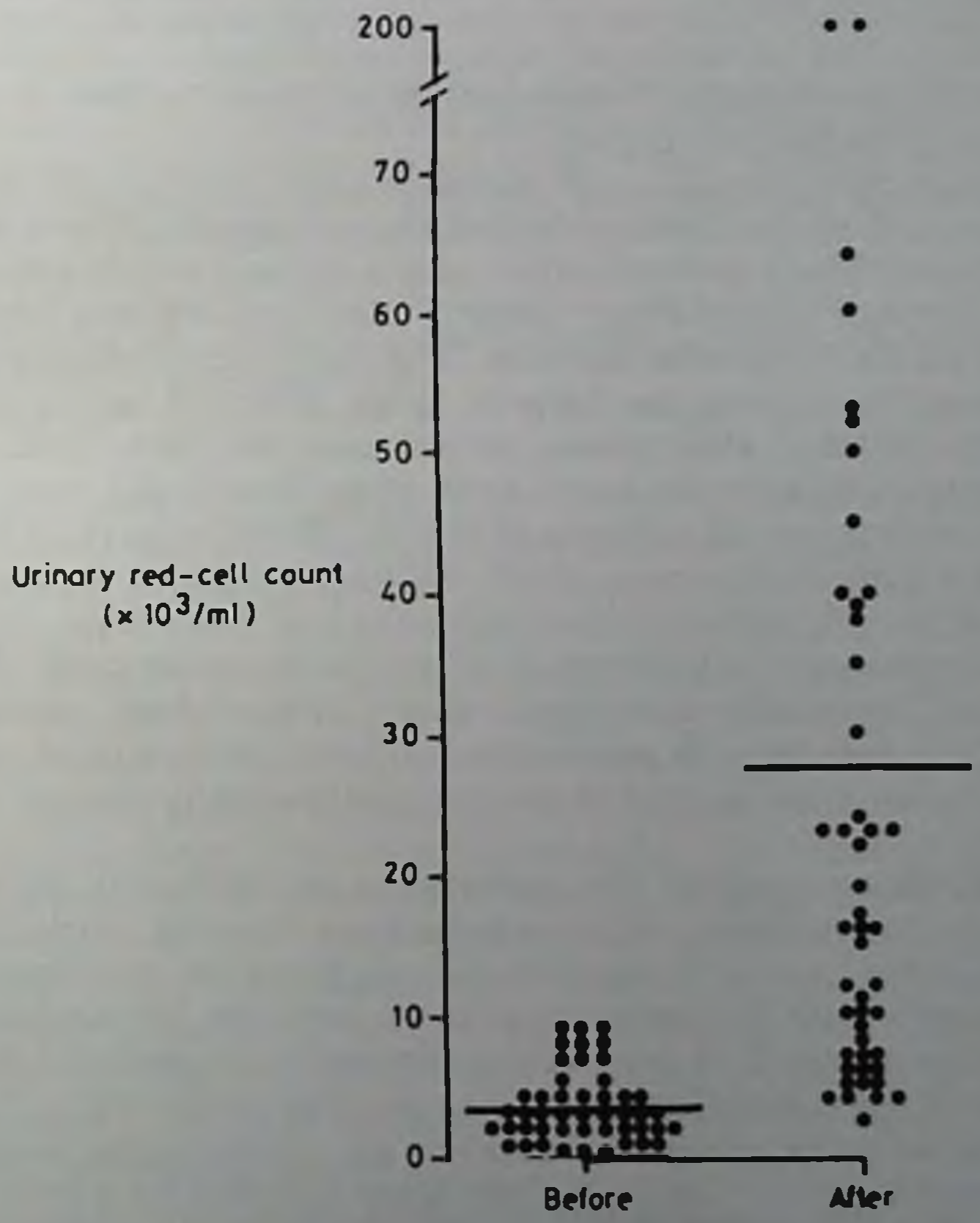
The use of laxatives, lubricants, and high fiber diets is rampant in this country—perhaps a reflection of the national philosophy of "leaving no stern untoned."—J.A.S., III] ◀

(6–18) J. Pediatr. Gastroenterol. Nutr. 1:223–226, 1982.

7. The Genitourinary Tract

7–1 **Urinary Red Cell Morphology During Exercise.** Hematuria has been found, with and without proteinuria and cylinduria, after a wide range of exercises. Recent studies have suggested that exercise hematuria arises from the lower urinary tract, and cystoscopy has shown bladder lesions. Robert G. Fassett, Julie E. Owen, Jacinth Fairley, Douglas F. Birch, and Kenneth F. Fairley (Melbourne) used phase-contrast microscopic study of midstream urine samples to determine the site of origin of exercise-induced hematuria. Samples were collected from 1 female and 47 male subjects aged 8–45 years

Fig 7–1.—Urinary red blood cell counts before and after exercise. (Significance of rise after exercise, $P < .0005$.) (Courtesy of Fassett, R. G., et al.: Br. Med. J. 285: 1455–1457, Nov. 20, 1982.)



(7–1) Br. Med. J. 285:1455–1457, Nov. 20, 1982.

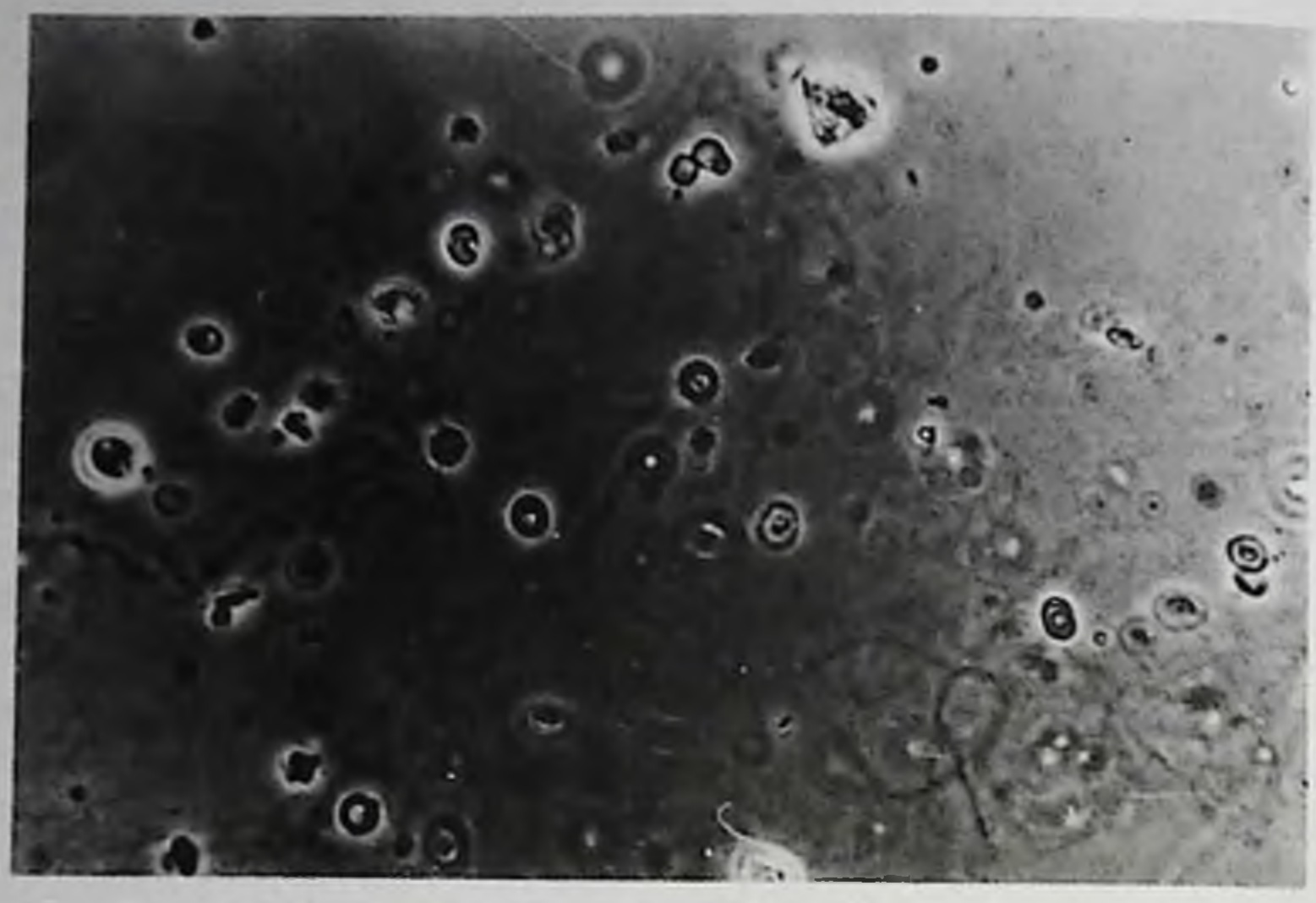


Fig 7–2.—Glomerular hematuria, showing dysmorphic red blood cells varying in size and shape. Phase contrast, ×1200 (original magnification). (Courtesy of Fassett, R. G., et al.: Br. Med. J. 285:1455–1457, Nov. 20, 1982.)

before and after a 9-km or 14-km run. Minor abnormalities were present in 6 samples before running.

Eleven samples showed 1+ proteinuria and 7, 2+ proteinuria after exercise, and 1 of the latter samples showed pyuria. Three subjects had a trace of blood after exercise, and 2 showed 1+ blood on Bili-Labstix testing. Thirty-three subjects had urinary red blood cell counts above 8,000/ml after exercise (Fig 7–1). Nineteen subjects had counts more than twice the highest value observed before exercise, over 20,000 cells/ml. Postexercise proteinuria and hematuria clearly were related. Urinary red blood cells were dysmorphic both before and after exercise in all subjects (Fig 7–2). The 2 subjects with postexercise red blood cell counts of 200,000/ml also had 2+ proteinuria and red blood cell casts. Of 8 subjects who had more than 100 casts/ml before running, all had hyaline or hyaline-granular casts. Ten had red blood cell casts after exercise. Urinary nucleated cell counts were increased after exercise in most subjects. Little change in urinary pH was noted after exercise, and there was no significant change in urine osmolality.

These findings confirm the occurrence of increased glomerular bleeding in most subjects after long-distance running. Some runners may have considerable hematuria accompanied by proteinuria and red blood cell casts. The presence of casts need not be assumed to be due to intrinsic renal causes. If nonglomerular hematuria develops after long-distance running, cystoscopy may be warranted.

▶ [The phenomenon of proteinuria, hematuria, and cylinduria after exercise has been documented, but there has been disagreement regarding the origin of urinary blood cells. Most of us learned early in our medical training of the complication of hemoglobinuria in individuals who stamped about in military uniforms, the so-called march hemoglobinuria. However, it was one of our British colleagues, a certain W. Collier, who in 1907 first described the fact that common exercise could induce uri-

nary abnormalities of the type described in this study. Indeed, this sort of "athletic pseudonephritis" probably occurs in the vast majority of adults and (by inference) children who are relatively heavy exercisers, especially our joggers. The pervasive nature of the latter sport, if it is such (see previous recent YEAR BOOKS for comments extolling the negative virtues of the excessive utilization of the fixed number of heartbeats we are born with) means that more than occasionally we will find urinary sediment abnormalities on routine urinalyses of apparently healthy children. Moreover, we now learn from this study by Fassett et al. that the urine sediment changes reflect a glomerular origin to the sediment abnormalities. These investigators resorted to the use of phase-contrast microscopy to document the urinary abnormalities. The value of this technique is that it easily permits visualization of red blood cell morphology. Glomerular disease causes dysmorphic red blood cells. Bladder pathology usually does not alter red blood cell morphology. Thus, if you just happen to have several thousand dollars worth of this equipment sitting around your office laboratory, you can tell if the upper or lower urinary tract is the culprit. Although phase-contrast examination of the urine sediment has been considered necessary for such morphological study, our neighbors from Germany tell us that by adding a little dye to the urine ("Sedicolor"), we all can use our routine light microscopes to examine urinary erythrocyte structure satisfactorily (Hauglustaine, D., et al.: *Ann. Intern. Med.* 98:1027, 1983). This obviously is a simple but nonetheless powerful tool in the differential diagnosis of hematuria. It goes without saying that the presence of casts, together with dysmorphic red blood cells, strengthens the likelihood of the glomerulus being the culprit, while the addition of leukocytes to the picture in the urinary sediment suggests interstitial nephritis.

Fortunately, exercise hematuria is one of the few glomerular causes of sediment abnormalities that is apparently totally benign. We still don't know when in the course of a vigorous workout this interesting finding is likely to occur, nor do we know if hematuria precedes the more rare but disastrous acute tubular necrosis that has been described in long-distance runners. Finally, a pearl to remember is that many marathon runners will have hematuria that is missed by routine "dipsticking." These are the persons who ingest so much fruit juice that they consume massive quantities of ascorbic acid, which even though it may not prevent the common cold, may cause a false negative dipstick result for hemoglobin or red blood cells. Ascorbic acid interferes with the peroxidation-dependent reaction on which the chemical color change in the dipstick is brought about.

The lesson to be learned from all of this is that as you shake your bootie (Nike or otherwise), you also are going to be rattling your kidneys.—J.A.S., III] ◀

7–2 **Bladder Capacity (Ounces) Equals Age (Years) Plus Two Predicts Normal Bladder Capacity and Aids in Diagnosis of Abnormal Voiding Patterns.** Robert M. Berger, Max Maizels, George C. Moran, James J. Conway, and Casimir F. Firlit (Northwestern Univ.) devised a formula for predicting bladder capacity from chronological age and tested it in 132 children without significant bladder disease or clinical voiding abnormality and in 68 children with significant clinical voiding pattern abnormalities. Bladder capacity was determined at cystoscopy or nuclear cystography. The bladder capacity in milliliters equaled 32 times age in years; a simplified formula is bladder capacity in ounces equals age in years plus 2. Mean bladder capacity appeared to plateau by age 9 years. The findings in children with voiding abnormalities are shown in Figure 7–3. Children with infrequent voiding had larger bladder capacities than predicted normal, whereas those with frequency or enuresis had smaller than predicted-normal capacities.

Bladder capacity correlates linearly with age from birth to 11 years. A knowledge of bladder capacity can expedite urodynamic

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(7–2) J. Urol. 129:347–349, February 1983.

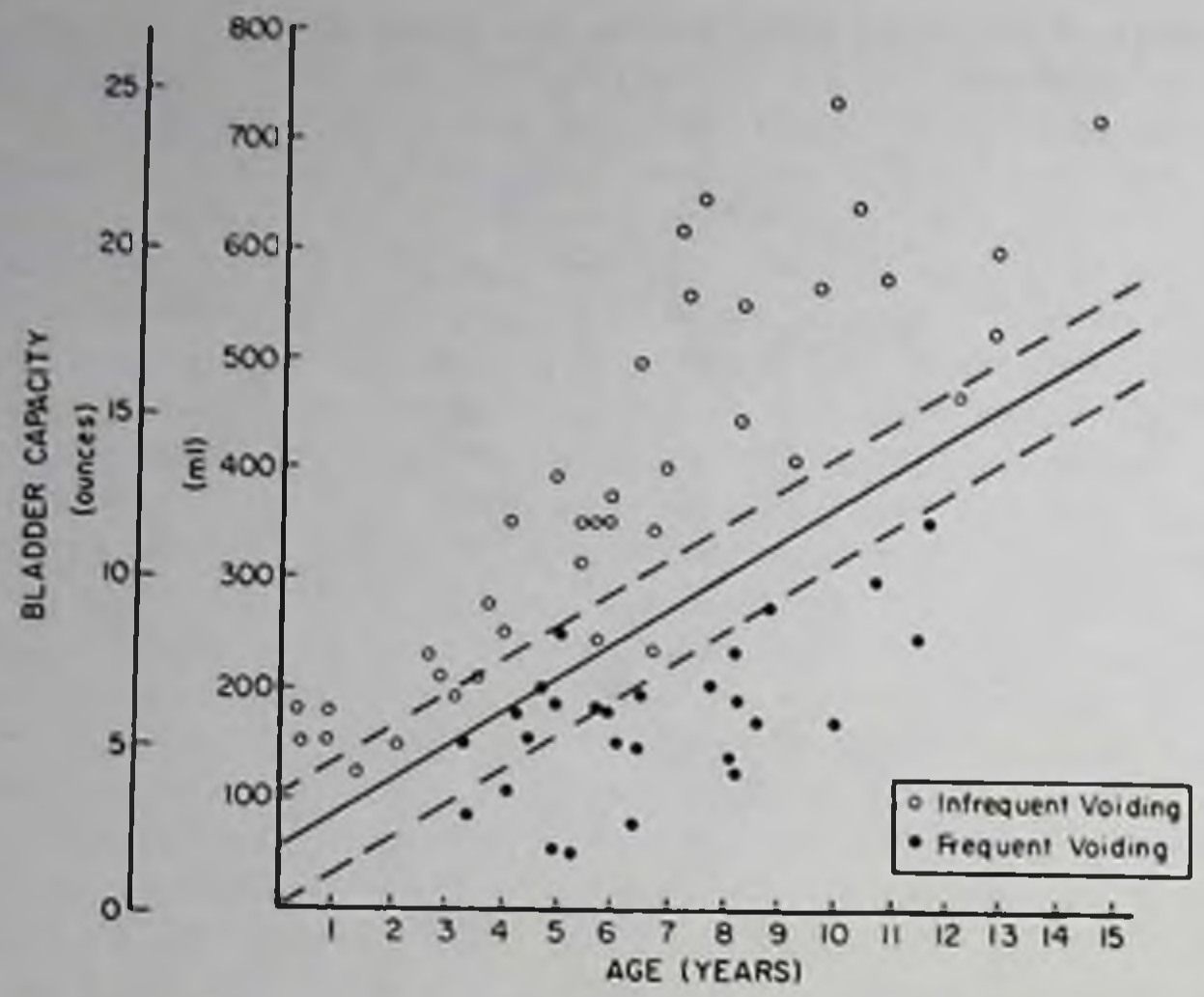

Fig 7–3.—Age versus bladder capacity of children with voiding abnormalities. Solid line represents approximate expected bladder capacity and broken lines indicate 95% confidence limits of predicted normal bladder capacity. (Courtesy of Berger, R. M., et al.: J. Urol. 129:347–349, February 1983.)

evaluation and preclude the need for complex urodynamic tests. The bladder capacity in ounces equals age in years plus 2, with a SD of 2 oz. Knowledge of the functional bladder capacity, with a detailed history, may suggest a diagnosis of large or small bladder capacity.

► [Three cheers for the urology group at Northwestern University! They have given us a simple, easily remembered formula in an article in which the title says it all. We should all learn a lesson from their brevity.—J.A.S., III] ◄

7–3 **Vulvovaginitis in Premenarcheal Girls: Clinical Features and Diagnostic Evaluation.** Jan E. Paradise, Joseph M. Campos, Harvey M. Friedman, and Gertrude Frishmuth studied 54 premenarcheal patients at the outpatient clinics at Children's Hospital of Philadelphia who had symptoms (Fig 7–4) or signs of vulvovaginitis. Median age was 5.8 years. Cultures of vaginal secretions were compared with those from age-matched controls.

Vaginal discharge was found on examination in 24 of 42 patients with a complaint of discharge or bleeding, or both, and in 2 of 12 patients without such a complaint. Convincing evidence of bacterial or monilial infection was found in 14 of the 26 patients with discharge on examination but in none of the 28 without discharge. One of the 28 had pinworm infestation. Moniliasis occurred only in girls who were pubertal. Four patients were found to have gonorrhea. No patient appeared to have symptoms or signs caused by *Bacteroides* sp., *Chlamydia trachomatis*, viruses, or *Trichomonas vaginalis*.

Noninfectious causes (table) were identified in 4 patients with and 13 without discharge. The most common cause was poor hygiene, which was implicated in 6 patients. Bubble bath use was implicated in 1. No specific cause could be identified in 22. All patients with poor

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(7–3) Pediatrics 70:193–198, August 1982.

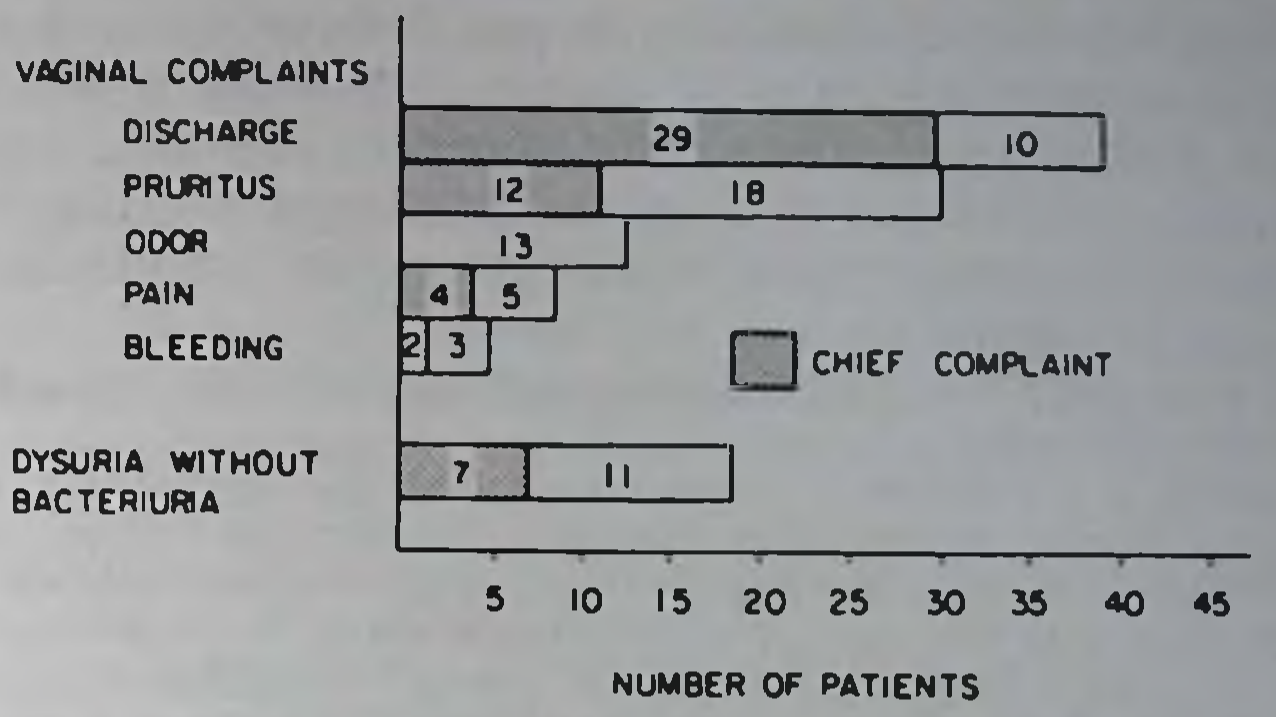

Fig 7–4.—Symptoms of 54 premenarcheal girls with suspected vaginitis. (Courtesy of Paradise, J. E., et al.: Pediatrics 70:193–198, August 1982. Copyright American Academy of Pediatrics 1982.)

hygiene as the only cause and most with no demonstrable etiology recovered after being advised to institute improved perineal hygiene.

This study indicates that among premenarcheal girls with complaints that suggest the presence of vulvovaginitis, the clinical features and one specimen for bacterial and fungal culture can usually provide a specific diagnosis. Physical examination provides two crucial bits of information: pubertal status and presence or absence of vaginal discharge. The finding that 4 patients with gonorrhea and 2 with unexplained genital pain had been victims of sexual abuse underscores the importance of inquiring about sexual abuse in all cases of genital complaints in children, particularly those with gonorrhea. Patients with vaginal discharge are likely to have specific infections, and therefore cultures should be taken, especially for *Neisseria gonorrhoeae*.

Etiologic Factors Among 54 Premenarcheal Girls With Symptoms or Signs of Vulvovaginitis

	Patients With Vaginal Discharge	Patients Without Vaginal Discharge	Total	*P* Value*
Specific infection	14	1	15	<.001
Noninfectious etiology (all)	(4)	(13)	17	<.025
Physiologic leukorrhea	2			
Ectopic ureter	1			
Presumed trauma	1	1		
Poor hygiene		6		
Sexual abuse		2		
Chemical irritant		2		
Stevens-Johnson syndrome		1		
Cystitis		1		
No cause found	8	14	22	>.05
Total	26	28	54	

*The χ^2 test was used to compare etiologic categories of patients with and without discharge.

(Courtesy of Paradise, J. E., et al.: Pediatrics 70:193–198, August 1982. Copyright American Academy of Pediatrics 1982.)

Genital pruritus in prepubertal girls has little or no etiologic specificity; most prepubertal girls with vulvitis or normal-appearing genitalia have relief of symptoms with attention to hygiene. Among pubertal patients, physiologic leukorrhea is the usual explanation for discharge unaccompanied by other symptoms, but moniliasis is likely if pruritus is a complaint.

▶ [Dr. Robert Cavanaugh, Assistant Professor of Pediatrics, State University of New York at Syracuse, comments:

"Vaginal discharge is a common problem in children and adolescents. The differential diagnosis is lengthy and includes infections, dermatologic entities, neoplasms, hormonal changes, anatomical lesions, pregnancy-related conditions, etc. Sexually transmitted diseases are more likely to occur postpubertally, but also should be considered in the differential diagnosis of vaginal discharge in prepubertal patients. Their presence in patients of any age should arouse suspicion of a sexual encounter. The younger the patient, the more likely this is secondary to sexual abuse. The authors emphasize that gonorrhea is an important cause of genital symptoms in prepubertal as well as postpubertal patients. In addition, like syphilis, gonorrhea may be asymptomatic. Therefore, whenever sexual contact is suspected, a culture for gonorrhea as well as a serology should be obtained. A wet preparation for *Trichomonas vaginalis* is also a convenient diagnostic tool that we routinely employ.

"Inflammation of the vulva or vagina, or both, may be accompanied by dysuria as well as discharge or itching. In fact, a recent article emphasized that dysuria in adolescents is more likely to be caused by vaginitis and other gynecologic infections than by a urinary tract infection (*Pediatrics* 70:299, 1982). In the present study 18 patients had dysuria without bacteriuria, and in 7 this was the chief complaint.

"Pruritus is an important symptom of moniliasis, particulary in pubertal girls. When itching is present, however, scabies, pediculosis pubis, contact dermatitis, pinworms, and other conditions that may involve the perivulvar skin should be considered.

"Physiologic leukorrhea is a common cause of vaginal discharge that becomes more pronounced near menarche. Many girls and parents are concerned that an underlying medical condition exists and seek advice from the physician. The secretions are usually clear or white and unaccompanied by other signs or symptoms. All laboratory tests are negative."] ◀

7–4 **Isolated Proteinuria: Analysis of a School-Age Population.** V. Matti Vehaskari and Juhani Rapola (Univ. of Helsinki) report that proteinuria (more than 25 mg/dl or Albustix [Ames Co.] reading 1+ or more in a random specimen, or more than 6 mg/hour/sq m in a timed collection) was found in at least 1 of 4 specimens in 10.7% (959 children) and in at least 2 of 4 specimens in 2.5% of 8,954 schoolchildren aged 8–15 years. To determine the risk of renal disease in isolated proteinuria, the screening program was followed by systematic clinical evaluations of proteinuric children.

After 59 children with both proteinuria and hematuria were excluded (1 of whom had focal glomerulosclerosis and 1, collagen vascular disease nephritis), none of 272 remaining children clinically evaluated was found to have overt renal disease. Two cases of urinary tract infection were detected. Despite urinary protein concentrations in excess of 1,000 mg/dl and protein excretion rates of up to 1 gm in 24 hours, proteinuria proved to be transient or intermittent in every child when enough urine samples were tested.

Renal function studies, intravenous pyelography, and renal biopsy were done in 34 children with the highest protein excretion rates (more than 6 mg/hour/sq m at night or more than 20 mg/hour/sq m

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(7–4) J. Pediatr. 101:661–668, November 1982.

during the day) and with the most persistent patterns of proteinuria. No significant abnormalities were found. Mild nonspecific changes were seen in 12 of 28 biopsy specimens, with mesangial deposits in 4; because glomerular immunofluorescence was negative in 3 of them, the deposits probably represented old immune complexes.

The results show that if hematuria and other signs have been excluded, a benign renal morphological picture is almost invariably to be expected in intermittent proteinuria; renal biopsy, therefore, is not indicated.

▶ [Dr. Adrian Spitzer, Professor of Pediatrics and Director, Division of Nephrology, Albert Einstein College of Medicine, comments:

"Almost 150 years have passed since Richard Bright established the relationship between proteinuria and parenchymal renal disease. Yet, the diagnostic and prognostic significance of isolated proteinuria remains elusive. Among the factors that may account for the uncertainty that still surrounds the clinical significance of isolated proteinuria is the variability of the criteria used for the selection of the sample population subjected to investigation. This has generated a broad array of descriptive terms, such as *juvenile, physiologic, orthostatic, persistent, constant, cyclic, intermittent, isolated, benign, minimal,* and *transient* proteinuria, making comparisons among various studies almost impossible.

"In essence, what the article of Vehaskari and Rapola demonstrates is that *intermittent* proteinuria, even when quantitatively substantial, is not associated with 'definable' histologic glomerular abnormalities. This is not surprising. Several other surveys performed among children and adults have provided similar evidence. Consequently, one cannot but concur with the conclusion of the authors that a renal biopsy is not warranted in children presenting with isolated intermittent proteinuria. The reader should not forget, however, that some of these children may develop *persistent* proteinuria and that a few of those may progress toward renal failure. The incidence of 'significant,' albeit variable, glomerular lesions, has been described to occur in as many as 70% of the patients with persistent asymptomatic proteinuria (Sinniah, R., et al.: *Clin. Nephrol.* 7:1–14, 1977). In one such study, age over 16 years or heavy proteinuria, with or without hematuria, were indicative of marked glomerular sclerosis (Yoshikawa, N., et al.: *Nephron* 25:127–133, 1980). It appears safe to conclude that in this latter group of patients, renal biopsy remains the only means of distinguishing between those with and those without renal structural abnormalities."] ◀

7–5 **Early Identification of Frequent Relapsers Among Children With Minimal-Change Nephrotic Syndrome** is discussed in a report of the International Study of Kidney Disease in Children. The most difficult problem in children with minimal-change nephrotic syndrome is the occurrence of frequent relapses in those who respond initially to steroid therapy. Repeated or continuous steroid therapy often leads to severe toxicity, and exposure to the toxic effects of cyclophosphamide or chlorambucil may not be warranted. Review was made of data on 218 steroid-responsive children with minimal-change nephrotic syndrome over the 2-year period after their initial response to prednisone therapy.

The rate of relapse could not be related to clinical or laboratory features at the time of diagnosis, histopathologic subgroups of disease, the time of initial response, or the interval from initial response to the first relapse. The number of relapses in the first 6 months, however, was highly predictive of the subsequent course. Only 6 of 99 patients with no relapses in this time had 3 or more relapses in the

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(7–5) J. Pediatr. 101:514–518, October 1982.

next 18 months. Of 37 patients with 3 or more relapses in the first 6 months, 17 had more than 6, and 13 had 10 or more relapses subsequently. Children with 1 or 2 relapses in the first 6 months had an intermediate subsequent course. The number of relapses in the first 6 months was related closely to the duration of treatment in the total follow-up period.

The earliest reliable predictor of frequent relapses of minimal-change nephrotic syndrome is the number of relapses in the first 6 months after an initial response to prednisone. Frequent relapse is not in itself an indication for either initial or repeat renal biopsy or for the institution of treatment with drugs other than prednisone. Even patients who relapsed frequently have shown little or no evidence of steroid toxicity.

▶ [Preventing the occurrence of frequent relapses and, until that is possible, finding more effective and safer methods of treating them, remain the major unresolved problems in the care of patients with minimal-change nephrotic syndrome (MCNS). Children with nephrotic syndrome of the idiopathic type who respond to prednisone with disappearance of proteinuria have an excellent long-term prognosis for maintenance of a normal glomerular filtration rate and eventual resolution of the syndrome. The response to prednisone is such an accurate predictor of underlying MCNS in some people's minds that, in most centers, renal biopsies are not routinely performed on these children. To say this differently, most patients with nephrotic syndrome and renal histologic patterns known to be associated with progressive disease do not respond to treatment with prednisone during the initial episode. Although as many as 20% to 30% of patients with focal segmental glomerular sclerosis may respond to prednisone initially, they generally become nonresponsive after a few relapses. What the International Study of Kidney Disease in Children has attempted to do, in this investigation, is to identify early the child who is likely to relapse frequently. This would prepare the patient and the family for the events to come and would provide a basis for selecting patients for trials of treatments designed to prevent or minimize the number of relapses. Many earlier reports had suggested that the presence of hematuria, transient azotemia, or hypertension at the time of diagnosis predicted the frequent relapser. "Not so," says the International Study! The source of the confusion apparently lies in the requirement for a minimal-change biopsy for inclusion in the International Study. As noted previously, most people don't do this initially, but if you do and if it shows only MCNS, apparently the only predictor of frequent relapsers is early frequent relapse. Although this is somewhat like guessing how well off a man is by checking his bank account, it is the best predictor the study group could find. If a trial is designed, and fear not that it won't be, to determine the effectiveness of a new form of treatment in preventing or minimizing relapses in patients with MCNS, without the risk of unacceptable toxicity, selection of patients who have 3 or more relapses during the 6-month period after initial response would insure the predominance of children likely to have a frequently relapsing course subsequently.

There is one other class of patients with MCNS who may not respond to steroids well either. These are the patients with an underlying T cell deficiency. Tabin et al. (*Pediatrics* 71:93, 1983) described 2 sisters with MCNS who demonstrated a pronounced deficiency of T lymphocytes. Neither sister responded well to steroids. An earlier report by Fodor et al. from Chile, suggests that milder defects in cell-mediated immunity are very common in those children with MCNS (*Am. J. Dis. Child.* 136:713, 1982). Whether these immunologic peculiarities are causative of MCNS remains to be seen.

Here are a few other comments concerning the nephrotic syndrome: Although furosemide has been getting some bad renal press lately, because this diuretic can cause kidney stones in preterm infants, according to Peterson et al. (*J. Pediatr.* 97:139, 1980) and Hugnagle et al. (*Pediatrics* 70:360, 1982), it is still among the best drugs for managing fluid retention in children with the nephrotic syndrome. The newer classes of diuretics that act as angiotensin-converting enzyme inhibitors, captopril being a prime example, don't work very well for this disorder. Despite the fact

that many children will retain sodium and have high plasma renin levels, this drug just doesn't seem to work in MCNS. In fact, the fluid is usually better left alone until steroids are given a chance to work. If all else fails, you can always try water immersion. In the nephrotic patient, dunking up to the neck can result in a water and sodium diuresis (Sutton, J. V., et al.: *Nephron* 32:108, 1982) from suppression of vasopressin and aldosterone. If you are just a bit incredulous, just recall what the most frequent urge is about 10 minutes after entering a swimming pool.—J.A.S, III] ◀

7–6 **Idiopathic Membranous Nephropathy in Children.** Idiopathic membranous nephropathy is uncommon in children. To determine the prognosis in children, Felix Ramirez, Ben H. Brouhard, Luther B. Travis, and Eileen N. Ellis (Univ. of Texas, Galveston) reviewed the clinicopathologic features and outcome of 11 male and 11 female patients aged 11 months to 19.9 years (mean, 12.9 years). Patients had biopsies within 6 months of onset of symptoms and were divided into two groups according to biopsy findings: group 1 (stages I and II) and group 2 (stages III and IV). Follow-up time was the same in both groups (mean, about 4.8 years).

The nephrotic syndrome was present in 12 of 16 patients in group 1 and in all 6 patients in group 2. In group 1, 8 patients had repeat biopsies 1–11 years (mean, 3 years) after onset. Of these, 2 progressed to stages III and IV, but only 1 progressed to renal insufficiency. The only patient without proteinuria presented with microscopic hematuria. Improvement of the nephrotic syndrome occurred in 6 of 12 patients, who currently remain in remission; of these, 5 were treated with steroids.

In group 2, 2 patients had repeat biopsies 2 years after onset and remained in the same group; progression to renal insufficiency occurred in 5 of the 6 patients. Improvement of the nephrotic syndrome occurred in 2 patients. The difference in progression to renal insufficiency between the two groups was significant (6% of group 1 versus 84% of group 2).

No patient without nephrotic syndrome progressed to renal insufficiency. Of 3 patients younger than age 10 years, only 1 progressed to renal insufficiency within 4 years. Four of 8 patients hypertensive at the time of onset progressed to renal insufficiency; they all had stage III or IV membranous nephropathy. The remaining hypertensive patients were in stage I or II, and they did not progress to renal insufficiency. Of 11 patients (50%) who received alternate-day steroid therapy, 4 (36%) progressed to renal insufficiency, as compared with 3 of 11 (27%) of the untreated group.

The stage of glomerular lesion at the time of onset seems to be a factor in predicting the prognosis of membranous nephropathy in pediatric patients. The age at onset and the degree of proteinuria, but not hypertension, also may be predictors of progression to chronic renal failure. In general, patients with heavy proteinuria or the nephrotic syndrome have a worse prognosis. Because the series represents a small number of patients, it is difficult to judge the benefit of steroid therapy.

▶ [Membranous nephropathy also is known as "epimembranous glomerulonephri-

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(7–6) J. Pediatr. 101:677–681, November 1982.

tis." This is histologically characterized by the presence of granular deposits of immunoreactants such as IgG or the third component of complement along the glomerular capillary wall. Children with this disorder usually present with what appears to be a "run of the mill" nephrotic syndrome that quickly becomes atypical in its response to steroids, leading to the need for renal biopsy. The disease is unusual in children, and the authors of this study have done us all a great service by carefully reviewing the course of this form of glomerular nephritis in 22 children. Clinically, the children had varying degrees of proteinuria and edema. Most did not have hematuria or hypertension. Unlike the benign disease that membranous nephropathy initially mimics, this form of nephritis can cause a poor outlook for preservation of renal function—thus our need to be aware of the illness. Some investigators believe that steroid treatment is beneficial in idiopathic membranous neuropathy, but this impression is based on adult patients. The number of children so treated makes the reports of the successful use of steroid in this condition anecdotal.—J.A.S., III] ◀

7–7 **Multicenter Study of IgA Nephropathy in Children: Report of the Southwest Pediatric Nephrology Study Group.** R. J. Hogg (Univ. of Texas, Dallas) reports the findings in a study of 62 children with IgA nephropathy, diagnosed from mesangial IgA deposit on renal biopsy and the absence of systemic lupus erythematosus, chronic liver disease, and Henoch-Schönlein purpura. The age and sex distributions are shown in Figure 7–5. All patients had microscopic hematuria, and a large majority had at least one episode of gross hematuria before renal biopsy. Nephrotic syndrome had occurred in 3 patients. Fewer than half the patients initially had 2+ or greater proteinuria. Four patients were hypertensive, and 16 had low glomerular filtration rates before biopsy. Biopsy was performed a mean of 15 months after clinical onset.

Mean follow-up after renal biopsy was 25 months. Seven of 16 patients followed for 5 years or longer have proteinuria, 1 is hypertensive, and 3 have reduced glomerular filtration rates. One of the last patients has end-stage renal disease. Renal biopsy showed focal and segmental proliferative changes, segmental necrosis, synechia for-

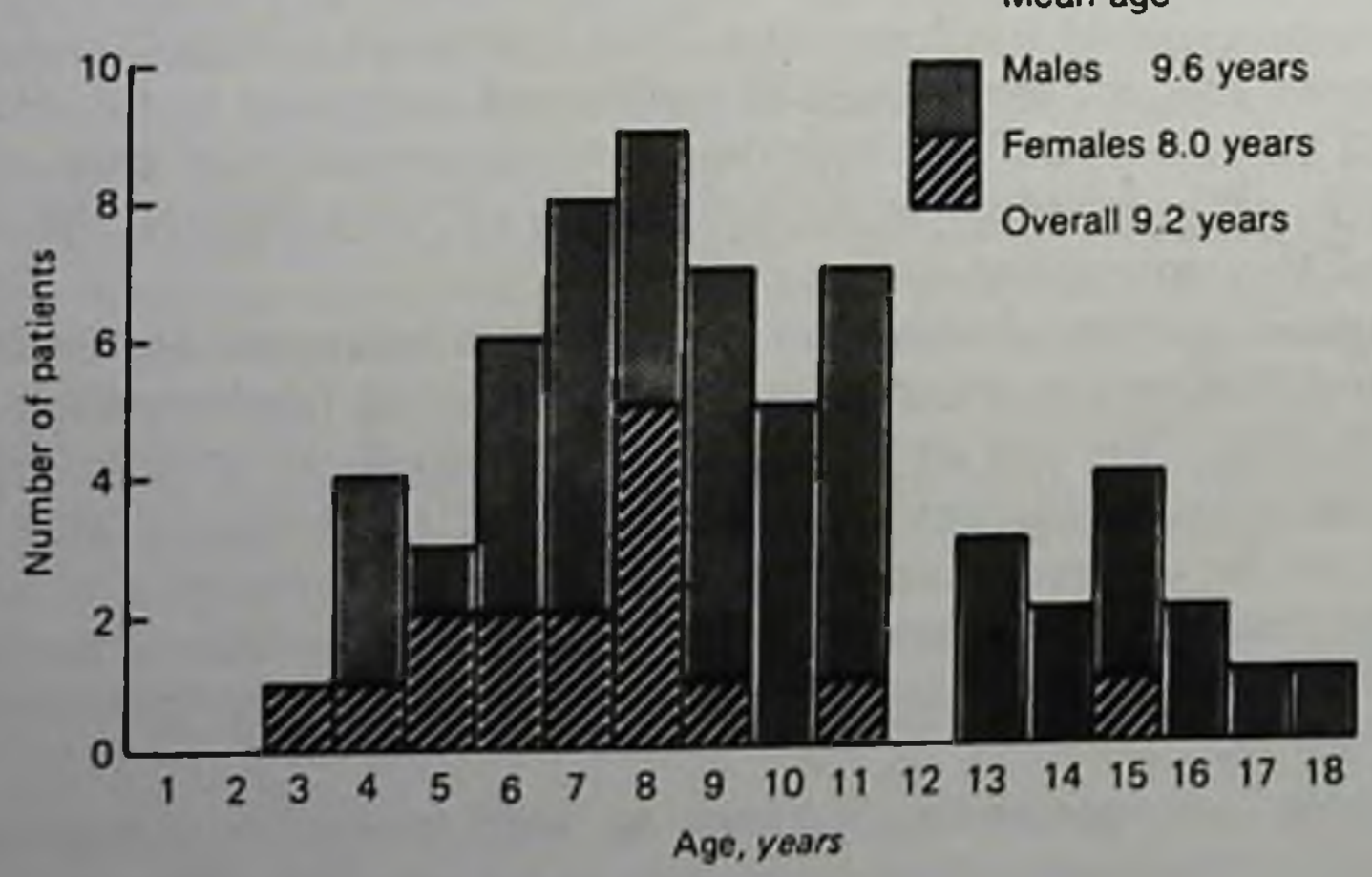

Fig 7–5.—Distribution of patients with IgA nephropathy according to sex and age at clinical presentation. (Courtesy of Hogg, R. J.: Kidney Int. 22:643–652, December 1982; Berlin-Heidelberg-New York: Springer.)

(7–7) Kidney Int. 22:643–652, December 1982.

mation, crescent formation, glomerular capillary wall collapse, and sclerosis in 21 cases. Glomerular patterns and tubulointerstitial damage were not related to the presence, intensity, or location of immunofluorescence IgA staining. Proteinuria at biopsy correlated significantly with marked glomerular abnormalities and with peripheral glomerular capillary wall changes on electron microscopic examination.

Both peripheral glomerular capillary wall changes and tubulointerstitial damage are not infrequent in children with IgA nephropathy. These features may indicate a more serious outcome than was previously thought, but the long-term outlook remains uncertain. A significant proportion of children with IgA nephropathy may have progressive renal failure as they enter the third or fourth decade. Long-term longitudinal studies of patients first seen in childhood are necessary.

▶ [The association of idiopathic glomerular nephritis and diffuse mesangial deposition of IgA was first described in 1968 (Berger, J., and Hinglais, N.: *J. Urol. Nephrol. (Paris)* 74:694, 1968). Since that time, large numbers of reports of the disorder in children have appeared. The pathology is that of nephritis with extensive deposits of IgA in the glomerular mesangium. Fortunately for us in the United States, this form of nephritis occurs far less frequently here than in other parts of the world. While we have been embraced by Lyme disease, acquired immune deficiency syndrome (AIDS), and Legionnaires' disease, IgA nephropathy is one of the most common forms of glomerular disease in France, Spain, Italy, Japan, Singapore, and Australia. In these areas, the chance of finding the pathology, if a renal biopsy is being performed, is as great as 40%.

The overall prognosis for children with IgA nephropathy is probably better than that of adults, in whom the incidence of renal insufficiency varies from 10% to 50%. Unfortunately, not enough children have been followed sufficiently long to "concretize" the predictions of the preceding sentence. There is general agreement that both adults and children with IgA nephropathy will have significantly elevated serum IgA levels. While it would be intriguing to suspect that this causes the renal deposition of IgA, attempts to define a relationship between serum levels and deterioration of renal function have been unsuccessful to date. Despite this lack of correlation, some investigators have attempted to capitalize on the fact that phenytoins, such as Dilantin, can lower serum IgA levels and have used anticonvulsants to treat children with this form of nephropathy (Navas-Palacio J. J., et al.: *Ultrastruct. Path.* 2:151, 1981). The results of this form of therapy were quite predictable—I would assume that no child had a seizure (but not much happened to improve the nephritis). This is a typical example of "leaving no turn unstoned." Thus, we are still caught in the position of saying that the overall prognosis of patients with IgA nephropathy remains to be confirmed. A limited number of patients also have been treated with tonsillectomy, steroids, and Cytoxan. Of these various therapeutic regimens, only steroids hold any promise, but in this series the response was transient.—J.A.S., III] ◀

7–8 **Prospective Comparison of Urinary Tract Infections in Patients Treated With Either Clean Intermittent Catheterization or Urinary Diversion.** Clean intermittent catheterization (CIC) has replaced urinary diversion as the treatment of choice for patients with neurogenic bladder. Owen Ehrlich and Andrew S. Brem (Brown Univ.) compared CIC with ileal loop diversion (ILD) with respect to urinary tract infection and short-term morbidity in a prospective series of patients seen in a meningomyelocele clinic. All either received CIC over 12 months or underwent ILD. Twenty-four children with a mean age of 7.1 years had CIC as treatment for meningomyelocele,

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(7–8) Pediatrics 70:665–669, November 1982.

NUMBER AND TYPE OF ORGANISM RECOVERED FROM PATIENTS MAINTAINED ON CIC AND ILD

	CIC	ILD
No. of positive urine cultures	85	34
No. of organisms recovered	91	41
Organisms		
Escherichia coli	31/91 (34%)	18/41 (44%)
Klebsiella	19/91 (21%)	4/41 (10%)
Proteus	4/91 (4%)	11/41 (27%)
Pseudomonas	9/91 (10%)	2/41 (5%)
Enterococcus	12/91 (13%)	...
Enterobacter	5/91 (6%)	1/41 (2%)
Streptococcus	5/91 (6%)	...
Staphylococcus aureus	3/91 (3%)	...
Other	3/91 (3%)	5/41 (12%)

(Courtesy of Ehrlich, O., and Brem, A. S.: Pediatrics 70:665–669, November 1982. Copyright American Academy of Pediatrics 1982.)

whereas 9 with a mean age of 15.2 years were operated on. Patients undergoing CIC who had positive urine cultures received appropriate antibiotics, usually by mouth. Only symptomatic infections were treated in the surgical patients.

The rates of positive urine cultures were 36.8% in CIC patients and 61.8% in ILD patients, a significant difference. Only five episodes in the CIC group were symptomatic. One child with ILD had symptomatic urinary tract infection. Chronic or recurrent infection appeared to be present in 7 of the 9 surgical patients and in 5 of the 24 patients undergoing CIC. One patient in the CIC group developed progressive hydronephrosis and subsequently had ILD. No patient in either group had a permanent reduction in renal function. *Escherichia coli* was the most common organism isolated from patients in both groups (table). Gram-negative organisms caused most infections in both groups.

A significantly lower rate of asymptomatic bacteriuria was found in patients managed by CIC than in those with ILD in this study. Short-term morbidity rates associated with positive urine cultures were comparable in the two groups. Whether CIC will prove to be a better form of management in terms of long-term morbidity will require further study.

7–9 **Prune Belly Syndrome: Report of 47 Cases.** The prune belly syndrome in pure form consists of complex malformations of the urinary tract, bilateral undescended testes, and absence of anterior abdominal wall muscles. C. R. J. Woodhouse, P. G. Ransley, and D. Innes-Williams (London) reviewed the findings in 47 boys with the syndrome, born in 1948–1977. The diagnosis was generally apparent at birth, but in 9 boys it was delayed for up to 9 years. There was no family history of the syndrome. No particular pregnancy or labor problems were reported. Other major anomalies were rare. A universal mesentery was a frequent finding. Five infants died perinatally

(7–9) Arch. Dis. Child. 57:856–859, November 1982.

despite high diversion (Table 1). Thirteen presented as neonatal emergencies with infection and gross urinary tract dilatation. High diversion was done in 12 of these cases, and renal function was stabilized in 10 patients. Reconstruction was attempted in 6 cases, and stable renal function was achieved in 3 of them. Twenty-nine patients were well neonatally and had good renal function despite very abnormal radiologic findings. The current status of the patients is indicated in Table 2. Renal function remained stable during the pubertal growth spurt. Only 3 patients deteriorated in adolescence.

It always should be possible to diagnose prune belly syndrome at birth. Renal function is assessed by plasma urea and creatinine concentrations, chromium-EDTA clearance study, and DMSA scanning. Ultrasonography, done before and after voiding if possible, is the best means of estimating dilatation. Rapid deterioration calls for high diversion so that renal function may stabilize. Complete bladder emptying otherwise is necessary. Cystourethroscopy is done under general anesthesia, and a urethrotomy is done if necessary. Minimal surgical interference is the rule in group 3 cases. Chronically infected, poorly functioning kidneys that fail to improve on adequate drainage are removed. Otherwise, upper tract surgery is done only for proved

TABLE 1.—CLINICAL EVALUATION OF 47 CASES OF PRUNE BELLY SYNDROME

Group		*Number of cases*
1	Perinatal death, often with hypoplastic or atretic urethra	5
2	Neonatal emergency presentation with infection and gross urinary tract dilatation	13
3	Well in the neonatal period. Good renal function despite very abnormal radiology	29

(Courtesy of Woodhouse, C. R. J., et al.: Arch. Dis. Child. 57:856–859, November 1982.)

TABLE 2.—PRESENT CONDITION OF 42 GROUP 2 AND GROUP 3 PATIENTS WITH PRUNE BELLY SYNDROME

Condition	*No of patients*	
	Group 2	*Group 3*
Healthy (normal levels of blood urea and creatinine, normal micturition, and negligible urinary infection)	3	22
Healthy but with diversion	4	
Unsatisfactory		
Hypertensive		2
Early renal failure and diversion	3	1
End stage renal failure	2	1
Renal calculi and psychiatric problems		1
Postoperative respiratory arrest leading to brain damage		1
Teratoma of the testis		1
Died (in uraemia aged 14 years)	1	

(Courtesy of Woodhouse, C. R. J., et al.: Arch. Dis. Child. 57:856–859, November 1982.)

obstruction and after lower tract obstruction is eliminated. Group 2 patients should have urinary tract reconstruction before attending school if there is some evidence of ureteric muscle activity. The absence of anterior abdominal muscles does not seem to be a handicap. The testes are brought down at the time of definitive ureteric surgery, or at about age 7 years.

7–10 **Incidence of Radiographically Evident Bone Disease, Nephrocalcinosis, and Nephrolithiasis in Various Types of Renal Tubular Acidosis.** R. James Brenner, David B. Spring, Anthony Sebastian, Elisabeth M. McSherry, Harry K. Genant, Alphonse J. Palubinskas, and R. Curtis Morris, Jr. (Univ. of California, San Francisco) reviewed the x-ray findings in 56 children and 36 adults with renal tubular acidosis to determine whether the findings could be related to the type of syndrome. Forty-four patients had type 1 renal tubular acidosis, with an inappropriately high urinary pH and persistent bicarbonate excretion. Eighteen had type 2 disease, with a high urinary pH and bicarbonaturia only during mild acidosis. Thirty patients had type 4 disease, with highly acidic urine during severe acidosis and an extremely small fractional excretion of bicarbonate.

Skeletal abnormalities were found in 14 patients, 7 of them nonazotemic. All 7 of the latter patients had type 2 renal tubular acidosis. The others were mildly azotemic. Nephrocalcinosis was found in 29% of the 82 evaluable patients, only in those with type 1 renal tubular acidosis. Over half the patients with type 1 disease had evidence of nephrocalcinosis. These were predominantly adults. Nephrocalcinosis was usually of the "classic" pattern. Two thirds of patients with type 2 renal tubular acidosis had skeletal abnormalities. All affected children had rickets, whereas the adults had osteopenia without pseudofractures. Osteopenia was evident in 12% of patients with type 4 renal tubular acidosis. No patient with type 2 or type 4 disease had nephrocalcinosis or nephrolithiasis.

The x-ray manifestations are influenced by the physiologic type of renal tubular acidosis that is present. Nephrocalcinosis is more frequent in adults than in children with type 1 renal tubular acidosis. This change was not found in patients with type 2 or 4 renal tubular acidosis. The possibility that metabolic acidosis alters bone mineral metabolism directly or alters vitamin D metabolites or the action of active vitamin D metabolites requires further study.

▶ [Dr. Russell W. Chesney, Professor, Department of Pediatrics, University of Wisconsin, Madison, comments:

"Brenner et al. clearly discuss the radiologic manifestations of patients with various types of renal tubular acidosis (RTA). Bone disease—osteopenia, osteomalacia, and/or rickets, all representative of bone undermineralization—was confined to patients with type II RTA (Fanconi's syndrome) unless the patient was azotemic. With azotemia, bone disease was evident in all varieties of RTA.

"At least three physiologic processes could account for this bone demineralization. First, due to the chronic elevated systemic hydrogen ion concentrations, the calcium carbonate in bone would be consumed to serve as a buffer. This would result in hypercalciuria as well as osteopenia. Second, hypophosphatemia will impair the mineralization of cartilage and the organic matrix of bone. Third, acidosis may impair

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(7–10) N. Engl. J. Med. 307:217–221, July 22, 1982.

the conversion of 25-hydroxyvitamin D (25[OH]D) to its active metabolite, 1,25-dihydroxyvitamin D ($1,25[OH]_2D$). Clearly, the first mechanism is relevant, since patients with RTA have hypercalciuria that is reversed by oral alkali (bicarbonate) therapy. Hypophosphatemia is also important as a pathogenic factor and probably accounts for the rickets and osteopenia evident in type II RTA patients, since the excessive renal tubular phosphate loss in this type leads to chronic hypophosphatemia. This second mechanism may be the most important, because patients with all types have systemic acidosis, but only type II patients who have hypophosphatemia actually have bone disease.

"The third mechanism, impaired conversion of $25(OH)D$ to $1,25(OH)_2D$, is found in vitamin D-deficient animals in which acidosis is superimposed. However, entirely normal serum $1,25(OH)_2D$ concentrations are found in children with either type I or type II RTA and chronic acidosis (Chesney, R. W., et al.: *J. Pediatr.* 102:592, 1983). One potential difference between these findings in children and results in animal studies is that the children were not vitamin D-deficient.

"Conversion of $25(OH)D$ to $1,25(OH)_2D$ is impaired in moderate renal failure in children (Chesney, R. W., et al.: *Kidney Int.* 21:65, 1982; and Portale, A. A., et al.: ibid., pp. 627). Accordingly, RTA patients with azotemia may have demineralization by this mechanism in this study.

"Brenner et al. found that nephrocalcinosis was confined to type I patients. One contrasting finding in type I RTA is that the urine is always alkaline ($pH > 6.2$), and urinary citrate excretion is always low (Norman, M. E., et al.: *J. Pediatr.* 92:394, 1978). In types II and IV RTA, the urine is often acidic, and citrate excretion is higher; hence, calcium phosphate precipitation causing nephrocalcinosis is less likely, as indicated by this study.

"Despite the clear-cut results of this study, we and others have seen some patients with type I RTA who have hypophosphatemia, probably due to secondary hyperparathyroidism, and who actually develop osteopenia. Alkali therapy alone in these patients will reverse hypophosphatemia and hypercalcuria, thereby permitting bone remineralization."] ◀

7–11 **Continuous Ambulatory Peritoneal Dialysis in Children: Comparison With Hemodialysis.** Michel Baum, David Powell, Sadie Calvin, Tarran McDaid, Kathy McHenry, Henkin Mar, and Donald Potter (Univ. of California, San Francisco) compared the clinical and biochemical effects of continuous ambulatory peritoneal dialysis in 20 children and of hemodialysis in 16 children during a 2½-year period.

Statistically significant differences between the groups included higher hematocrit, higher serum carbon dioxide and cholesterol levels, larger intake of calories and protein, and lower systolic blood pressure and rates of transfusion in patients receiving continuous ambulatory peritoneal dialysis. These patients had more complications than patients receiving hemodialysis (table), but hospitalization rates in the two groups were similar. Dietary restriction of sodium was required in 61% of patients receiving ambulatory dialysis and in 94% of those receiving hemodialysis ($P < .05$). Symptomatic hypotension was a complication of ambulatory dialysis in 3 patients.

There were 4 treatment failures with continuous ambulatory peritoneal dialysis (3 resulting from recurrent peritonitis and 1 from a catheter-tunnel infection) and 1 with hemodialysis (resulting from loss of vascular access). The cost of continuous ambulatory peritoneal dialysis was $19,600 per patient-year; the cost of hemodialysis was $54,300 per patient-year.

(7–11) N. Engl. J. Med. 307:1537–1542, Dec. 16, 1982.

COMPLICATIONS IN DIALYSIS PATIENTS

	AMBULATORY DIALYSIS	HEMODIALYSIS
	number of patients	
Peritonitis	16	—
Catheter change or reposition	13	—
Dialysate leak	7	—
Catheter-tunnel infection	4	—
Hernia	3	—
Hypotension	3	—
Hydrocele	1	—
Hepatitis	1	4
Pancreatitis	1	—
Skeletal deformities	1	1
Shunt or fistula failure	—	6
Convulsions	—	2
Hypermenorrhagia	—	2
Bleeding diathesis	—	1
Hydralazine lupus erythematosus syndrome	—	1

(Courtesy of Baum, M., et al.: N. Engl. J. Med. 307:1537–1542, Dec. 16, 1982.)

Continuous ambulatory peritoneal dialysis is an important alternative to hemodialysis in children. The motivation and ability of the parents and child must be assessed before responsibility for ambulatory dialysis is assigned, and families receiving this form of treatment must receive ongoing supervision and support. The primary advantage of ambulatory dialysis is the ease with which it is performed in the home, without need for a machine and without repetitive needle insertions.

Children treated with both forms of dialysis preferred ambulatory dialysis because of the greater freedom it gave them to perform their usual activities and the feeling of increased independence and responsibility for their own medical care. Perhaps for these reasons, or because ambulatory dialysis is associated with steady-state rather than fluctuating serum biochemical levels, children reported increased energy and a sense of well-being with ambulatory dialysis.

▶ [Few things have been as well received in this country as apple pie, video games, Charlie Brown, and continuous ambulatory peritoneal dialysis (CAPD). In fact, CAPD has been so well accepted that one wonders why a study had to be undertaken for further underpinning its existence. Although thousands of children were treated successfully with long-term dialysis beginning around 1962, many undergoing this treatment had problems, including retarded growth and sexual development and difficulty in psychosocial adjustments. Continuous ambulatory peritoneal dialysis was developed in 1975 but not widely used until 1978, when the technique was adapted to the use of dialysate in plastic bags. Children were first treated with CAPD in Toronto in 1978. This study by Baum et al. enumerates the obvious benefits, although potshots have been taken at the design of this report. Its obvious defect is that it examined the biochemical status of the patients on CAPD in a steady state, while on continuous dialysis, while the numbers for hemodialysis appear poor because the chemistries of the patients were taken just prior to the next time on a dialysis machine. As Harman

pointed out in a letter to the editor (*N. Engl. J. Med.* 308:968, 1983), the technique of hemodialysis entails the intermittent removal of solutes and water in a highly efficient manner to approximately normal levels and subsequent reaccumulation of these prior to the next removal. On the other hand, CAPD maintains the child in a steady, albeit uremic, state by prolonged low-efficiency clearances. Either way will probably work, but only a large well-designed and controlled study could resolve the important issue of the advantages of cyclic versus steady-state clearances. Without controversy, however, is the fact that CAPD has a higher failure rate (some 20%) and a high incidence of peritonitis. These problems are not unique to pediatric programs or to the United States. A report from Great Britain reviewing a 4-year period of CAPD in 10 children noted 11 separate episodes of peritoneal infection (*Arch. Dis. Child.* 57:677, 1982). All patients did well, although 1 child had a curious eosinophilic exudative peritonitis. Despite the complication rate, the patients continue to return to CAPD.

This past year has seen a report of aluminum intoxication in a nondialyzed uremic child receiving aluminum hydroxide by mouth to control hyperphosphatemia (*Pediatrics* 71:56, 1983). This unusual case warns us to be cautious when using Amphojel. The amount used should be limited to 100 mg/kg/day and all patients receiving aluminum therapy should be watched carefully for signs of toxicity (largely encephalopathy). I trust our readers in Great Britain will overlook the spelling of *aluminum*. In Great Britain, as throughout much of the world, this word is spelled *aluminium* (which is probably the correct spelling). The story has it that many years ago in Canada when Henry Kaiser opened his first ALCOA plant, the sign company forgot the second *i*. The old boy did not want to pay to have the sign changed, so the name *aluminum* became the common usage over here—or so the story goes. I personally believe this story, as I have never been one to let the truth stand in the way of a good anecdote.—J.A.S., III] ◄

7–12 **Effect of HLA-A and HLA-B Matching on Survival of Grafts and Recipients After Renal Transplantation.** Guido G. Persijn, Bernard Cohen, Quirijn Lansbergen, Joseph D'Amaro, Neville Selwood, Antony Wing, and Jon J. van Rood (Leiden, The Netherlands) combined data from the European Dialysis and Transplant Association and the Eurotransplant Foundation to examine the effects of human leukocyte antigen (HLA)-A and HLA-B matching on renal transplant and patient survival. Data were reviewed on 2,522 patients receiving a first cadaveric renal graft between 1967 and 1979.

Patients given a well-matched kidney had better graft survival at 5 years than those given a graft mismatched for 4 antigens (51% vs. 32%). The overall actuarial graft survival at 5 years was 43%. The difference in patient survival with and without HLA-A and HLA-B matching also was significant (72% vs. 54%). Overall patient survival at 5 years was 66%. The 2-year renal graft survival in 84 patients treated urgently because they were expected to die within a few months if not transplanted was 57%. The 2-year patient survival in this group was 79%. All 9 high-urgency patients who received a graft without HLA-A and HLA-B mismatches were living at 2 years with viable grafts. Of 19 recipients of a three-antigen or four-antigen mismatched kidney, 78% were alive at 2 years, and graft survival was 61%.

It appears that matching for HLA-A and HLA-B antigens has important beneficial effects on both renal allograft survival and patient survival in recipients of first cadaveric allografts. Better results may be obtained with the use of new immunosuppressive agents causing

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(7–12) N. Engl. J. Med. 307:905–908, Oct. 7, 1982.

fewer side effects and with prospective HLA-DR selection procedures combined with a planned blood transfusion program.

▶ [There are many interesting new aspects to the field of renal transplantation. One of them is this study from the Eurotransplant Foundation showing that it is worthwhile to take the time to get reasonable matching for HLA antigens between renal transplant recipients and unrelated donors. Obviously, many other factors enter into the decision to temporize transplantation until the most ideal donor is available (such as how ill the recipient is and how rare the antigens are). It is also fair to say that others in the United States, such as Kaplan et al. (*N. Y. Acad. Sci* 80:1819, 1982), have found poor correlation between HLA typing and graft survival. Nonetheless, transplantation from whatever source is a superior alternative to chronic dialysis for most children. Growth and development of dialyzed children usually are delayed. Catch up growth after transplantation is very often possible, according to Bosque et al. (*Arch. Dis. Child*. 58:110, 1983). Also, the quality of life with successful transplants is most often better than that for children on dialysis. Therefore, the aim in the vast majority of cases is for transplantation when feasible.

Not only do we know more about from whom and to whom renal transplants should go, we also now know how to carry this off with less morbidity. For example, it now generally is agreed that pretransplant blood transfusions are beneficial to kidney recipients. Somehow or other, being stimulated by foreign antigens in blood products produces a lesser risk of rejection of an engrafted kidney. How this little piece of black magic works is speculative, but almost all transplant centers now have followed this practice of transfusing one or more units of blood into a transplant recipient well in advance of transplantation. Horimi et al. (*Transplantation* 35:320, 1983) have shown that with each unit of blood given, up to 14 units, an improvement in graft survival occurs. It is postulated that antibodies developed by a patient help to select donors against whom the patient is nonreactive (as demonstrated in a routine crossmatch) (MacLeod et al.: *Lancet* 2:468, 1981). Others feel that transfusions cause the elaboration of enhancing antibodies or suppressor cells that help the graft.

Europeans also are telling us how to prolong graft survival and how to identify early rejection when it occurs. The European Multicenter Trial (ibid. 2:57, 1982) demonstrated the effectiveness of cyclosporin A, a fungal peptide, over steroids as a powerful immunosuppressant to prevent graft rejection. This drug is a T lymphocyte suppressant. A group in London, Corbett and associates (*Clin. Chim. Acta* 128:141, 1983), show that an increase in the quantity of urinary *N*-acetyl-β-D-glucosaminidase heralded the onset of kidney rejection. This enzyme, found in the proximal renal tubule, is let loose when the kidney begins to be damaged by rejection.

Last, but not least, we know much more about infections and their consequences in transplanted patients. Herpesvirus infections (cytomegalovirus and herpes simplex, varicella-zoster, and Epstein-Barr virus) can all have devastating effects after transplantation. An inversion in the T lymphocyte subset ratio of helper lymphocytes known as "OKT4 cells" to suppressor lymphocytes (OKT8 cells) similar to that reported in victims of acute immune deficiency syndrome is a marker of severe immunosuppression and identifies an increased risk for opportunistic infections after transplantation. Scholey et al. (*N. Engl. J. Med*. 308:307, 1983) show that you can use an inversion in the OKT4/OKT8 ratio to make a presumptive diagnosis of herpesvirus infection in renal transplant recipients because the two seem to go hand in hand. Because determining these ratios is a quick procedure in the laboratory compared to conventional virologic techniques, as antiviral chemotherapy becomes more effective, a diagnostic approach that includes monitoring of T lymphocyte subsets will become increasingly more important.

As a spin-off of these lymphocyte studies, it has been shown that patients with normal or increased ratios of OKT4/OKT8 lymphocyte subsets are likely to have classic rejection that is 90% responsive to immunosuppressives such as steroids or cyclosporin. In contrast, apparent rejection associated with inverted OKT4/OKT8 ratios usually means the engrafted kidney has cytomegalovirus-associated glomerular damage, which, despite all available treatments, usually means loss of the kidney.

If all this lymphocyte subset business means nothing more to you than it sounds a bit like the title of the recent best seller on self-help *(I'm O.K.–You're O.K.)*, I would advise, "Do not pass go," but move to Chapter 9, "Blood," in this YEAR BOOK, for more information on the subject.—J.A.S., III] ◀

7–13 **The Scrotal Mass: Cause and Diagnosis.** The occurrence of serious and fatal conditions affecting the scrotal contents makes prompt evaluation of all scrotal masses mandatory. Michael J. Macksood and Robert E. James, Jr. (Hurley Med. Center, Flint, Mich.) reviewed the records of 278 patients seen between 1974 and 1980 with either painful or asymptomatic scrotal or testicular masses. Those with inguinal hernia or hydrocele associated with hernia were excluded. Inflammatory states accounted for 48% of the cases and hydrocele for 24% (table). The incidence of testicular or appendiceal torsion was about 9%. All 11 testicular scans correctly diagnosed testicular inflammation and ruled out torsion. Most inflammatory masses were in the left hemiscrotum, whereas hydroceles were evenly distributed between the two sides. Scanning correctly diagnosed testicular torsion in all 7 patients examined. Two patients with torsion were operated on for strangulated hernia. All varicoceles were correctly diagnosed by physical examination alone. All cysts were asymptomatic, and none was diagnosed preoperatively. About 10% of all patients were operated on to exclude malignancy. Hydrocele and cyst were found in most of these patients. Four patients were found to have malignant disease and 2, benign tumors.

A protocol for investigation of patients with scrotal pain or a mass of undetermined origin is presented in Figure 7–6. An asymptomatic scrotal mass of undetermined cause should be explored through an inguinal approach if it is clearly intratesticular. If it is extratesticular, ultrasound study is a useful means of distinguishing a cystic from a solid lesion. Cystic lesions may be followed, whereas solid lesions should be explored through an inguinal approach to exclude malig-

INCIDENCE OF LESIONS CAUSING SCROTAL MASSES

Masses	Number	Percent
Total scrotal masses	278	
Inflammatory masses	133	47.8
Hydrocele	66	23.7
Torsion testicular	20	9.35
Appendix testis	6	
Varicocele	19	6.8
Spermatocele	12	4.3
Various cysts	11	3.96
Epidermoid cyst of testis	2	
Epididymal cyst	2	
Testicular cysts	3	
Spermatic cord cyst	1	
Epithelial cysts of tunica albuginia	1	
Sebaceous cyst	1	
Calcified nodule	1	
Malignant tumors	6	2.16
Embryonal cell cancer	3	
Teratocarcinoma	2	
Seminoma	1	
Benign tumors	2	0.72
Hematocele	2	0.72
Aberrant adrenal tissue	1	0.36

(Courtesy of Macksood, M. J., and James, R. E., Jr.: Am. J. Surg. 145:297–299, February 1983.)

(7–13) Am. J. Surg. 145:297–299, February 1983.

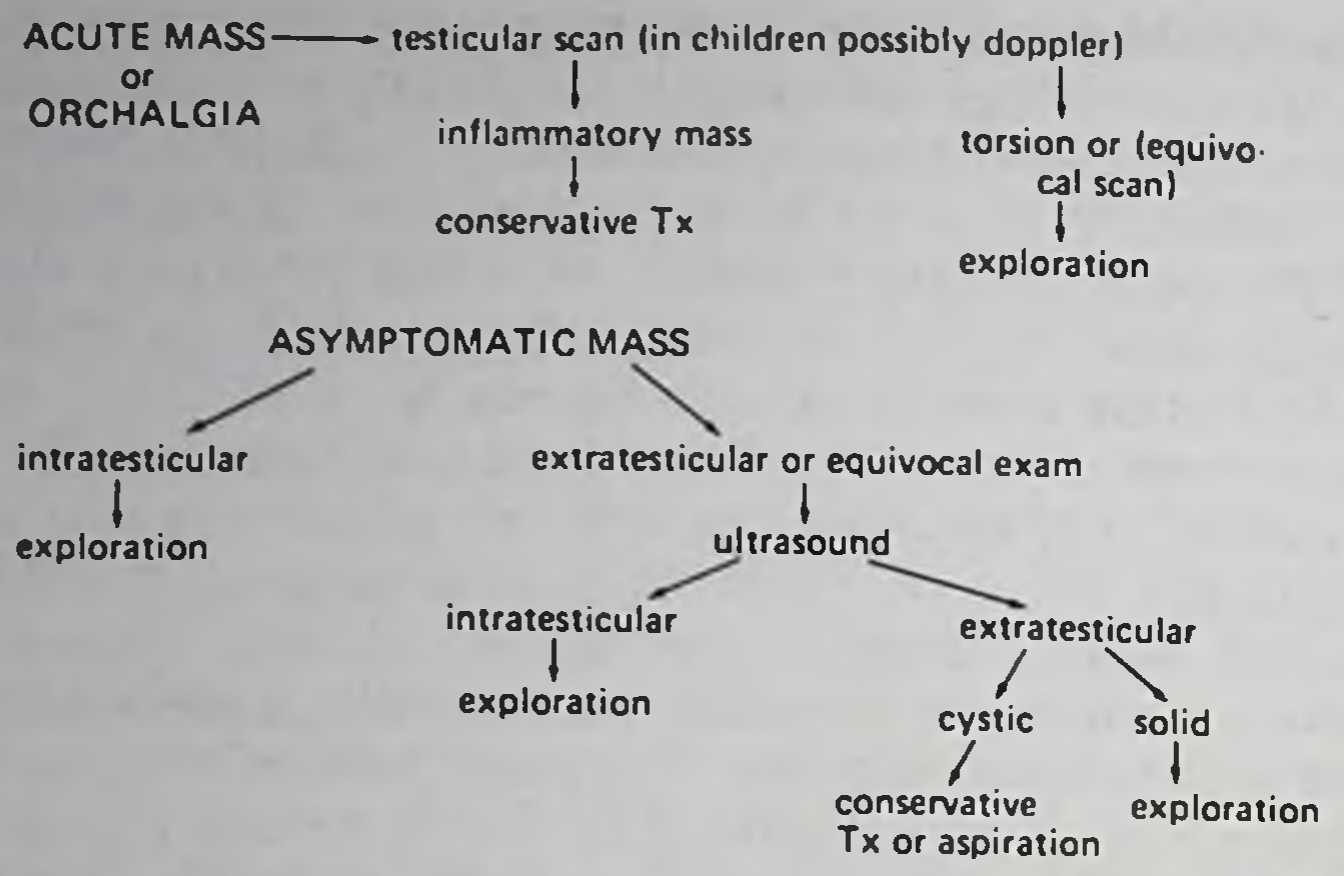

Fig 7–6.—Protocol for scrotal pain or mass of undetermined cause. (Courtesy of Macksood, M. J., and James, R. E., Jr.: Am. J. Surg. 145:297–299, February 1983.)

nant disease. The acute scrotal mass or painful hemiscrotum of undetermined cause should be evaluated by testicular scanning. Management is guided by the results of scanning and by the knowledge that torsion is rare in patients older than age 30 years.

► [The algorithm (Fig 7–6) benefits from its simplicity but suffers from its overall reliance on nuclear scanning as the first step in the evaluation of the acute scrotal mass. Scrotal imaging must not replace a thorough physical examination. Nuclear scanning should only be used in those cases where, after a careful physical examination, the diagnosis is still equivocal. Testicular torsion should not become a nuclear medicine diagnosis alone. The urgency of diagnosis in treatment of testicular torsion cannot be overemphasized, so unless your local nuclear medicine man has the initials "J.O.S." (Johnny on the Spot), don't be pressured into waiting for a procedure that may or may not add anything to what you already feel is going on. Undue delay in obtaining a scrotal scan in initially evaluating all cases would dilute the efficacy of scanning, which approaches 100% in at least one series (*Am. J. Dis. Child.* 136:831, 1982).

If somehow you missed the blitz of commentaries concerning the report from two Dublin hospitals of an association between cold weather and testicular torsion (*Br. Med. J.* 285:1459, 1982), let someone from a colder area of the world than Dublin say that there could be 100 unprintable reasons why there might be an apparent association between frigidity and testicular torsion. Next, I suppose someone will try to do a study of the pitch of the male voice in the Adirondacks.—J.A.S., III] ◄

7–14 **Childhood Nocturnal Enuresis: Factors Associated With Outcome of Treatment With an Enuresis Alarm.** Use of an alarm is currently the most effective treatment for nocturnal enuresis, but some failures continue to occur, and lack of uniformity in defining success makes it difficult to interpret reported results. Sylvia Dische, William Yule, John Corbett, and David Hand (London) examined the factors that may influence the outcome of a single course of treatment of childhood enuresis with an enuresis alarm. A total of 113 children with a mean age of 8.1 years were included in the study. The male-female ratio was 1.5:1. All patients had continued to wet at least 3 nights each week despite reassurance and encouragement. The alarm was used until the child was dry consistently for 3 weeks, and its use

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(7–14) Develop. Med. Child. Neurol. 25:67–80, February 1983.

was resumed if wetting occurred any time in the 3 weeks after treatment was discontinued. Six weeks of dryness were necessary for treatment success.

Only 1 child in 6 failed to achieve the criterion of 42 dry nights, but the relapse rate was 42%. Over half the relapses occurred within 6 months after initial arrest of wetting. Thirty-one children were retreated after relapse, some of them more than once, and 16 of them became and remained dry, for a final success rate of 63%. Five children failed totally to respond to treatment. The outcome is related to various factors in the table. The immediate outcome was influenced only by unsatisfactory housing conditions. Children who relapsed had deviant scores on a teacher rating scale and had family difficulties. The same factors compromised long-term success. Occasional wetting

ASSOCIATION OF OUTCOME OF SINGLE COURSE OF TREATMENT BY ALARM WITH VARIABLES STUDIED*

			Failure of initial arrest			*Relapse*	*Long-term success*	
		Total No.	*No.*	%	*No.*	% *of those initially dry with alarm*	*No.*	%
Total treatment group		113	18	16	40	42	55	49
Variable								
Age at which alarm used	under 7	31	4	13	13	48	14	45
	7 and 8 years	42	6	14	14	34	22	52
	9 and 10 years	26	6	23	8	40	12	46
	11 years and over	14	2	14	5	42	7	50
Sex	boys	68	14	21	22	41	32	47
	girls	45	4	9	18	44	23	51
Birth order	only and eldest	34	9	26	9	36	16	47
	middle	45	6	13	15	38	24	53
	youngest	34	3	9	16	52	15	41
Family size	1 child	5	0	—	3	60	2	40
	2	38	8	22	9	30	21	55
	3	30	4	13	15	58	11	37
	4	26	4	15	8	36	14	54
	more	14	2	14	5	42	7	50
Social class	II & III NM	16	3	19	5	38	8	50
	III M (all skilled)	51	6	12	18	40	27	53
	IV & V	22	4	18	6	33	12	54
	unemployed	11	4	36	3	43	4	36
	single parent	13	1	8	8	66	4	31
Behavioural rating:								
Parent rating A-scale	non-deviant	61	12	20	18	37	31	51
	deviant	50	6	12	21	48	23	46
	not available	2			1		1	
Teacher rating B-scale	non-deviant	65	9	14	17	30	39	60
	deviant	45	9	20	20	56	16	36
	not available	3			3			
Previous treatment tried	no	43	6	14	15	41	22	52
	yes	70	12	17	25	43	33	47
Type of enuresis	primary	93	14	15	33	42	46	49
	secondary	20	4	20	7	43	9	45
Family difficulties	absent	61	5	8	16	29	40	66
	present	52	13	25	24	62	15	29
Unsatisfactory housing	absent	78	7	9	32	45	39	50
	present	35	11	31	8	33	16	46
Mother works outside as well as at home	no	46	10	22	15	42	21	46
	yes	67	8	12	25	42	34	51
Family history of enuresis	absent	38	8	21	10	33	20	53
	present	75	10	13	30	46	35	47

*Relapse is expressed as percentage of those whose wetting was initially arrested with alarm. Numbers of children with urinary tract infection (3), marked day wetting (7), and soiling (2) were so small that these variables were omitted from table.

(Courtesy of Dische, S., et al.: Develop. Med. Child. Neurol. 25:67–80, February 1983.)

by children who represented long-term successes was related nearly always to physical illness or transient environmental stress; it remitted spontaneously.

Children who respond to alarm therapy for nocturnal enuresis can relapse some time after initial arrest of wetting, suggesting that contact be maintained for 2 years after treatment. Retreatment can succeed, but more than one course may be necessary. Occasional wetting is not the proper criterion for relapse. Family difficulties and deviant behavior were factors in the outcome of therapy in this study, but other factors remain to be identified.

7–15 **Dry-Bed Training in the Treatment of Nocturnal Enuresis in Childhood: A Research Report.** Dry-bed training, based on an operant rather than a classic conditioning model, has been developed as an alternative to traditional urine-alarm conditioning in the treatment of nocturnal enuresis. The child is specifically taught that he or she is the locus of control. The procedure incorporates social learning and self-correction techniques such as cleanliness training, nighttime awakening through bladder proprioception, retention control, and differential positive reinforcement for dryness. Peter Griffiths, Clair Meldrum (Univ. of Stirling, Scotland, and Robert McWilliam (Univ. of Glasgow) evaluated the dry-bed approach in a sample of enuretic children from a typical pediatric hospital outpatient department. Twelve children with an average age of 7½ years who had chronic nocturnal enuresis were studied. All had failed to respond to other treatment, including medication and urine-alarm conditioning. A single intensive training night, with hourly awakenings, was followed by a posttraining supervision period during which cleanliness training and positive practice (rehearsal in movement to the toilet) were made contingent on a bed-wetting accident.

All 11 children who remained in the trial achieved 2 weeks without wetting after having previously been wet 6 or 7 nights a week. The median time to this dryness criterion was 4 weeks, but training periods ranged from 2 to 20 weeks. Eight children remained dry 9 months after the start of treatment. The parents initially found the procedure very tiring and stressful and felt that considerable determination was necessary, but parents of children who remitted consistently reported that their children were happier and had greater self-esteem.

All children who remained in the dry-bed treatment program were managed successfully in this study. The children, aged 5–9 years, initially had severe nocturnal enuresis. Nearly three fourths of the patients remained completely dry after 9 months. This procedure makes heavy demands on parents and clinicians, especially at the outset, and further feasibility studies are necessary in the context of routine care.

▶ [There is something in this study and the preceding one for every child with enuresis. Alarms remain among the first-line treatment approaches. The pros are that they are relatively effortless for the child and the parents. The initial success rate is prob-

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(7–15) J. Child. Psychol. Psychiatry 23:485–495, October 1982.

ably the highest of all known approaches, even if the relapse rate is fairly high. If relapses do occur, you can start all over again. There are even newer and better alarm systems that weigh less than 2 oz and have an automatic reset mechanism. These were first designed in Great Britain (Malem et al.: *Br. Med. J.* 285:22, 1982). Word has it that when People Express Airline announced its $149 Newark to London flights, the schedule was backlogged for months with people trying to fly over to Great Britain to pick up one of these new devices.

The dry-bed technique is not for everyone. It is for the child who cannot be "alarmed" and for whom more simple approaches have failed. It would appear to be too labor intensive to be applied as the first line of attack on the problem of enuresis. Literally, both child and parents are up hour after hour during the night. Besides sounding like a deodorant commercial, if the technique were used initially for every enuretic child, it probably would generate many referrals to the psychiatrist for the bleary-eyed parents. When all else fails, the dry-bed approach, as outlined by Griffiths et al., may be worthwhile attempting. The recurrence rate apparently is low. Obviously, these two approaches are as different as can be. The alarm technique, in the jargon of the 1980s, is "quick and dirty," i.e., initially successful, but likely to need repetition for relapses. The dry-bed technique is almost a trial by torture, but the end product is a prolonged interval of success. All of this is sort of reminiscent of the story of the three little pigs. If you build your house out of straw, it's fast and easy, but you may have to do it over again. If you build it out of bricks (and survive the process), it will last. The analogy ends here—the little piggy with the house of sticks had a better idea, sold her straw to a mattress company, and made it rich as Miss Piggy.—J.A.S., III] ◄

8. The Heart and Blood Vessels

8–1 **Symptomatic Pectus Deformities of the Chest.** Aspects of exercise tolerance and pulmonary mechanics in 8 male patients, aged 9–22 years, with symptomatic and asymptomatic pectus deformities were studied by Robert G. Castile, Bruce A. Staats, and Philip R. Westbrook (Mayo Clinic). Seven patients had pectus excavatum and 1 had pectus carinatum. Although symptom free at rest, 5 patients had complaints related to exercise intolerance.

Standard measures of pulmonary mechanics in patients with pectus excavatum showed that mean total lung capacity (TLC) was 79% of predicted capacity—compatible with a mild restrictive deficit. The mean ratio of residual volume to TLC was 21.4% and the mean flow at 50% of vital capacity was 82%; the mean ratio of forced expiratory volume in 1 second to forced vital capacity was 81%. There was no evidence of airway obstruction as the decreased flows appeared to be related to reduced lung volumes. The normal response to exercise of dead space to tidal volume and alveolar-arterial oxygen difference indicates that there was no significant ventilation-perfusion abnormality in 4 symptomatic patients.

In symptomatic patients, measured oxygen uptake increasingly exceeded predicted values as work loads approached maximum and exceeded predicted values by 25.4%. There was a normal linear relationship of mean oxygen uptake to mean heart rate.

These results demonstrate that patients with symptomatic pectus deformities have oxygen uptake values that are normal at low work loads but progressively exceed predicted values at greater work loads. Initial increases in ventilation during exercise are accomplished predominantly by increases in tidal volume. As greater levels of ventilation are approached, tidal volume increases diminish and further increases in ventilation are the result of increases of respiratory frequency. Patients with restrictive lung disease have a depressed tidal volume response during exercise that may be partly related to reduced vital capacity. Whether reported respiratory mechanical abnormalities of function can be ameliorated at present by surgical procedures awaits further documentation of preoperative and postoperative functions.

▶ [Dr. Rae-Ellen Kavey, Associate Professor of Pediatrics, State University of New York at Syracuse, comments:

"Pectus excavatum is a common orthopedic anomaly pediatricians are asked about frequently. It occurs approximately three times as often in boys as in girls. Although some patients are symptomatic from pectus, many are not, and surgery is usually cosmetic. Still, symptomatic improvement is said to occur in some cases, and several investigators have tried to document a physiologic abnormality of the respi-

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(8–1) Am. Rev. Respir. Dis. 126:564–568, September 1982.

ratory or cardiac system in this condition. The paper by Castile et al. is a pulmonary study of 8 adolescents, 5 of whom reported exercise intolerance. Very minor abnormalities are documented, i.e., a small decrease in total lung capacity at rest and a small increase in oxygen uptake at submaximal exercise. No patients were studied postoperatively.

The only study I am aware of that documents a physiologic improvement with pectus surgery is a cardiac study by Beiser et al. (*N. Engl. J. Med.* 287:267–272, 1972), from the National Institutes of Health, that shows an increase in cardiac output at peak exercise in restudied surgical patients performing upright exercise. The study by Beiser et al. should be an example to the investigators in this field, as serial studies should be performed in operative patients at peak exercise. Clearly, the resting physiologic state in pectus excavatum is nearly normal. Significant abnormalities with exercise must be documented and their disappearance with surgery affirmed if a physiologic basis for surgery for this consideration is to be proposed. Castile et al., in the conclusion to their article, acknowledge that just such an argument cannot be made from the preoperative data."] ◄

8–2 **Incidence of Postextraction Bacteremia Under Penicillin Cover in Children With Cardiac Disease.** It has been recommended that patients susceptible to bacterial endocarditis receive antibiotic prophylaxis when undergoing dental extraction, but the efficacy of this practice has not been examined in children. J. Hess, Y. Holloway, and J. Dankert (Univ. of Groningen) examined the value of penicillin prophylaxis in 82 children with heart disease undergoing extraction of primary or permanent teeth. Mean age was 9.7 years. Children younger than age 6 received 450,000 units of procaine penicillin G and 150,000 units of aqueous penicillin G intramuscularly. Older children received doses of 900,000 and 300,000 units, respectively, 45 minutes before extraction.

Postextraction bacteremia was diagnosed in 21% of the children, 6

MICROORGANISMS ISOLATED FROM POSTEXTRACTION BLOOD CULTURES IN RELATION TO THEIR SUSCEPTIBILITY TO PENICILLIN*

Microorganisms Isolated	No. of Penicillin-Sensitive Strains	No. of Penicillin-Resistant Strains	Total No. of Isolates
Aerobes	21 (9)	6 (5)	27 (13)
Viridans streptococci†	15 (7)	4 (3)	19 (10)
Streptococcus faecalis		1 (1)	1
Micrococcus sp	2 (2)		2 (2)
Staphylococcus epidermidis	1		1
Corynebacterium sp	2 (2)		
Bacillus sp	1		1
Haemophilus parainfluenzae		1 (1)	1
Anaerobes	3 (3)	2 (2)	5 (5)
Bacteroides capillosus		1 (1)	1
Veillonella parvula		1 (1)	1
Clostridium sp	1		1
Eubacterium ventriosum	1		1
Propionibacterium jensenii	1		1
Total	24 (12)	8 (7)	32 (17)

*Number of patients is shown in parentheses.
†Viridans streptococci were subdivided into species: six blood cultures contained more than one strain.
(Courtesy of Hess, J., et al.: Pediatrics 71:554–558, April 1983. Copyright American Academy of Pediatrics 1983.)

(8–2) Pediatrics 71:554–558, April 1983.

of whom had polymicrobial bacteremia. *Streptococcus viridans* was isolated from 10 children. Serum penicillin concentrations were similar in children with and those without positive blood cultures. The sensitivity of the organisms isolated is shown in the table. The mean serum penicillin concentration in children with bacteremia due to penicillin-sensitive organisms, determined 5 minutes after extraction, did not differ from that in children with bacteremia due to penicillin-resistant organisms.

Transient postextraction bacteremia can occur in children receiving parenteral penicillin prophylaxis as recommended by the American Heart Association. Bacterial endocarditis did not develop in any of these patients, but endocarditis apparently due to failure of penicillin prophylaxis has been described, and a high proportion of the organisms causing postextraction bacteremia are resistant to penicillin. Further studies are needed to evaluate penicillin plus streptomycin or a single oral dose of amoxicillin for prevention of postextraction bacteremia.

▶ [I have the suspicion that the results of this study will be overinterpreted. This report did not show any problem with endocarditis resulting from dental procedures under the cover of penicillin. It showed a 21% incidence of postextraction bacteremia despite the penicillin. About one fourth of the organisms causing the bacteremia were penicillin resistant.

What all this means is unquestionably speculative. One thing it does not mean, I hope, is that we should be seriously thinking about some other antibiotic combination as a form of dental prophylaxis. M. P. Glauser et al. (*Lancet* 1:237, 1983) did a very interesting animal model study in order to determine what the best mechanism for prophylaxis against bacterial endocarditis would be. These investigators also showed a high incidence of penicillin resistance. Nonetheless, they concluded that bacterial killing did not seem to be a requisite for successful prophylaxis of bacterial endocarditis. In one of their studies in rats, they suggested that prophylaxis may be achieved by prevention of bacterial adherence to the abnormal endocardium. I think the reason the study by Hess et al. found what it did was based simply on the phenomenon of drawing blood cultures so soon after the extraction that the antibiotics had not yet had a chance to do their job. One cannot expect antibiotics to prevent organisms from getting into the bloodstream initially. The job the dentist has to do in cleaning the gingiva or pulling out a tooth is so much of a manhandling (I'm sorry, people-handling) of the tissue that nothing in the world short of sterilizing the mouth would prevent the first seeding of the blood.

Unequivocal documentation of the effectiveness of penicillin prophylaxis has never taken place because of the infrequency with which bacterial endocarditis occurs. One would hope that the very rare cases of endocarditis occurring in the face of penicillin prophylaxis are not enough to change our thinking about this old-time excellent drug. If we do make a switch, I think it would be about as effective as the Australian trying to throw away his old boomerang. It will come back to haunt us or smack us right in the face.—J.A.S., III] ◀

8–3 **Surgical Treatment of Purulent Pericarditis in Children.** Antibiotic therapy and pericardial drainage have reduced mortality from purulent pericarditis in children, but the type of drainage necessary and the risk of subsequent constrictive pericarditis if the pericardium is not removed are unknown. Richard J. Morgan, Larry W. Stephenson, Paul K. Woolf, Richard N. Edie, and L. Henry Edmunds, Jr. (Univ. of Pennsylvania) reviewed experience with 15 children seen since 1971 with a diagnosis of acute bacterial pericarditis. All had

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(8–3) J. Thorac. Cardiovasc. Surg. 85:527–531, April 1983.

Case No.	Age	Organism	Clinical Presentation: Duration of illness (days)	Clinical Presentation: Initial presentation	Associated sites of infection
1	30 mo	*H. influenzae* type B	3	Fever, tachypnea respiratory distress	—
2	3 yr	*H. influenzae* type B	2	Fever, abdominal pain, vomiting	—
3	3 yr	*H. influenzae* type B	7	Fever, abdominal pain, vomiting	—
4	9 mo	*H. influenzae* type B	3	Fever, vomiting	
5	3 yr	*H. influenzae* type B	3	Tamponade, respiratory distress	Pneumonia
6	4 yr	*H. influenzae* type B	4	Fever, vomiting, disorientation, shock	None
7	11 mo	*H. influenzae* type D	7	Fever, knee pain, respiratory distress	Left knee
8	14 mo	*S. aureus*	4	Respiratory distress	Submandibular abscess, bilateral hip arthritis
9	21 mo	*S. aureus*	7	Fever, anorexia	Scalp, buttock abscess
10	3 yr	*S. aureus*	4	Fever, anorexia	Femoral osteomyelitis
11	9 mo	Streptococcus Group A	2	Fever, respiratory distress	—
12	19 mo	Pneumococcus	7	Fever, anorexia, lethargy	—
13	6	Meningococcus	9	Fever, meningitis, abdominal pain, vomiting	Meningitis, arthritis
14	7 days	Klebsiella	1	Fever, respiratory distress	Pneumonia
15	19 mo	Gram-positive diplococci	?	Otitis, sepsis, renal failure, adrenal necrosis, shock	Otitis

(Courtesy of Morgan, R. J., et al.: J. Thorac. Cardiovasc. Surg. 85:527–531, April 1983.)

evidence of pus in the pericardium, and in 7 the causative organism was cultured from pericardial fluid.

The clinical features are summarized in the table. All patients initially had febrile illness of short duration. One was admitted in septic shock after intravenous antibiotic therapy elsewhere and died within 24 hours. The other patients had respiratory distress, anorexia, or abdominal discomfort. Eight patients had significant infection at an-

other site. None of the patients was found to have immune deficiency. The most common causative organism was *Hemophilus influenzae*. Nine patients had positive blood cultures. All surviving patients received antibiotic therapy for 2 to 6 weeks, and all underwent pericardial decompression. Four patients had simple needle aspiration, and 2 recovered without further pericardiocentesis. Ten patients were operated on. Seven had anterior interphrenic pericardiectomies and 1 had a total pericardiectomy. None of the 14 survivors has had recurrent purulent pericarditis on follow-up for up to 13 years. All are in New York Heart Association class I without cardiac medication.

Patients with purulent pericarditis can be treated successfully by pericardial drainage and appropriate antibiotic therapy. Pericardiocentesis is adequate if the infected pericardial fluid is thin enough to flow through a needle or a percutaneously placed drainage catheter. Patients with recurrent pericardial sepsis or tamponade are not helped by repeated pericardiocentesis. Pericardiostomy frequently provides inadequate drainage. A theoretical advantage of pericardiectomy is prevention of late constrictive pericarditis. Immediate pericardiocentesis is indicated in all suspect cases and early pericardiectomy if *H. influenzae* is found to be the causative organism. Otherwise, pericardiectomy is done immediately if tamponade follows initial pericardiectomy or if fever persists after appropriate antibiotic therapy.

▶ [These authors attempt to throw some sanity toward the vagarious approaches that surgeons have used to manage purulent pericarditis. There are two considerations in treating patients with purulent pericarditis: (1) resolution of the acute infection and (2) prevention of constrictive pericarditis. Early and complete evacuation of the infected pericardial space and use of antibiotics are necessary to eliminate the acute infectious process. Morgan et al. nicely demonstrate that needle or small-bore catheter pericardiocentesis and drainage are inadequate to evacuate the pericardial space effectively in most patients with purulent pericarditis. However, the safest and most effective method of surgical drainage of the pericardial space remains to be defined. In a commentary on their article, D. J. Driscoll et al. (*J. Thorac. Cardiovasc. Surg.* 85:531, 1983) suggest that it might be possible to avoid the need for pericardiectomy in cases of *H. influenzae* pericarditis if a very-large-bore pericardiostomy tube is placed immediately on diagnosis. The authors of this study counter by saying that in their experience the consistency of the purulent material with *H. influenzae* infection is similar to that of scrambled eggs and the material cannot be removed by simple drainage (I find their analogy to an edible food substance disgusting, especially because this commentary is being written at 8:30 A.M.; they could have used the words "friable lumps" and they would have gotten their point across). What everyone agrees on is that it is vital that appropriate antibiotic therapy be utilized. Appropriate antibiotic therapy includes the correct antibiotic (confirmed by in vitro sensitivity testing), the correct dose (confirmed by serum antibiotic assay), the correct route of administration (intravenous), and the correct timing (begun immediately on diagnosis).—J.A.S., III] ◀

8–4 **Respiratory Syncytial Viral Infection in Infants With Congenital Heart Disease.** Although occasional reports of fatal respiratory syncytial virus (RSV) infections in infants with congenital heart disease have appeared, the relation between the two has not been studied. Noni E. MacDonald, Caroline Breese Hall, Stephen C. Suffin, Chloe Alexson, Peter J. Harris, and James A. Manning prospectively

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(8–4) N. Engl. J. Med. 307:397–400, Aug. 12, 1982.

TABLE 1.—Comparison of Infants With and Without Congenital Heart Disease Infected With Respiratory Syncytial Virsus (RSV)

	Patients with RSV Infection *		P Value
	With congenital heart disease	Without congenital heart disease	
Number of infants	27	202	
Mean age (mo)	5.7	5.3	
Mean hospitalization for RSV (days)	20	8	
Number in intensive care †	17 (63)	29 (14)	<0.001 ‡
Number on assisted ventilation †	6 (22)	11 (5)	<0.01 §
Number of deaths	10 (37)	3 (1.5)	0.03 §
Number with nosocomial RSV	9 (33)	40 (20)	0.17 §
Mortality rate for nosocomial RSV	4 (44)	2 (5)	<0.01 §

*Figures in parentheses are percentages.
†Required for the RSV infection.
‡By χ^2 test.
§By χ^2 test with Yates's correction.
(Courtesy of MacDonald, N. E., et al.: N. Engl. J. Med. 307:397–400, Aug. 12, 1982.)

examined infants with congenital heart disease to determine if they had increased risk of severe illness from RSV. During the winters of 1976–1980, when RSV was prevalent in the community, the 699 infants younger than age 2 years who were admitted to Strong Memorial Hospital, Rochester, New York, were studied. Nasal wash solutions were used to isolate virus; infection was considered nosocomial if negative wash was followed by positive wash 7 or more days after admission.

Two hundred twenty-nine infants had proved infections with RSV either before admission or during hospitalization. Twenty-seven had both congenital heart disease and RSV infection, whereas 46 had congenital heart disease without infection. Infected infants with congenital heart disease had significantly more severe illness than those without congenital heart disease, as judged by the requirement for intensive care and assisted ventilation, as well as by the mortality (37% vs. 1.5%, $P < .01$) (Tables 1 and 2).

TABLE 2.—Comparison of Fatal and Nonfatal Cases of Respiratory Syncytial Viral Infection in Infants With Congenital Heart Disease*

	Fatal Cases (n = 10)	Nonfatal Cases (n = 17)
Mean age (mo)	5.8	5.6
No. with cyanosis	8 (80)	7 (41)
No. with increased pulmonary blood flow	9 (90)	14 (82)
No. with pulmonary hypertension	8 (80)	3 (18)

*Figures in parentheses are percentages.
(Courtesy of MacDonald, N. E., et al.: N. Engl. J. Med. 307:397–400, Aug. 12, 1982.

The infection was acquired nosocomially by 21% of infected infants; mortality from nosocomial infection was also higher in infants with (44%) than in those without (5%; $P < .01$) congenital heart disease. Pulmonary hypertension was the one condition particularly associated with severe RSV illness. Eight of the 11 infants (73%) with congenital heart disease and pulmonary hypertension died during RSV illness.

Ages, types of cardiac lesions, and incidence of pulmonary hypertension were similar in infants with congenital heart disease with and without RSV infection, but the infants with RSV infection had a higher mortality (37% vs. 6.5%; $P < .01$).

▶ [Respiratory syncytial virus (RSV) continues to be a bad actor. The 73% mortality associated with this infection in the presence of pulmonary hypertension is truly alarming. What this exactly is due to is not clear. Most of the infants apparently died of irreversible hypoxia. One might speculate, therefore, that infants with congenital heart disease associated with pulmonary hypertension are less able to compensate for the altered distribution of ventilation that occurs with RSV infection. It is unfortunate that some of the infants acquired their RSV infection from other babies in the hospital. As the authors point out, it seems prudent, therefore, to avoid elective admissions of infants with congenital heart disease during periods when RSV is present in the community. If some such infants must be admitted, staff should be aware of the potential hazard to these babies of nosocomial transmission of RSV. The infection is highly contagious, and control of nosocomial spread is difficult, at best. Respiratory syncytial virus appears to be spread by contact with infectious secretions through direct inoculation of large droplets or contaminated hands. Careful hand washing should be stressed. Also, isolation in a single room, if feasible, might help to protect these infants. The importance of developing an effective vaccine or antiviral agent for this group is emphasized by the facts that 1% of infants born alive have congenital heart disease and as many as 50% may acquire RSV infection during the first year of life. These same investigators reported at the spring meetings of the Society for Pediatric Research in 1982 that the synthetic nucleoside, ribavirin, may be administered safely to infants and may be beneficial in ameliorating the course of severe RSV pneumonia.

All of us should hope that the group in Rochester, New York, continues with their excellent studies on RSV. The design of these investigations is sterling and always done right the first time. One wonders if Doctors MacDonald et al. were not carpenters in their youth and learned the basic principle of "measure twice, saw once."—J.A.S., III] ◀

8–5 **Furosemide Promotes Patent Ductus Arteriosus in Premature Infants With Respiratory Distress Syndrome.** Patent ductus arteriosus is a frequent complication of respiratory distress syndrome in premature infants. It may further impair lung function and is associated with delayed pulmonary recovery and a higher risk of chronic lung disease. There is retrospective evidence that furosemide, which often is given to avoid or treat fluid overload and which stimulates the renal production of prostaglandin E_2, a ductal smooth muscle dilator, may increase the incidence of patent ductus. Thomas P. Green, Theodore R. Thompson, Dana E. Johnson, and James E. Lock (Univ. of Minnesota, Minneapolis) administered furosemide to 33 premature infants with respiratory distress syndrome and administered chlorothiazide, a diuretic that does not stimulate prostaglandin E synthesis, to 33 other infants. Furosemide, 1mg/ml concentration, or chlorothiazide, 20 mg/ml concentration, was given at a dose of 1 mg/

(8–5) N. Engl. J. Med. 308:743–748, Mar. 31, 1983.

kg. Fluids were restricted to 60–80 ml/kg daily as long as mechanical ventilation was necessary.

Patent ductus occurred in 18 of the 33 furosemide-treated infants and in 8 of 33 given chlorothiazide. Eleven and 7 infants, respectively, required ductal ligation. Six other infants, all in the furosemide group, later were found to have a patent ductus. Overall survival was 76% in the furosemide group and 61% in the chlorothiazide group. Small increases in urinary prostaglandin E followed the initial doses of both drugs. After the fifth day of life, prostaglandin E excretion increased threefold after furosemide but did not increase after chlorothiazide administration.

Furosemide appears to increase the incidence of patent ductus arteriosus in premature infants with respiratory distress syndrome, probably through a prostaglandin-mediated process. Mortality was lower in furosemide-treated infants than in those given chlorothiazide. The duration of ventilation was unaffected by the diuretic used. The findings do not support a role for the wider use of chlorothiazide in infants with respiratory distress syndrome. The large doses needed for effective sustained diuresis might increase the risk of kernicterus in jaundiced infants.

▶ [Diuretics are used widely in the management of premature infants. It is thought that fluid restriction by any means (including by the administration of diuretics such as furosemide) helps prevent many of the complications seen in preterm infants. Thus, furosemide is used to avoid and treat fluid overload, which predisposes preterm infants with the respiratory distress syndrome to deleterious pulmonary and cardiovascular effects, as well as to treat patients with signs and symptoms of a patent ductus arteriosus (PDA). It is ironic, therefore, that these investigators are now showing that furosemide promotes the patency of the ductus arteriosus. They have shown that furosemide stimulates the renal production of prostaglandin E_2, a potent ductal smooth-muscle dilator.

Despite the fact that furosemide administration seems to increase the incidence of PDA, on the balance scales, it produces neither beneficial nor harmful effects in the treated patients. Presumably it works so well as a diuretic for the main purposes for which it is intended, to prevent the consequences of fluid overload, that these effects outweigh the harmful side effect of a greater incidence of PDA. Apparently other diuretics such as chlorothiazide just don't work as well as Lasix in terms of water unloading in the tiny baby.

Patent ductus arteriosus continues to be common in our nurseries. A multicenter collaborative project reported by Ellison et al. (*Pediatrics* 71:364, 1983) has shown that the incidence of PDA in babies lighter than 1,000 gm is 42%. This incidence drops to 20% for babies weighing between 1,000 gm and 1,500 gm. For babies weighing 1,500 to 1,750 gm, the incidence is 7%. What to do about this high frequency still remains controversial. We all look forward to definitive collaborative reports on the real effectiveness of indomethacin in closing the PDA. Most small series of reports have failed to show the very high effectiveness described in the earlier reports with the use of indomethacin. In the aggregate, it seems that about 50% of babies are continuing to respond to this pharmacologic closure approach. The main resistance to the use of indomethacin has been its renal toxicity. Curiously, furosemide may prevent the renal side effects of indomethacin while at the same time not affecting the efficacy of this drug in the closure of PDA (Yeh, T. F., et al.: *J. Pediatr.* 101:433, 1982). How furosemide works for this purpose is certainly unclear. There also has been a suggestion during this past year that antenatally administered glucocorticoids may help in lowering the incidence of symptomatic PDAs (Waffarn, F., et al.: *Am. J. Dis. Child.* 137:336, 1983). This is a smart observation and is based on the fact that women who have prolonged rupture of the membranes (and who therefore probably have high endogenous glucocorticoid levels) have babies with a remarkably low incidence of PDAs.

I think some conclusions can be drawn from all of the information. Symptomatic babies with PDAs are likely to benefit from good supportive care. Aggressive therapy directed at immediate closure of the ductus is indicated in the very immature infant, whereas the infant near term will almost certainly experience spontaneous closure of the ductus without serious sequelae. Treatment prior to postnatal age 7 to 10 days results in less moribidity and better response than delayed closure of the ductus. Definitive closure of the premature PDA by surgical ligation at this point in time must still be considered the treatment of choice in centers where surgeons experienced in this technique are housed. Pharmacologic closure with indomethacin is moderately effective when administered early, and a therapeutic trial with the medication may be justifiable. It also should be noted that although one of the major reasons for closing a PDA is to decrease the markedly pulsatile blood pressure changes to the brain (and, therefore, hopefully to decrease the rate of intraventricular hemorrhage), Marshall et al. (*J. Pediatr.* 101:749, 1982) have shown that an abrupt 30% increase in blood pressure occurs at the moment of ligation. Such abrupt changes are helpful to no one, and it was suggested that the ductus be closed gradually over the course of a minute or so rather than just quickly tied off.—J.A.S. III] ◄

8–6 **Noninvasive Tests in the Initial Evaluation of Heart Murmurs in Children.** Jane W. Newburger, Amnon Rosenthal, Roberta G. Williams, Kenneth Fellows, and Olli S. Miettinen (Harvard Med. School) prospectively studied the frequency with which routine electrocardiography, chest radiography, and M-mode echocardiography change the clinical diagnosis, made by a pediatric cardiologist, of the absence or presence of heart disease in 280 children older than 1 month newly referred for evaluation of a heart mumur.

After a history and physical examination were performed but before diagnostic tests were reviewed, the children were categorized as having "no heart disease" (142), "possible heart disease" (34), or "definite heart disease" (104). Among the children initially thought to have no heart disease, the diagnosis was changed after a review of diagnostic tests in 8—3 with mitral valve prolapse, 2 with possible cardiomyopathy, and 3 with no heart disease on follow-up. Among those initially thought to have possible heart disease, the tests changed the diagnosis to definite heart disease in 4, of whom only 1 had heart disease (mitral valve prolapse) on follow-up. In 8 of the 34 patients initially thought to have possible heart disease, the diagnosis was changed to no heart disease after review of the tests. In no case did a review of tests change the diagnosis of definite heart disease.

The results of noninvasive diagnostic tests are unlikely to change the clinical diagnosis of no heart disease or definite heart disease when made by a qualified pediatric cardiologist in children newly referred for evaluation of a heart murmur. When the initial diagnosis is definite heart disease, tests may be needed for quantification of severity or delineation of the type of disease. When the clinical evaluation of a child with a murmur is inconclusive, tests may be useful to exclude heart disease, but they do not commonly demonstrate its presence. The findings may not be generalizable to examinations performed by physicians less skilled in pediatric cardiology.

▶ [This study has created quite a stir in pediatric cardiology circles. The study concludes that when a qualified pediatric cardiologist makes a diagnosis either of no

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(8–6) N. Engl. J. Med. 306:61–64, Jan. 13, 1982.

heart disease or definite heart disease on the basis of history and physical examination alone, diagnostic tests provide little additional useful information concerning the presence or absence of heart disease. I suppose what they are suggesting is that when the cardiologist feels strongly that there is nothing going on, that nothing else should be done. They support this statement with the fact that further tests would only prove costly. Additionally, a major drawback of performing diagnostic tests routinely in children with innocent-sounding murmurs is the possibility of a diagnosis of heart disease resulting from falsely positive tests. They go on to suggest that in children whose history and physical examination by an experienced observer suggest absence of heart disease, any abnormality actually present is likely to be trivial. A priori, the discriminating power of diagnostic tests must be poor when the difference between normal and abnormal is minimal. Therefore, test results that are positive are most likely falsely positive, resulting in a false diagnosis of heart disease. I personally believe this concept. How many times have you ordered just one more test to be sure everything was all right, only to find that it was slightly out of line and you had to track that down, and on and on?

What I don't necessarily agree with is their statement that when they were initially wrong in making a diagnosis of no heart disease, what was found subsequently were relatively minor cardiac problems that would not have required any different management. The largest group of these were instances of mitral valve prolapse of a functionally insignificant variety. Many people feel very strongly that it is important to know whether someone has mitral value prolapse, even if there is no mitral regurgitation, so that these patients can receive prophylaxis with penicillin for dental procedures.

The only way of knowing if these investigators have the courage of their convictions would be to go into the cardiology clinic at the Children's Hospital Medical Center in Boston and see if they practice what they preach. In the last paragraph of their discussion of this article, the investigators "give an inch" when they say that the performance of tests in such patients (that is, those who are thought to have definitely no heart disease) might have other uses, such as reassurance of the parents and their families or providing a baseline for comparison if the possibility of heart disease is raised later. Once you have given up an inch in this regard, you have given up the ballgame. I wonder what the wager would be concerning whether these investigators are indeed practicing what they preach or whether they are telling us to do as they say, not as they do.—J.A.S., III] ◀

8–7 **Percutaneous Balloon Valvuloplasty: A New Method for Treating Congenital Pulmonary Valve Stenosis.** Surgical treatment of pulmonary valve stenosis is well established and carries little risk. However, the surgical approach involves a sternotomy, open heart operation, exposure to blood products, a surgical scar, and 1–2 weeks of hospitalization. Jean S. Kan, Robert I. White, Jr., Sally E. Mitchell, and Timothy J. Gardner (Johns Hopkins Univ.) considered balloon valvuloplasty of the congenitally stenotic pulmonary valve a reasonable alternative to open heart operation because of: (1) the early success of surgery in relieving pulmonary valve stenosis, (2) the ability to construct polyethylene balloons of almost any size in which high pressures can be applied without overdistension of the balloon, and (3) the ability of the right ventricle to function after removal of the pulmonary valve.

Patient, aged 8, asymptomatic, but with a diagnosis of pulmonary valve stenosis had a right ventricular impulse. Both S_1 and S_2 were single. A grade 3 of 6 systolic ejection murmur and a grade 2 of 6 low-frequency early diastolic murmur were present. A pulmonary ejection click was present at the left upper sternal border. The ECG demon-

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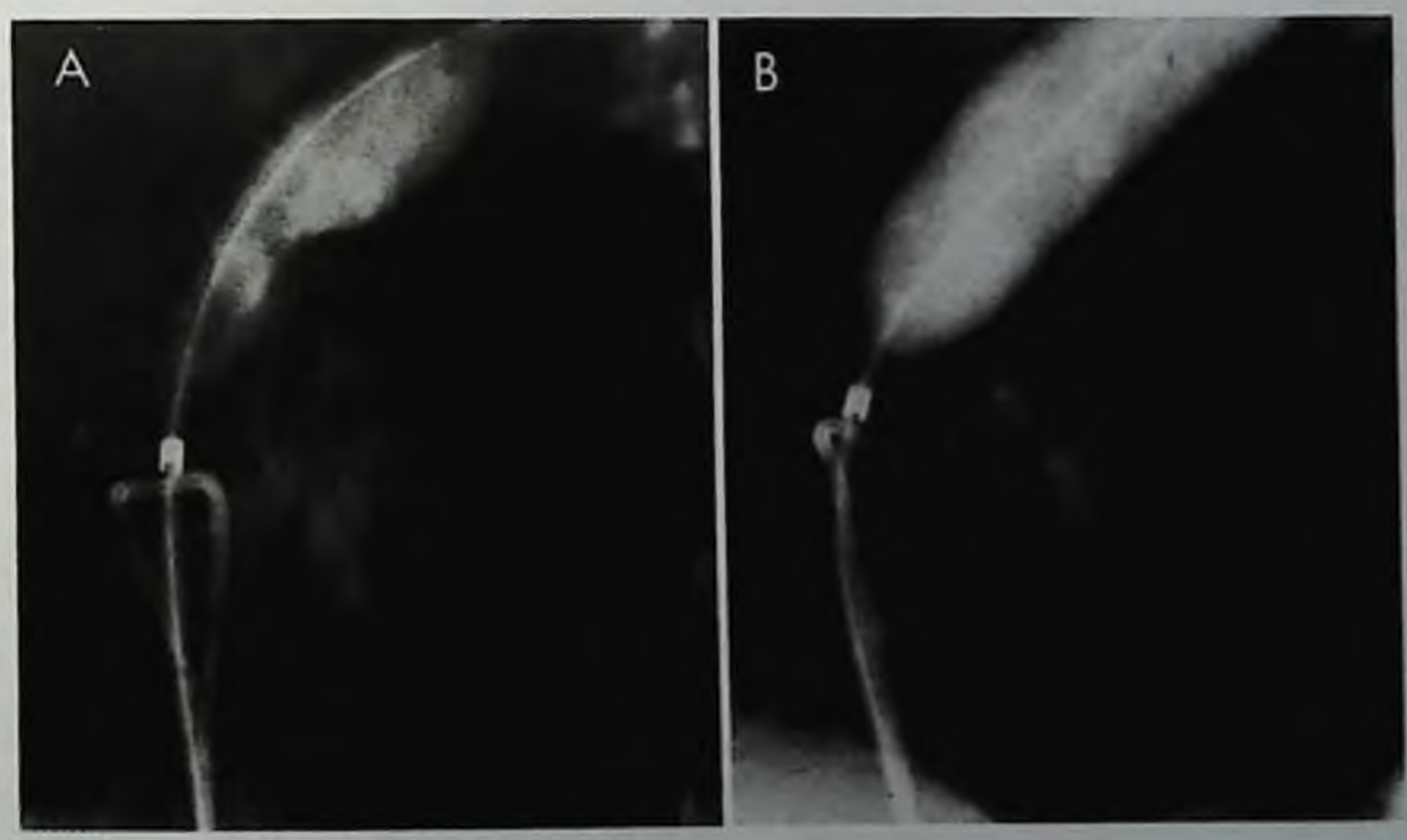
(8–7) N. Engl. J. Med. 307:540–542, Aug. 26, 1982.

strated right ventricular hypertrophy. Cardiac catheterization revealed pulmonary valve stenosis with right ventricular pressure of 60/4 mm Hg and a systemic arterial pressure of 100/50 mm Hg.

METHOD.—A 5 F catheter was placed into the right ventricle through the left femoral vein to monitor right ventricular pressure. An 18-gauge cannula was placed in the left femoral artery to monitor systemic pressure. Heparin (100 units/kg of body weight) was given during the procedure.

A 7 F balloon wedge catheter was advanced into the pulmonary artery from the right femoral vein. A 200-cm (diameter 0.035 in.) exchange tight "J" guide wire was passed through the catheter into the pulmonary artery of the left lower lobe. The wedge catheter was removed, leaving the guide wire in place. The dilatation catheter consisted of a 9 F catheter with a polyethylene balloon, 14 × 40 mm; it was advanced over the exchange guide wire and positioned across the stenotic pulmonary valve. The guide wire was left in place in the left pulmonary artery to stabilize the tip of the dilatation catheter. The balloon was briefly inflated by hand with dilute contrast material to a pressure of 45 psi (Figs 8–1, *A*, *B*) while right ventricular and systemic arterial pressures were recorded. The inflation-deflation cycle lasted 20–30 seconds, with less than 10 seconds of complete occlusion of the right ventricular outflow. At the end of the occlusion period, there was mild sinus bradycardia with an ectopic atrial pacemaker and an occasional isolated premature ventricular contraction. After deflation there was a transient rise in the right ventricular pressure, then a gradual decrease over 15 minutes to a stable value of 28 mm Hg.

Fig 8–1.—Left anterior oblique projection of the heart with dilatation balloon positioned across the pulmonary valve. *Left*, initial phase of inflation of the balloon with contrast material shows the balloon constricted by the stenotic valve *(arrow)*. *Right*, the balloon fully inflated with a consistent diameter of 14 mm. (Courtesy of Kan, J. S., et al.: N. Engl. J. Med. 307:540–542, Aug. 26, 1982.)



The patient was discharged the day after the procedure. A decrease in the right ventricular hypertrophy was noted on ECGs at 1 and 4 months after the procedure.

Balloon valvuloplasties have since been performed on 4 additional patients, between ages of 3 months and 14 years, with immediate reductions in the ratio of right ventricular pressure to systemic artery pressure.

Balloon valvuloplasty will require careful selection of patients. Pulmonary stenosis secondary to dysplasia of the pulmonary valve probably will not be corrected by this procedure. Balloon valvuloplasty may become an attractive alternative to open heart surgery for the treatment of congenital pulmonary valvular stenosis if more patients can be treated successfully with this technique.

▶ [William J. Rashkind, Professor of Pediatrics and Director of the Cardiovascular Laboratories, Children's Hospital of Philadelphia, comments:

"Kan et al. reported the experimental basis for balloon valvoplasty for pulmonary valve stenosis, and in this paper describe a clinical success. They have subsequently reported using the method in 7 more patients. Others have performed the procedure and have described favorable results to this commentator. Since balloon atrioseptostomy was reported in 1966, a wide variety of procedures has been developed to expand the cardiac catheter from a solely investigational and diagnostic device to a therapeutic instrument. The following interventional cardiac catheterization procedures have been reported to have been used in children: balloon atrioseptostomy, blade atrioseptotomy, transvenous or transarterial pacemaker insertion (temporary or permanent), retrieval of foreign bodies from the cardiovascular system, transcatheter closure of atrial septal defect, transcatheter closure of patent ductus arteriosus, occlusion of arteriovenous fistulas, occlusion of collateral vessels, occlusion of shunts (natural or surgical), transvalvar balloon angioplasty, transcoarctation balloon angioplasty, and dilatation of stenosed and/or hypoplastic arteries.

"Our studies on transcatheter closure of atrial septal defects and patent ductus arteriosus are well advanced. For atrial septal defect closure, a six-rib miniumbrella, up to 35 mm in diameter, can be delivered in a 10 F catheter sheath. Twenty-five patients have been treated with this technique without untoward complications, and adequate closure has been achieved in 60%–70% of them. A smaller system of similar design has been used in 30 children as small as 2.4 kg, for closure of patent ductus arteriosus. There has been a similar success rate without significant complications.

"Therapeutic cardiac catheterization has come of age. It is now possible to dilate stenoses, retrieve foreign bodies, and implant prostheses to close holes or occlude vessels, as well as to produce atrial septal defects. Further technical developments and clinical experience will improve the results, making it possible to avoid thoracotomy for more and more children."] ◀

8–8 **Incidence of Mitral Valve Prolapse in Adolescent Scoliosis and Thoracic Hypokyphosis** was studied by Stephen S. Hirschfeld, Charles Rudner, Clyde L. Nash, Jr., Eliezer Nussbaum, and Eleanor M. Brower to determine the overall incidence of mitral valve prolapse (MVP) in idiopathic scoliosis. A subgroup with familial skeletal abnormalities was assessed to determine whether a strong common inheritance existed for both disorders. From the scoliosis clinic 8 male and 66 female patients (average age 16.8 years) were selected randomly. The standard Cobb method was used to measure the lateral or scoliotic thoracic curvature and the anteroposterior or hypokyphotic thoracic curvature. Presence of thoracic hypokyphosis was established from lateral chest/or lateral spine x-ray films. Hypokyphosis

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(8–8) Pediatrics 70:451–454, September 1982.

was considered present with a curvature of less than 20 degrees on expiratory lateral spine x-ray studies or less than 30 degrees on inspiratory lateral chest x-ray studies.

Cardiac auscultation was performed to evaluate the presence of a systolic nonejection click or late systolic murmur of mitral regurgitation. The mitral valve leaflets were studied with M-mode echocardiograms recorded with the transducer in several positions. Mitral valve prolapse was considered present when the movement of the mitral valve leaflets was detected posterior to an imaginary reference line drawn parallel to the chest wall, passing through the mitral valve closing point.

Twenty-one (28%) of the study group had echocardiographic evidence of MVP, and 18 had ausculatory findings of a nonejection click or late systolic murmur. A subgroup of 41 patients had a family history of scoliosis and 37% had MVP. Incidence of MVP increased to 41% when a first-degree relative had scoliosis. Thirty-six patients with scoliosis also had hypokyphosis and 13 of them (36%) had MVP. The incidence of MVP was 48% when the scoliosis and hypokyphosis were hereditary and increased to 53% when a family history of first-degree scoliosis was present. If the skeletal abnormality was not familial, the incidence of MVP was only 13%.

Three patients with echocardiographic evidence of MVP did not have auscultatory findings of the disorder. Children with a diffuse soft tissue defect might have laxity of the mitral valve apparatus before clinical insufficiency occurs. Scoliosis progresses with time and the mitral defect also may develop with age. Therefore, cardiac evaluation should be performed periodically. Mitral valve prolapse tends to be a benign disorder in children but has been associated with arrhythmias, bacterial endocarditis, and nonspecific chest pain. Antibiotic prophylaxis to prevent infective endocarditis is obligatory, and symptomatic arrhythmias should be treated.

► [It is not surprising that mitral valve prolapse (MVP) occurs often in patients with idiopathic scoliosis because thoracic skeletal abnormalities have been well documented to occur in as many as 75% of adults with MVP, and prolapse occurs with a very high incidence in connective tissue disorders like Marfan's syndrome and Ehlers-Danlos syndrome, where scoliosis also occurs very commonly. In a similar study performed here, 73% of 33 adolescent patients with idiopathic scoliosis had clinical and echocardiographic evidence of MVP.

These associations suggest that a pervasive development abnormality of connective tissue may underlie both idiopathic scoliosis and MVP. This concept is further supported by the fact that development of the mitral valve and the thoracic vertebrae, ribs, and sternum all proceed simultaneously, early in the seventh week of embryonic life. The common familial patterns in idiopathic scoliosis and MVP suggest that a single collagenous abnormality may influence the development of both the mitral valve and the spine.

Evidence continues to accumulate on the clinical setting of MVP in childhood. Despite the suggestive findings described here, most isolated MVP diagnosed in childhood is not familial and not associated with thoracic skeletal abnormality. Studies such as this one probably select a subset of more homogenous patients in whom a common etiologic factor can be suspected. While the vast majority of patients with isolated MVP have a benign prognosis, ventricular arrhythmias, bacterial endocarditis, and progressive mitral insufficiency can occur and orthopedists and pediatricians certainly should look carefully for MVP in the clinical context of scoliosis. The spectrum of MVP in childhood and its implications clearly require further elucidation.—J.A.S., III] ◄

8–9 **Congenital Heart Diseases in the Neonate: Results of Surgical Treatment.** E. L. Bove, C. Bull, J. Stark, M. de Leval, F. J. Macartney, and J. F. N. Taylor (Hosp. for Sick Children, London) reviewed the results of cardiac surgery in 212 neonates who underwent 224 operations on the heart and great vessels in 1976–1980. Forty patients required open heart surgery under cardiopulmonary bypass. Cardioplegia was used routinely in the last 3 years of the review period. Nonbypass procedures were carried out in 82 patients with inadequate pulmonary blood flow, in 33 with increased pulmonary blood flow or inadequate mixing, and in 59 with coarctation of the aorta, alone or with associated lesions. The shunt of choice was the Blalock-Taussig procedure. Several different procedures were used to repair coarctation of the aorta. Mortality in the group having open heart surgery was 57% and that in the group having nonbypass procedures, 25%. Two neonates in the latter group required bypass surgery subsequently. Metabolic acidosis was more evident in infants who did not survive, and they had a greater need for respiratory support preoperatively. Mortality was not significantly related to preoperative seizures, cardiac arrest, renal failure, or complications from cardiac catheterization.

Many neonates with congenital heart disease now are surviving and require medical and operative treatment. Early correction of several specific lesions now is warranted, and even gravely ill neonates with complex lesions can be operated on successfully. Further studies are needed to establish guidelines on the type and timing of surgery and to identify preoperative conditions that might alter the type of operation done or change the indications.

▶ [Refinements in the surgical treatment of congenital heart disease in the neonate continue to evolve. Previous reports of surgery in the newborn have shown small numbers of patients and a high operative mortality. In most centers, cardiac surgery performed on infants within the first month of life represents a small percentage of all cardiac operations. It is particularly in this select group of patients, however, that an accurate effective treatment plan must be conceived and initiated. The decision regarding the choice of procedure often is based on the mortality and morbidity of palliation versus complete repair in the neonate. For some patients there is no choice to be made; early correction is the only appropriate treatment for obstructed total anomalous pulmonary venous drainage, whereas only palliation is currently available for neonates with tricuspid atresia. If a choice is available, the trend toward early correction rather than initial palliation corresponds with an increase in confidence both in the techniques of intracardiac repair and the management of cardiopulmonary bypass in infants. The strategy of early definitive correction has been justified by studies of surgical results for several particular lesions—such as ventricular septal defect, transposition of the great arteries, and truncus arteriosus. Such patients now commonly undergo complete repair in the neonatal period, should their cardiac condition demand operation. Debate still exists over the best strategy for management of some lesions, particularly those for which mortality would be expected to be higher even with current techniques. This would include, for example, coarctation of the aorta with ventricular septal defects. The authors of this study were unable to identify a subset of patients whose cardiac defect is, when viewed in isolation, correctable, and yet whose associated risk factors add up to such a high probability of death or permanent disability that operation is contraindicated. Thus, they continue to recommend offering surgical treatment even to gravely ill neonates with complex lesions.—J.A.S., III] ◀

(8–9) Arch. Dis. Child. 58:137–141, February 1983.

8–10 **Transposition of the Great Arteries With Intact Ventricular Septum: Results of Mustard and Senning Operations in 123 Consecutive Patients.** Gerald R. Marx, Thomas J. Hougen, William I. Norwood, Donald C. Fyler, Aldo R. Castaneda, and Alexander S. Nadas (Harvard Med. School) reviewed the results of the Mustard and Senning operations in 123 consecutive children operated on for d-transposition with intact ventricular septum. Those with complex associated lesions were excluded. Sixty-six children had a Mustard operation at a mean age of 15.5 months in 1972–1978 and were followed up for a mean of 43.5 months. The 57 who had a Senning operation at a mean age of 6.6 months in 1978–1980 were followed up for a mean of 13.6 months. Nearly all children in both groups had a balloon atrial septostomy preoperatively. Surgical septectomy was done in 50% of the Mustard group and in 20% of the Senning group.

The operative mortality was 11% in the Mustard group and 5% in the Senning group, and the respective late death rates were 8% and 4%. Reoperation was necessary for pulmonary venous obstruction in 4 patients in each group. Reoperation was done for systemic venous obstruction in 11 of 32 affected patients in the Mustard group and in 3 of 7 in the Senning group. No patient in either group required reoperation for intracardiac shunting. One child in each group died of sick sinus syndrome. Two had transient right ventricular failure after a Senning repair. No tricuspid regurgitation occurred.

The authors continue to prefer the Senning operation in infants with d-transposition and intact ventricular septum. The incidence of pulmonary venous obstruction has declined, and systemic venous obstruction requiring reoperation is less frequent than after the Mustard procedure. The use of autologous tissue in the Senning operation may reduce the occurrence of late baffle obstruction. Potential risks of right ventricular failure, tricuspid regurgitation, and death from serious arrhythmias persist. Continued use of the Senning operation seems warranted until the long-term results of intra-atrial baffle procedures and arterial switch operations are known.

▶ [Most of us who are not involved directly with the care of cardiology patients during their operative periods follow what goes on in the surgical literature with just a passive interest. It is good, however, every now and then to see what changes are occurring in this field. This study by Marx et al. is one of the changes that we probably should know about if only to know the names of the people involved.

In 1959, Senning introduced an intra-atrial baffle repair for the correction of transposition of the great arteries in hope of avoiding the use of prosthetic material that later, when the child grows, may lead to obstruction of the bloodstream. Five years after, Mustard reported the first successful correction of transposition of the great arteries using an intra-atrial pericardial patch to redirect systemic venous return. Since then, the Mustard procedure has been used for correction of transposition of the great arteries at most institutions. However, now we are seeing long-term follow-up studies that are documenting a disquieting incidence of morbidity and mortality related to systemic and pulmonary venous obstruction, as well as arrhythmias, with the Mustard procedure. Because of these problems, some institutions, including that from which this report appears, have switched back to the Senning procedure. This approach seems reasonable when something doesn't cut the mustard (pardon me).

I have a feeling that this story isn't over yet and that we may well see some vindi-

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(8–10) J. Am. Coll. Cardiol. 1(Pt. 1):476–483, February 1983.

cation of the Mustard technique. Doctor Mustard must be so used to pressure, that, if it stopped, he would probably get the bends.—J.A.S., III] ◀

8–11 **Carnitine Deficiency Presenting as Familial Cardiomyopathy: A Treatable Defect in Carnitine Transport.** Carnitine is a cofactor in the system that transports long-chain fatty acids across the inner mitochondrial membrane. Carnitine deficiency blocks the mitochondrial oxidation of fatty acids. Lewis J. Waber, David Valle, Catherine Neill, Salvatore DiMauro, and Austin Shug report data on a boy with cardiomyopathy and carnitine deficiency.

Boy, 3½, presented with cardiomegaly, a distinctive ECG (particularly, extremely high T waves best seen in midprecordial leads), and a history of a brother dying with cardiomyopathy. From age 3½ to 5 years, cardiac disease progressed, resulting in intractable congestive heart failure. Skeletal muscle weakness developed; a muscle biopsy showed lipid myopathy. Muscle and plasma carnitine levels were reduced to 2% and 10% of normal mean values, respectively, but there was significant urinary excretion of carnitine. There were no documented episodes of hypoglycemia. The patient's hepatic carnitine content apparently was adequate, as evidenced by an exaggerated ketogenic response to fasting, which was protective against hypoglycemic episodes.

Therapy with L-carnitine (174 mg/kg/day) was begun at age 5½ years and continued to the present (age 6½ years). The cardiac disease has resolved, and muscle strength has returned to normal. Plasma carnitine concentrations have risen to the low-normal range; urinary carnitine excretion has increased to 30 times normal values. Renal clearance of carnitine exceeds normal at all plasma concentrations, and plasma nonesterified carnitine values do not change acutely after an oral carnitine load. Urinary excretion of carnitine does not increase immediately after an oral load.

The parents are of Germanic origin and share a common ancestor several generations back; their plasma carnitine values are in the low-normal range, and their fractional carnitine clearances are above the normal range.

The results suggest that there is a form of carnitine deficiency that presents with cardiomyopathy and may be treated successfully with L-carnitine. Attention might be called to this cause of cardiomyopathy by abnormal ketogenesis and the unusual ECG. A defect in renal and possibly gastrointestinal transport of carnitine is a likely cause of this patient's disorder.

▶ [Before this report appeared, I was not aware that carnitine deficiency could present as cardiomyopathy without other findings. Carnitine deficiency in human beings customarily is divided into two forms, myopathic and systemic, on the basis of tissue carnitine contents. In myopathic carnitine deficiency, carnitine levels are reduced only in muscle; in systemic carnitine deficiency, carnitine levels are reduced in several tissues (muscle, plasma, and liver). Patients with the latter disorder often present in infancy or early childhood with episodes of hypoglycemia, hyperammonemia, cardiomegaly, and hepatomegaly. We have discussed the latter presentation in earlier YEAR BOOKS. Any time a child is seen with hypoglycemia of unexplained origin with hyperammonemia, the diagnosis of carnitine deficiency should be entertained.

Why a deficiency of carnitine that blocks the mitochondrial oxidation of fatty acids and causes lipid accumulation in the cytosol of skeletal and cardiac muscles should present with an acute onset at several years of age is beyond me. Nonetheless, with the appearance of this report, we probably should try to remember carnitine deficiency as a possible cause in a child who presents with atypical myocarditis or myocardiopathy.—J.A.S., III] ◀

(8–11) J. Pediatr. 101:700–705, November 1982.

8–12 **Heart Disease in a Total Population of Children: The Bogalusa Heart Study.** A cross-sectional survey was made of a semirural biracial group of 4,074 children, 5–17 years of age, representing 87.8% of the eligible population. David Akman, Gerald S. Berenson, Caroline V. Blonde, Larry S. Webber, and Aluizio R. Stopa (Louisiana State Univ. Med. Center, New Orleans) report that after a complete physical examination conducted according to a written protocol, 146 children were thought to have significant heart murmurs. The study group to determine the etiology of the heart murmurs included 113 of these children. They received a posteroanterior chest roentgenogram and 12-lead ECG and were examined by 2 adult cardiologists and 1 pediatric cardiologist. Each physician was required to record the physical assessment and the interpretations of the x-ray film and the ECG, to specify the presence or absence of cardiac disease, and to list the most likely anatomical diagnosis. Immediately after these evaluations, the cardiologists discussed each child, attempting to arrive at a consensus regarding diagnosis. A phonocardiogram or echocardiogram or both were performed subsequently on 33 children to clarify the diagnosis. The complete data then were reviewed during a second discussion by the 3 physicians to generate a consensus. A final diagnosis was recorded by each cardiologist and further studies were recommended when warranted.

The results of studies and discussions indicated that 25 children (0.6%) of the total population had cardiac disease (table). Most of those affected had congenital heart disease, with atrial septal defect

PRESENCE OF SPECIFIC HEART DISEASE BY RACE AND SEX

		Race		*Sex*	
Anatomic Diagnosis	*No.*	*Black*	*White*	*Male*	*Female*
Congenital heart disease	13	6	7	7	6
VSD	3	1	2	2	1
ASD	3	2	1	1	2
ECD	2	1	1	1	1
PDA	2	2		1	1
TGV	1		1	1	
TA, PS, VSD	1		1	1	
CHB	1		1		1
Rheumatic heart disease	2	2		1	1
AI	1	1		1	
MR	1	1			1
Mitral valve prolapse	5	4	1	2	3
Unknown	5	4	1	4	1
Total	25	16	9	14	11

VSD, ventricular septal defect; *ASD*, atrial septal defect; *ECD*, endocardial cushion defect; *PDA*, patent ductus arteriosus; *TGV*, transposition of great vessels; *TA*, tricuspid atresia; *PS*, pulmonic stenosis; *CHB*, complete heart block; *AI*, aortic insufficiency; *MR*, mitral regurgitation.

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(8–12) South. Med. J. 75:1177–1181, October 1982.

and ventricular septal defect being the most common. Two patients had rheumatic heart disease and 5 patients had mitral valve prolapse.

It is likely that the prevalence of mitral valve prolapse is higher than this survey suggests. Mitral valve prolapse can be a silent event and may only be detected by echocardiography or angiography. Mitral valve prolapse is more prevalent than rheumatic heart disease and may surpass congenital heart disease as the most common cardiac abnormality.

8–13 **Coronary Heart Risk Factors in 177 Children and Young Adults Whose Fathers Died From Ischemic Heart Disease Before Age 45.** K. K. Ibsen, P. Louis, and G. E. Andersen compared the occurrence of hyperlipidemia, hypertension, smoking, and diabetes in 177 Danish children, whose fathers had died of ischemic heart disease before age 45, with occurrence in a reference population of healthy children and young adults. Eighty subjects were aged 4–17 years and 97, aged 18–29. If either blood pressure or serum lipoprotein levels were above the 95th percentile values, conditions of subjects were evaluated as many as three more times.

The 80 children aged 4–17 had no elevated blood pressure. Among the 97 subjects aged 18–29, 7 had a blood pressure of about 160/95 mm Hg at one visit; however, only 2 had permanently elevated blood pressure. None of the 7 subjects had a family history of elevated blood pressure. Twenty children (11%) had hypercholesterolemia at their first visit. Thirteen at the second visit and 11 at the third remained hypercholesterolemic, which comprised a total of 6% with permanent hypercholesterolemia. In 2 the condition was familial, whereas in 9 no cause was found. Of 9 children who had hypertriglyceridemia at the first visit, 7 remained hypertriglyceridemic after the third evaluation. Two subjects had familial hypertriglyceridemia; in the others, the cause was unknown.

Distributions of serum lipoproteins were compared in 80 study subjects and in 350 healthy children. Levels were significantly higher ($P < .05$) for girls in the study group than for girls in the reference group, although levels for boys were comparable in both groups. Eighteen subjects, aged 14–27, jogged regularly. Among the 80 study children aged 4–17, 3 had smoked previously and 21 smoked at the time of the study. Among the 97 older subjects, 28 had never smoked, 6 had smoked previously, and 62 smoked at the time of the study. Mean daily cigarette consumption was 11.9. No child had diabetes mellitus.

Blood pressure, exercise, smoking, and incidence of diabetes appeared to be no different among the study population and controls. However, hyperlipidemia occurred far more often in children whose fathers died of heart disease than in the control children.

8–14 **Cardiovascular Risk Factors in Children: Should They Concern the Pediatrician?** There is evidence that atherosclerosis, coronary artery disease, and essential hypertension begin early in life. Gerald S. Berenson, Gail C. Frank, Sandra MacD. Hunter, Sathanur

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(8–13) Acta Pediatr. Scand. 71:609–613, July 1982.
(8–14) Am. J. Dis. Child. 136:855–862, September 1982.

TABLE 1.—Median and 95th Percentiles for Serum Lipid and Lipoprotein Values in Children by Age*

	Cholesterol, mg/dL (Percentile)								Triglycerides, mg/dL (Percentile)	
	Total		HDL†		LDL†		VLDL†			
Age, yr	50th	95th	50th	95th	50th	95th	50th	95th	50th	95th
2-3	157	203	61	87	92	131	5	18	58	115
4-5	159	204	60	90	91	135	4	17	53	104
6-7	160	208	61	93	92	138	4	19	52	109
8-9	161	207	64	94	91	138	5	23	55	130
10-11	162	212	61	93	93	142	6	24	57	132
12-13	154	203	61	93	88	133	7	23	58	124
14-15	149	208	59	90	83	131	7	23	60	124
16-17	148	200	58	90	81	129	7	23	60	126
18-19	152	190	59	85	83	122	8	25	64	162

*Lipid values are from fasting children.
†HDL = high-density lipoprotein (α-lipoprotein); LDL = low-density lipoprotein β-lipoprotein); VLDL = very-low-density lipoprotein (pre-β-lipoprotein).
(Courtesy of Berenson, G. S., et al.: Am. J. Dis. Child. 136:855–862, September 1982; copyright 1982, American Medical Association.)

R. Srinivasan, Antonie W. Voors, and Larry S. Webber (Louisiana State Univ.) reviewed data on cardiovascular risk factors and their determinants from the Bogalusa Heart Study of 5,000 children in Louisiana, 37% of them blacks. Bogulusa is a semirural community typical of many small towns in the southern United States. Measure-

TABLE 2.—Median and 95th Percentiles for Relaxed, Right Arm, Sitting Blood Pressure Readings in Children by Height

	Systolic BP, mm Hg (Percentile)		Diastolic BP, mm Hg (Percentile)	
Ht, cm	50th	95th	50th	95th
90-99	97	117	61	77
100-109	97	114	61	75
110-119	94	110	58	72
120-129	96	111	59	72
130-139	98	113	60	73
140-149	101	117	63	75
150-159	107	123	67	80
160-169	110	126	69	83
170-179	112	129	70	83
180-189	115	131	72	85

(Courtesy of Berenson, G. S., et al.: Am. J. Dis. Child 136:885–862, September 1982; copyright 1982, American Medical Association.)

ments were analyzed to identify "tracking" of risk factors over time, and clusters or aggregates of various risk factors at high levels. Over 90% of children in the community participated in most of the studies.

Serum lipid and lipoprotein levels are shown in Table 1 and blood pressures in Table 2. The levels of serum lipoproteins, obesity, blood pressure, and the plasma insulin level all correlated after administration of glucose. Interrelationships between risk factor variables increased with age, most noticeably in white boys, suggesting a progressive environmental impact on the development of cardiovascular risks. Children whose blood pressures ranked high relative to their peers tended to maintain a high ranking in later years. Blood lipid and lipoprotein levels showed tracking similar to that of blood pressure, as did obesity.

The associations among risk factor variables in children potentially enhance the development of premature atherosclerosis. Factors such as cigarette smoking and type A behavior also may contribute to the occurrence of early coronary artery disease. Risk factors should be assessed in children, and encouragement should be given for changes in life-style to attempt to reduce the incidence of coronary artery disease and essential hypertension. Children in the upper tenth percentiles for levels of low-density lipoprotein and very-low-density lipoprotein, blood pressure, and obesity should be monitored. Repeated measurements are essential.

▶ [This article and the preceding one certainly give the impression that there are various risk factors for coronary heart disease. Although a number of medical authorities have advocated modification in dietary cholesterol and total and saturated fat since about 1970, it was not until 1976 that these recommendations were endorsed by the Canadian Government and the United States Senate's select Committee on Nutrition and Human Needs. Conclusive long-term prospective studies to demonstrate that lowering or maintaining lower plasma total cholesterol and low-density lipoprotein-cholesterol levels early in life will delay or prevent atherosclerosis development are not, and probably never will be, available. Nevertheless, there is still logic

in early nutritional modification, and this will be strengthened considerably if current large-scale national studies such as the Bogalusa report reveal reduced coronary heart disease mortality or morbidity.

In an excellent editorial commentary, Weldon Walker (*N. Engl. J. Med.* 308:649, 1983) nicely puts into perspective the changes in coronary artery disease that have come about in the past decade or so. The first drop in the rate of coronary mortality in the United States was noted around the time when the Surgeon General first warned of the hazards of cigarette smoking. Almost simultaneous with this was the dissemination to the American population of the recommendations of the American Heart Association for a general change in the national diet to reduce dietary cholesterol and saturated fat. The American Heart Association specifically recommended a reduction in per capita consumption of tobacco, milk, cream, butter, eggs, animal fats, and oils. These extremely pragmatic recommendations seem to have a favorable effect on both vascular mortality and on the life-styles of many individuals. All of these trends were well under way before the comprehensive population surveys that we are reading so much about these days were even thought of. For example, between 1963 and 1980, the United States experienced a 27% reduction in the amount of tobacco used per person. Consumption of milk and cream was reduced by 24%, butter by 33%, eggs by 12%, and animal fats and oils by 40%, whereas that of vegetable fats and oils increased by almost 60%. While all this was taking place, a decline in age-specific cerebrovascular mortality occurred at a magnitude of about 50%. Coronary mortality was down by about one third. All of this was occurring at a time when the tobacco, dairy, and egg industries continued to create confusion among the public, and even among a few scientists. Some changes were going on in the tobacco industry not because of risk factors for heart disease, but because of economics in that industry. For example, I think most Americans are unaware of the fact that the average American cigarette now contains 20% less tobacco than it did 2 decades ago. God knows how many lives this one maneuver may have saved inadvertently.

There are many things that can be tried to decrease the coronary risk factors for our children. One is to reduce cigarette consumption as much as possible. This has been discussed in other YEAR BOOKS, and I don't know that anyone has any better way of doing this at present. The data as they currently exist suggest that smokers have a threefold risk of coronary heart disease (ibid., p. 409). Despite early reports to the contrary, investigators in Norway feel that coffee consumption also may be a contributor to the high levels of cholesterol seen in heavy consumers of this substance (ibid., p. 1454). I don't know if this report is entirely accurate because it failed to control for other dietary intakes. It seems pretty obvious to me that people who drink a lot of coffee also tend to put other things into their mouth at the same time. It still would seem wise to try to convince our adolescents and young adults to refrain from excessive coffee consumption. Retinoic acid is now widely used in the United States as part of the management of cystic acne. This drug causes very pronounced and predictable hyperlipidemia. Fortunately, lipid levels seem to return to normal once the drug is stopped. It has been suggested, however, that administration of this drug might best be excluded for subjects who are predisposed to vascular disease or who have known preexisting hyperlipidemia (*Lancet* 1:471, 1983).

For patients who are really likely to get into trouble (those with familial hypercholesterolemia), a relatively new class of drugs could be of tremendous benefit. These are the competitive inhibitors of the enzyme that tends to raise serum cholesterol levels. Two drugs in this class, compactin and mevinolin, promptly moved the cholesterol levels into the normal range in several treated patients in one study (*N. Engl. J. Med.* 308:609, 1983).

I take a much more simplistic approach to all of the issues dealing with diet and high blood levels of fats. I feel that being overweight is often just desserts and that seconds count when dieting. It also seems that our society may be going overboard in the degree of emphasis it places on the fine points of regulation of the most intricate aspects of our diets. Frankly, the whole goal of medicine is not to help people to die young as late as possible. It seems to me that there is much more honesty in a man who eats ice cream now and then on impulse than the man who eats Grape-Nuts on principle.—J.A.S., III] ◀

8–15 **Kawasaki Syndrome in the United States: 1976 to 1980.** David M. Bell, David M. Morens, Robert C. Holman, Eugene S. Hurwitz, and Miriam K. Hunter (Centers for Disease Control, Atlanta) reviewed 523 confirmed cases of Kawasaki syndrome reported to the Centers for Disease Control between 1976 and 1980. Only cases in which a serologic test or throat culture ruled out group A β-hemolytic streptococcal infection were included. Seventy-two percent of cases appeared to occur sporadically; the rest were associated with four outbreaks. The average annual incidence during the review period was 0.59 cases per 100,000 children younger than age 5 years. It was greater for boys than girls at all ages. Nearly 60% of patients were white, whereas 18% were black and the rest were Asian or Pacific Islanders and Hispanics. Asians had the highest incidence of Kawasaki syndome. Median patient age was 2.3 years. Second episodes were demonstrated in 0.8% of cases. Both sporadic and outbreak-associated cases were reported most often in the winter and spring.

Apart from fever lasting 5 days or longer, the most common features were a rash, typical extremity changes, oral mucosa changes, conjunctival injection, and cervical lymphadenopathy. All but 15% of patients were hospitalized. Laboratory abnormalities included elevated leukocyte and platelet counts and an increased sedimentation rate (Table 1). Complications are listed in Table 2. The case-fatality ratio in 505 evaluable cases was 1.2%. The mean duration of the four outbreaks of Kawasaki syndrome, all occurring in metropolitan areas, was 3.8 months, and the mean attack rate was 32 cases per 100,000 children younger than age 5 years. There was no evidence of person-to-person transmission of the syndrome or of recent common exposures. In all the outbreaks, many patients had had illnesses with chiefly respiratory symptoms within 30 days before the onset of Kawasaki syndrome.

Some cases of Kawasaki syndrome may be caused by an exogenous agent or toxin that is most prevalent in the late winter and spring. Investigation of a recent outbreak showed an apparent association

TABLE 1.—Laboratory Test Results for Patients With Kawasaki Syndrome in the United States (July 1976 to December 1980)

Laboratory Test	Mean Peak Value With 95% Confidence Limits	Range	No. of Cases Analyzed
Leukocyte count	19,508 ± 844/cu mm	3,900-68,000/cu mm	412
ESR	68.7 ± 3.5 mm/hr	10-150 mm/hr	301
Platelet count*	680,476 ± 32,397/cu mm	174,000-2,400,000/cu mm	315

*Count may be underestimated by these data, which reflect laboratory values obtained during hospitalization, i.e., relatively early in illness; platelet counts in patients with Kawasaki syndrome tend to peak during third week of illness (Morens, D. M., et al.: National surveillance of Kawasaki disease, Pediatrics 65:21, 1980).

(Courtesy of Bell, D.M., et al.: Am. J. Dis. Child. 137:221–224, March 1983; copyright 1983, American Medical Association.

(8–15) Am. J. Dis. Child. 137:211–214, March 1983.

TABLE 2.—REPORTED COMPLICATIONS OF KAWASAKI SYNDROME IN THE UNITED STATES (JULY 1976 TO DECEMBER 1980)

Nature of Complication*	% With Complication
Cardiac	
ECG abnormalities (N = 295)	25.4
Coronary artery aneurysms (N = 82)†	13.4
Other (N = 274)‡	
Arthritis or arthralgias	27.0
Hepatomegaly or splenomegaly	7.7
Pneumonitis§	5.1
CSF pleocytosis§	4.7
Abdominal distention	3.3
Gallbladder hydrops	2.9

*N indicates number of patients studied.

†Reported for 82 persons who underwent ECG or coronary artery angiography, or on whom autopsy was performed.

‡Other noncardiac complications included facial nerve palsy (5 patients), cerebellar ataxia (4), and anterior uveitis (4).

§Number of patients who had chest roentgenograms or lumbar punctures is unknown.

(Courtesy of Bell, D. M., et al.: Am. J. Dis. Child. 137:221–224, March 1983; copyright 1983, American Medical Association.)

with use of rug shampoo in patients' homes. Host, environmental, or other cofactors are likely to be important determinants of personal susceptibility to the syndrome.

▶ [Things seem to have settled in for Kawasaki syndrome in the United States. This report from the Center for Disease Control nicely summarizes the first experiences with this unusual disorder in the United States. It seems fair to say that we still know very little about the etiology of this syndrome (unless something sensational happens in the short time that the YEAR BOOK takes to get ready). We saw a couple of ripples in this stream this past year suggesting a possible association of the illness with rug shampooing and with mites. In the outbreak of Kawasaki syndrome in eastern Colorado in the spring of 1982, 48% of the patients had been exposed to the application of a rug shampoo within the home in the month prior to the onset of the disease, compared with 10% of matched neighborhood controls. (Patriarca P. A., et al.: *Lancet* 2:578, 1982). These data must have seemed convincing enough, because they again appear in this article by Bell et al., which was published some 6½ months later. The data seem sufficiently weak that no one is suggesting everyone send their rugs out for shampooing. In a subsequent letter to the editor of the *Lancet*, K. Ohga et al. (ibid. 1:930, 1983) reviewed their own experience with a 1982 epidemic of Kawasaki disease in Japan. They found that children with Kawasaki disease were significantly more likely to have rugs in their home, but none of these children's rugs had been shampooed in the month prior to onset of the disease. These little pieces of information, if they are correct, might suggest that the rugs themselves (shampooed or not) might harbor some infectious agent that can be stirred up. Around the time all this was going on, the business purporting to link mites with the etiology of Kawasaki syndrome appeared in the literature. About 3 years ago, the suggestion was raised that mite antigens may have a causative role in Kawasaki disease. Then someone showed what looked like rickettsia-like particles in skin biopsy specimens from patients with Kawasaki disease. These particles look very similar to those seen inside mites. Finally, T. Fujimoto et al. (Ibid. 2:980, 1982) claimed to have found immune complexes in two thirds of patients with Kawasaki disease. These immune complexes were positive for mite antigen. Fujimoto et al. suggested that the mite may have some etiologic role, not as an allergen, but as the vector for a microorganism. All this sounded like a "mitely" tall story, but just about the same time all this was going on, a similar story was being carried out in the United States showing a similar pathogenesis for Lyme's disease (see Chapter 13, "The Musculoskeletal System," in this YEAR BOOK, for more details). Obviously, stranger things can happen.—J.A.S., IIIj ◀

8–16 **Use of Continuous Saralasin Infusion to Control Hypertension.** Edward J. Ruley, Glenn H. Bock, and Douglas Smith (Children's Hosp. Natl. Med. Center, Washington, D.C.) used saralasin acetate, a competitive inhibitor of angiotensin II, as a continuous infusion in 2 pediatric patients for 8 and 13 days respectively, to control hypertension.

CASE 1.—White male infant, born at 24–26 weeks' gestation to a primigravida, aged 15, was 800 gm at birth. By age 38 days, bronchopulmonary dysplasia, intraventricular hemorrhage, staphylococcal sepsis, and acidosis had complicated the postnatal course; weight was 980 gm, heart rate was 148, and mean blood pressure was 76 mm Hg. Intravenous doses of furosemide (1 mg/kg), hydralazine, and methyldopa (20 mg/kg/day) failed to reduce the blood pressure. On day 48, plasma renin and aldosterone values were 432 ng/ml/hour and >50 mg/dl, respectively. Ileus precluded oral administration of antihypertensive therapy. On day 51 a saralasin test was performed using a serially titrated intravenous infusion beginning at 0.05 μg/kg/minute and ending at 20 μg/kg/minute. Subsequent increases in saralasin were achieved by increasing the rate of infusion. Blood pressure was maximally reduced at 20 μg/kg/minute when systolic and diastolic blood pressure had decreased approximately 30 mm Hg to normal values. Because of the response to the saralasin test in the presence of continuous ileus and failure of conventional antihypertensive medications, approval and informed consent was obtained for constant saralasin therapy. The dose varied over the next 13 days from 9.1 to 2.8 μg/kg/minute. The mean ±1 SD systolic blood pressure (68.7 ± 6.2 mm Hg), mean blood pressure (54.2 ± 6.3 mm Hg), and diastolic blood pressure (41.8 ± 6.2 mm Hg) during saralasin treatment were significantly lower ($P < .001$) than the presaralasin systolic blood pressure (86.9 ± 7.7 mm Hg), mean blood pressure (72.3 ± 6.2 mm Hg), and diastolic blood pressure (59.3 ± 6.3 mm Hg). On day 63, with resumption of bowel function, treatment with captopril was begun and saralasin infusions were discontinued over the next 2 days. Blood pressure remained well controlled with captopril therapy alone.

CASE 2.—Black girl, 8, with a 50% second-degree and third-degree immersion burn, had blood pressure of 210/140 mm Hg on admission. Initial management included fluid therapy for the burn and diazoxide, nitroprusside, and diuretics to control hypertension. As a result of a favorable response to a saralasin test, continuous infusion of this drug was begun, resulting in successful control of hypertension; ileus resolved after 8 days of saralasin infusion. Subsequently, blood pressure was controlled with orally administered captopril alone.

Both patients had become unresponsive to conventional intravenously administered antihypertensive medications that could not be given orally because of ileus. Continuous infusion of saralasin controlled blood pressure without causing any recognizable adverse effects; blood pressure was not reduced below the normal range as has been reported with intravenously administered nitroprusside.

▶ [Saralasin acetate is now approved for general use as a screening test for suspected renovascular hypertension. This was discussed in the 1982 and the 1983 issues of the YEAR BOOK. The drug is a specific competitive inhibitor of angiotensin II. This report shows that when all other drugs fail, a continuous intravenous infusion of saralasin may help to control hypertension. Indeed, the children treated with saralasin had failed to have sustained responses with diazoxide, nitroprusside, and di-

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(8–16) J. Pediatr. 101:1013–1017, December 1982.

uretics. Saralasin is a welcomed agent in the therapeutic armamentarium for the management of refractory hypertension.

Perhaps of more significance in the world today is the question of mild or borderline hypertension in our adolescent population. The Minneapolis Children's Blood Pressure Study (*Am. Heart J.* 105:316, 1983) in a survey of 10,000 children found that the prevalence of blood pressures greater than 140/90 mm Hg at the first screening was approximately 1%. This may not seem like a high number, but when you multiply it by the number of young teenagers that we have in the United States the absolute number becomes staggering. The plot thickens even more when the consequences of this hypertension are seen. When the cardiac status in juvenile borderline hypertension was examined, W. S. Culpepper et al. (*Ann. Intern. Med.* 98:1, 1983) found that patients with an average blood pressure of 137/89 mm Hg had unquestionable echocardiographic changes in the left ventricular myocardium and left ventricular function, presumably as a result of the hypertension. Similar blood pressure-related echocardiographic changes in adolescents and young adults were reported elsewhere (Johnson, G. L.: *Am. Heart J.* 105:113, 1983). These sorts of data seem to be swinging the pendulum toward early treatment of these levels of mild hypertension. Until these papers appeared, the trend had been away from trying to do that, because of its long-term implications. Treatment of this kind of mild hypertension can be as minimal as attempting to restrict sodium in the diet. It probably is not appropriate to say "simple" when attempting to do this. An excellent review (*JAMA* 249:784, 1983) shows us how many different issues are involved with trying to eliminate excess sodium from our diets. As one example, McDonald's sells 700 million pounds of hamburger each year and 542 million bushels of french fries. Although the occasional hamburger will do no harm, some children seem to live on a diet of hamburger and chips and refuse to break the habit no matter how intensively they are counseled. In Great Britain, there appears to be much more attention paid to raising the potassium to sodium ratio in the diet. The feeling over there is that if you preserve the amount of potassium that occurs naturally in food substances, there may be less desire to add salt to improve the flavor (Smith, S. J., et al.: *Lancet* 1:362, 1983). One way of doing this is by steaming our foods rather than by boiling, especially when it comes to vegetables. We also should be encouraging our children to minimize their intake of caffeine-containing substances. This is considered controversial by many, but dogma by others. You will have to determine for yourself what the real role of caffeine might be in this regard. The story seems to be changing all the time. It also has been suggested that a regular exercise program may help in the management of mild hypertension. R. M. Schieken et al. (*Hypertension* 5:71, 1983) found quite the opposite. They determined that children with persistently elevated blood pressures continue to have higher blood pressures during exercise. This seems consistent with my observations. When was the last time you ever saw a jogger smile?—J.A.S., III] ◄

8–17 **Fab Fragments of Digoxin-Specific Antibodies Used to Reverse Ventricular Fibrillation Induced by Digoxin Ingestion in a Child.** Aaron R. Zucker, Samuel J. Lacina, D. S. DasGupta, H. A. Fozzard, David Mehlman, Vincent P. Butler, Jr., Edgar Haber, and Thomas W. Smith report that administration of purified Fab fragments of digoxin-specific antibodies can be lifesaving in children with digitalis poisoning. Prolonged cardiopulmonary resuscitation in children is justified when the cause of cardiac arrest is potentially reversible.

Boy, 2½, took a massive digoxin overdose that caused prolonged ventricular fibrillation refractory to conventional therapy. After about 2 hours, the boy was given digoxin-specific Fab fragments of antibody in sufficient quantity to bind his estimated dose of 10 mg. After propranolol and cardioversion, the child's heart could be captured by a transvenous pacemaker in the right ventricle at a rate of 130/minute. He sat up 35 minutes after the end of antibody administration.

(8–17) Pediatrics 70:468–471, September 1982.

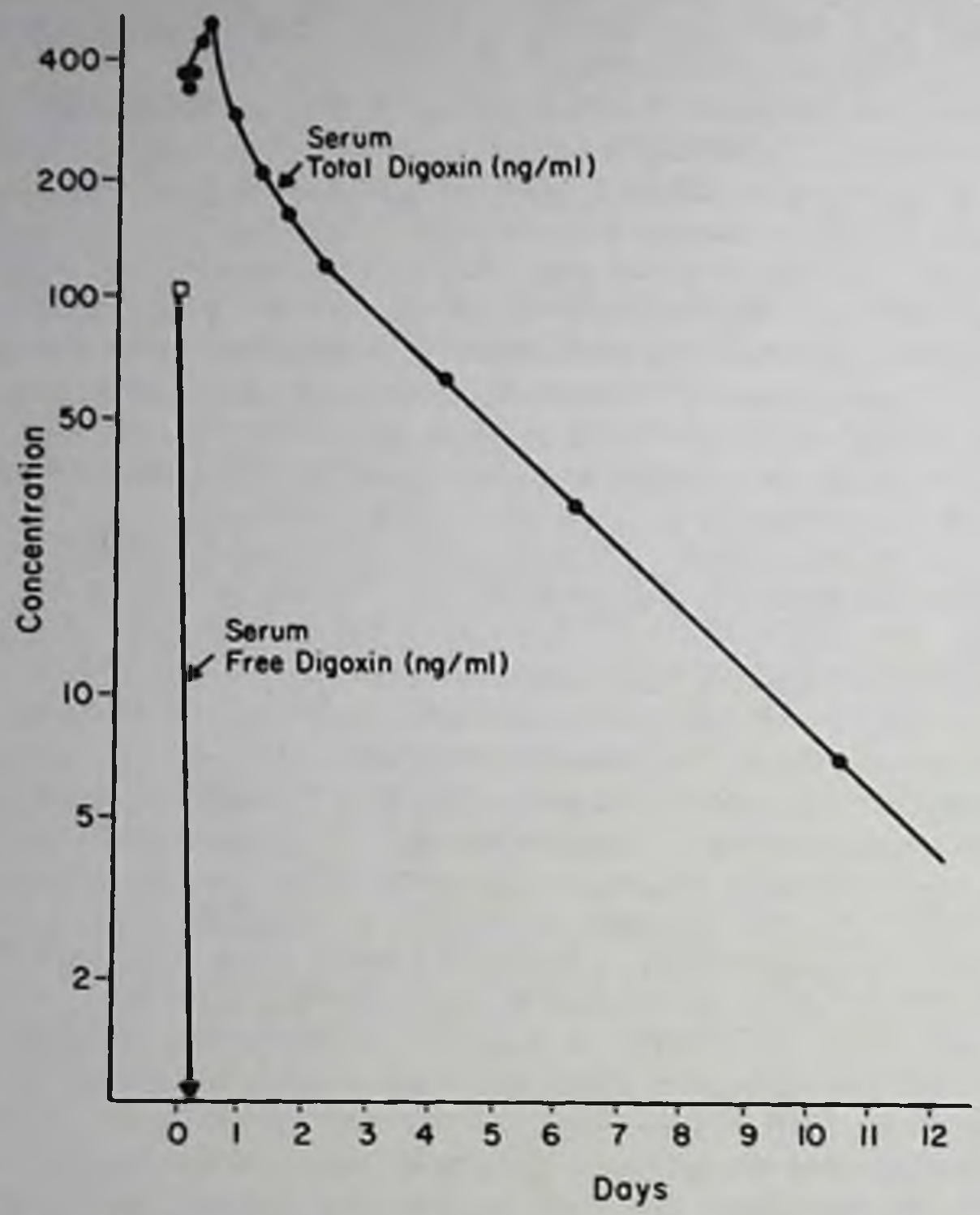

Fig 8–2.—Response of serum digoxin level to administration of digoxin-specific Fab fragments. Scale of ordinate is logarithmic. (Courtesy of Zucker, A. R., et al.: Pediatrics 70:468–471, September 1982. Copyright American Academy of Pediatrics 1982.

The serum free digoxin level before antibody administration (about 6 hours after ingestion) was >100 ng/ml; it fell to undetectable levels by 1 hour after antibody was given. Digoxin bound to the antibody had a clearance half-life of about 48 hours (Fig 8–2).

The child had no apparent neurologic damage, and his intellectual function was normal at discharge. He had a transient hematuria and a residual incomplete right bundle-branch block.

Transient microscopic hematuria and low creatinine clearance level are suggestive of glomerular dysfunction, renal tubular dysfunction, or both, probably related, at least in part, to initial renal hypoxia and ischemia, with resolution by several weeks after discharge. However, some glomerular damage from digoxin-antibody complexes cannot be excluded with certainty.

▶ [Antibody management of digoxin intoxication has been a long time coming. It has taken approximately a decade to purify out a Fab (fragment, antigen-binding) fraction of that antibody. Antibodies, in general, are quite easy to produce. What was needed in the case of digoxin, however, was an antibody that is really only part of an antibody to the entire digoxin molecule. Native whole antibody to digoxin would be antigenic in its own right and would have the same half-life as any intact antibody that is relatively long. Once the antigen and the antibody bound together, it might be floating around for a long time and could dissociate. The Fab fractions, however, are nonantigenic and clinically reduce digoxin toxicity extremely rapidly because the complex of antibody and digoxin is excreted rapidly in the urine. This article by Zucker was one of the two articles in the same journal that first described the clinical application of these antibodies in the management of digoxin toxicity. The other article was by D. J. Murphy et al. (*Pediatrics* 70:472, 1982). As of this writing, antibody

treatment of digoxin toxicity remains experimental in the sense that a Food and Drug Administration protocol must be followed if the treatment is to be used. You will have to refer to the articles in order to find the list of centers from which the antibody can be obtained.

As exciting as this antibody is for what used to be a very problematic situation, even more exciting is the fact that this type of technology obviously will be applied now toward ingestions of other toxic substances.—J.A.S., III] ◀

9. Blood

9–1 **Graft-Versus-Host Disease and Survival in Patients With Aplastic Anemia Treated by Marrow Grafts From HLA-Identical Siblings: Beneficial Effect of a Protective Environment.** Rainer Storb, Ross L. Prentice, C. Dean Buckner, R. A. Clift, Fred Appelbaum, Joachim Deeg, Kristine Doney, John A. Hansen, Mark Mason, Jean E. Sanders, Jack Singer, Keith M. Sullivan, Robert P. Witherspoon, and E. Donnall Thomas (Univ. of Washington) studied prognostic factors associated with graft-versus-host disease (GVHD) and survival in 175 patients with aplastic anemia conditioned with cyclophosphamide and given bone marrow transplants from HLA-identical siblings. Of the 175 patients, 130 survived more than 13 days and had grafts that were not rejected. Of these 130 patients, 39 were randomly assigned to rooms with laminar airflow for a minimum of 50 days, given sterile food, and treated with oral nonabsorbable antibiotics and skin cleaning.

Of the 130 patients with sustained engraftment, 97 (75%) are alive 16 months to more than 11 years (median, 5) later (Fig 9–1). Of the 33 patients who died 24 to 726 days (median, 110) after engraftment, 29 had moderately severe or severe acute, or chronic GVHD.

Moderately severe to severe acute GVHD had a strong adverse influence on survival among patients with sustained bone marrow

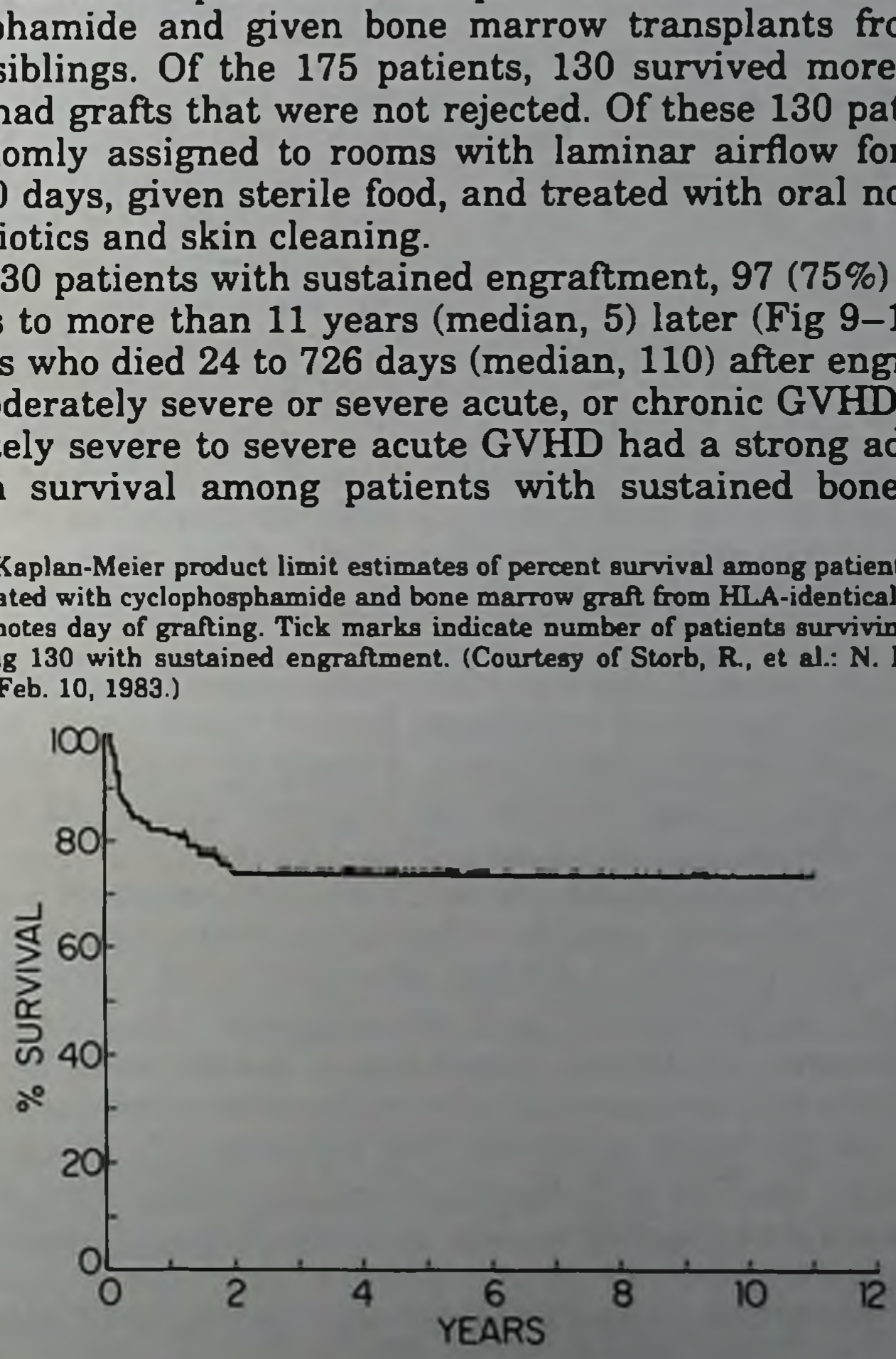

Fig 9–1.—Kaplan-Meier product limit estimates of percent survival among patients with aplastic anemia treated with cyclophosphamide and bone marrow graft from HLA-identical family member. Day 0 denotes day of grafting. Tick marks indicate number of patients surviving (as of June 1, 1982) among 130 with sustained engraftment. (Courtesy of Storb, R., et al.: N. Engl. J. Med. 308:302–307, Feb. 10, 1983.)

(9–1) N. Engl. J. Med. 308:302–307, Feb. 10, 1983.

grafts. Laminar airflow isolation was associated with reduced mortality, particularly in the first 4 months after marrow transplantation and corresponding, in part, to a reduction in the incidence or delay in onset, or both, of acute GVHD. Refractoriness to random-donor platelets was an important adverse prognostic factor, particularly in patients with acute GVHD. Increasing patient age was associated with increased mortality. Sex matching between donor and recipient might or might not have been an independent survival factor, but it was much less important than reported earlier. Addition of donor marrow buffy coat cells to the marrow inoculum, which has been shown to be effective in decreasing the rejection rate, did not worsen survival among patients with sustained engraftment despite an associated increase in chronic GVHD. Similarly, infusions of increasing numbers of marrow cells had no adverse effect on acute or chronic GVHD and survival, even in patients who did not receive infusions of buffy coat cells. Finally, in contrast to the findings of several other studies, engraftment with bone marrow from female and male donors led to comparable rates of GVHD and survival.

9–2 **Antithymocyte Globulin Treatment in Patients With Aplastic Anemia: A Prospective Randomized Trial.** Richard Champlin, Winston Ho, and Robert Peter Gale (Univ. of California, Los Angeles) evaluated the efficacy of antithymocyte globulin for treatment of moderate to severe aplastic anemia in a randomized, controlled study.

Eleven of 21 patients initially randomized to receive antithymocyte globulin (20 mg/kg/day intravenously on 8 consecutive days) had sustained improvement in hematopoiesis within 3 months of treatment. None of 21 control patients who received supportive care alone improved within 3 months of randomization ($P = .0005$). Two additional patients treated with antithymocyte globulin improved at 4½ and 5 months after treatment. Six of 12 control subjects who subsequently received antithymocyte globulin improved within 3 months of treatment.

Responders generally had only a partial response; peripheral blood counts typically remained unchanged for 1–3 months and then slowly increased, stabilizing in the lower normal or mildly pancytopenic range. Actuarial 2-year survival for responders was 100%, as compared with 14% for nonresponders ($P = .0001$).

Of the 17 responding patients, 16 have had sustained hematologic improvement for 5–27 months after antithymocyte globulin treatment. Of these patients, 14 have improved levels of granulocytes, erythrocytes, and platelets; 2 have a response only in granulocyte and erythrocyte levels. Recurrent pancytopenia developed in 1 patient responding, who has a syndrome and cytogenetic abnormality characteristic of preleukemia. Bone marrow biopsies in 8 responding patients showed 30–50% cellularity. Megakaryocytes were decreased. Erythropoiesis was macrocytic, and mild dysplastic changes involved all cell lines.

The severity of bone marrow failure, age, sex, cause of aplastic ane-

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(9–2) N. Engl. J. Med. 308:113–118, Jan. 20, 1982.

mia, pretreatment blood or lymphocyte counts, transfusion history, and bone marrow iron stores had no apparent bearing on treatment outcome. The interval from diagnosis to antithymocyte globulin treatment correlated inversely with chance of a treatment response, but the correlation was not statistically significant.

Antithymocyte globulin treatment was associated with fever, chills, rash, thrombocytopenia, and serum sickness in all patients. No mortality was related to this therapy.

The data indicate that antithymocyte globulin is effective in about half of the patients with moderate or severe aplastic anemia.

▶ [Dr. Joel M. Rappeport, Hematology Division, Brigham and Women's Hospital and Harvard Medical School, comments:

"During the past decade, two major but diverse therapeutic advances have improved survival in patients with severe aplastic anemia. In comparison to either untreated or androgen-treated patients (Camitta et al.: *Blood* 48:63, 1976), in whom survival was 20%, patients treated with bone marrow transplantation or antithymocyte globulin had improved survival of 55% to 76% in various reports. These two studies represent the major problems in the understanding of the pathophysiology of aplastic anemia as well as the current therapeutic alternatives. Although bone marrow transplantation in this disorder is a relatively standardized procedure (albeit a high-technology procedure), antithymocyte globulin is a biologic preparation produced in various animals, directed against a variety of target cells, and prepared as either a serum or globulin with variable potency. Hence, the results in any given study may not be applicable to other products or lots.

"Aplastic anemia has been thought of as a heterogenous disorder resulting from a variety of pathophysiologic processes. Most cases were felt to be due to damage to the pleuripotent stem cell, with a small percentage being caused by an autoimmune phenomena in which either a cytotoxic T cell or an antibody or both were directed against the hematopoietic stem cell. The high response rate to 'immunosuppressive therapy' would suggest that in at least 50% of the cases an autoimmune process could be evoked. Similar responses have been reported primarily by European centers utilizing high doses of methylprednisolone (Bacigalupo et al.: *Br. J. Haematol.* 47:423, 1981.) Bone marrow transplantation, on the other hand, is based on the premise that irreversible hematopoietic stem cell failure has occurred from a "toxin," and repopulation of the recipient with hematopoietic stem cells from an appropriate donor will suffice. However, evidence also exists from this experience suggesting the presence of an underlying autoimmune phenomena. The need for preparatory immunosuppression for allogeneic transplants in HLA-matched donor recipient pairs, the few reports of autologous recovery following preparation for allogeneic transplants, and, most impressively, the need for immunosuppressive therapy in 50% of identical-twin bone marrow transplants raises the spectra of autoimmunity. As noted, however, by Champlin et al., vigorous evidence both in vitro and in vivo for this disease to be largely ascribed to autoimmunity is still lacking. Antithymocyte globulin therapy in some cases may be no more than a mechanism to prevent transfusional sensitization, allowing long-term survival until spontaneous recovery occurs.

"From a therapeutic point of view, both this article and the preceding one leave the clinician in a dilemma. Both procedures have severe limitations and are, from all practical aspects, mutually exclusive. Bone marrow transplantation is limited currently to the 40% of patients with identifiable HLA-compatible donors. Although successfully treated patients have complete hematologic recovery, the problems of graft rejection and chronic graft-versus-host disease limit the success rate. In fact, for the original 175 patients described by Storb et al., the real survival rate of the patients offered bone marrow transplantation as therapy is 55%, and only 34% of patients survived without chronic graft-versus-host disease. On the other hand, none of the patients undergoing antithymocyte globulin therapy had complete hematologic recovery, although the survival rate was 50%. The long-term consequences of stress hematopoiesis in terms of future recurrent aplastic anemia or development of hematologic malignancy is unclear. Both this study and the Camitta study (*Blood*

60(Suppl):165a, 1982) have reported recurrent aplasia, and the occurrence of acute leukemia is recognized in long-term survivors of aplastic anemia.

"Improvement following antithymocyte globulin may require a matter of months, necessitating intensive transfusion support. Because of potential transfusion-induced sensitization to minor histocompatibility antigens, attempts at bone marrow transplantation after failure of antithymocyte globulin therapy would result in a high degree of graft rejection. Currently, no clearly reproducible tests exist to predict responsiveness to antithymocyte globulin. On the other hand, no predictive tests exist for the development of chronic or graft-versus-host disease. The choice of bone marrow transplantation also is an irreversible decision. Neither therapy is benign, and each is associated with substantive side effects.

"The problem of therapeutic choice is greater in adults, in whom the incidence of chronic graft-versus-host disease is higher. Although the dilemma is unsolved, the current state of the art would suggest early bone marrow transplantation for children with severe aplastic anemia in whom a histocompatible donor is identified, with the hope that current research efforts will overcome the problems of graft-versus-host disease and opportunistic infection. For those patients without donors, or those with a definable underlying autoimmune disorder, treatment with antithymocyte globulin is appropriate. The investigative nature of this therapy should be recognized and patients should be entered into appropriate studies where substantial numbers of patients with this rare disorder can be evaluated and followed appropriately."] ◀

9–3 **Marrow Transplantation for Thalassemia.** The ideal candidate for a bone marrow transplant for thalassemia would have a severe form of the disease, managed with few or no transfusions, and would have an HLA-identical sibling to serve as a marrow donor. E. Donnall Thomas, C. Dean Buckner, Jean E. Sanders, Thalia Papayannopoulou, Caterina Borgna-Pignatti, Piero De Stefano, Keith M. Sullivan, Reginald A. Clift, and Rainer Storb describe a successful bone marrow transplant in such a patient.

Boy, age 13 months, was seen at the University of Pavia with pallor and hepatosplenomegaly. Hemoglobin was 5.9 g/dl, white blood cell count was 3 $\times$ 10^9/L with 50% nucleated red blood cells, and the blood smear showed clear changes of thalassemia major. All family members showed thalassemia trait, with the exception of a sister, aged 16, who proved HLA-identical with the patient.

The boy received a total of 250 ml packed red blood cells and was brought to Seattle where the above findings were confirmed. Thirty-four percent of the red blood cells were found to contain fetal hemoglobin and 67% proved to be transfused cells. Of the total non-α chains, only 6–7% β chains were synthesized, with an α/non-α ratio of 2.7.

The patient was placed in a laminar-air flow room and prepared for transplantation with one dose of dimethyl busulfan, 5 mg/kg, intravenously, followed by cyclophosphamide, 50 mg/kg intravenously on 4 successive days. At marrow transplantation, 685 ml of bone marrow and blood was harvested from the donor, the cells were concentrated to a final volume of 202 ml, and a total of 1.7 $\times$ 10^9 nucleated marrow cells/kg of recipient body weight was infused intravenously. Methotrexate, 15 mg/sq m, was given intravenously on day 1 and 10 mg on days 3, 6, and 11 for prevention of graft-versus-host disease. The boy received 2.5 mg/sq m on day 24 and 5 mg/sq m on day 28, followed by 10 mg/sq m weekly until day 102. On the eighth day after transplantation, he became febrile and was started on antibiotics that were discontinued on day 26. He was discharged on day 29, when the hematocrit was 37%, white blood cell count 0.66 $\times$ 10^9/L, and platelet count 15.6 $\times$ 10^9/L.

(9–3) Lancet 2:227–229, July 31, 1982.

Hepatosplenomegaly had disappeared entirely by day 60 and the boy returned to Italy 3 months after bone marrow transplantation.

The described preparative regimen must damage the defective stem cells sufficiently to prevent regeneration, and adequate immunosuppression must achieve allogeneic engraftment. Bone marrow transplantation should be done when the patient has been little transfused, so that iron toxicity is unlikely and risk of graft rejection is minimal. Age 5 or younger is recommended because graft-versus-host disease is infrequent and not severe in young patients.

▶ [This report may represent the dawn of a new age in the treatment of thalassemia. For some 25 years it has been recognized that transplantation of bone marrow might constitute effective therapy for hereditary diseases of the marrow. The aim would be to destroy genetically abnormal marrow and replace it with normal marrow from another individual. Because most patients with hereditary hematologic disorders can live for some years while receiving conventional treatment, there has been reluctance to resort to this therapy, with its many hazards. However, continued improvement and long-term survival rates after transplantation for severe aplastic anemia and for immune deficiency indicate the need for reevaluation of marrow transplantation in disorders such as thalassemia. The best chance of success would be transplantation performed when the thalassemic patient has had few transfusions so that iron toxicity is minimal and the risk of graft rejection is as low as possible. Ideally, this would be done in children younger than age 5 years, because graft-versus-host disease is infrequent and not as severe in young patients. The patient should have an HLA-identical sibling, either normal or heterozygous, to serve as a donor. The child described in this report had all of these favorable characteristics. Despite even the most ideal conditions, it must be accepted that some children will die as a result of graft-versus-host disease or as a consequence of opportunistic infections. The authors of this report claim that although bone marrow transplantation is an expensive undertaking, it should be more cost-effective than prolonged conventional therapy with supportive transfusions and chelation agents as so commonly is used now in the management of thalassemia major. They also speculate that increasing success of marrow grafts from only partially matched or completely unrelated donors indicates that it soon may be possible to find donors for almost all patients. They also comment that if progress in this area continues, bone marrow transplantation might be applicable for other genetic diseases of the bone marrow, such as sickle cell disease.

The implications of bone marrow transplantation for genetic diseases of the bone marrow must be viewed with some caution. Sometimes early death will result from the procedure in a child who might otherwise have had 2 decades of reasonably healthy existence. In the aggregate, transplantation would seem the better way to go, but when one deals with a particular patient, a single loss of a child from transplantation will shake all of our confidences in whether this was the correct approach. Currently, for other diseases such as sickle cell anemia, the outlook with the natural course of the disease is much better than for thalassemia major. It is true that individual patients will have a horrendous time with sickle cell disease. These cases are not predictable in very early life in most instances, and therefore one wonders what the true role of transplantation might be in this disorder. I do not think we will see it applied for such uses until all of the bugs are worked out with the technique. Curiously, despite its obvious potential for controversy, bone marrow transplantation in this individual case report has not received much in the way of editorial redressment. This is unlike the report of Ley et al. (*N. Engl. J. Med.* 307:1469, 1982), who used 5-azacytidine to increase fetal hemoglobin synthesis selectively in a patient with β-thalassemia. 5-Azacytidine is largely used as an anticancer agent; it was found in that application to stimulate fetal hemoglobin production. There are obvious potential hazards associated with using a complex agent such as this drug. However, when used on a highly experimental basis in children and young adults with β-thalassemia major at an advanced stage of the disease, the drug did seem to stimulate fetal hemoglobin production. The goal here obviously is to help patients make more of their own blood to make them less transfusion dependent. This latter study did come under severe scrutiny in the British literature (*Lancet* 1:36, 1983; and ibid., p. 536). I

think you should read the original article and its subsequent editorial comments and letters to the editor to decide for yourselves if the human experimentation committees that approved the use of 5-azacytidine for this purpose were correct in their decisions. I, personally, feel that under the very strict guidelines that were used in patients with an advanced stage of hemosiderosis, these studies were justified. Editorial comments in journals and letters to the editor regarding published reports usually do serve a purpose. It is unfortunate, however, that more and more of us confuse the function of such criticism with that of being a sort of racing tip sheet.—J.A.S., III] ◄

9–4 **Prevention of Anemia and Iron Deficiency in Very Low Birth Weight Infants.** Martti A. Siimes and Anna-Liisa Järvenpää (Univ. of Helsinki) examined age-dependent changes in hemoglobin concentration in 28 preterm infants weighing 1,000 gm or less at birth who survived the neonatal period. Mean gestational age was 27.5 weeks. Twenty-six surviving infants were followed to age 15 months. All the very low birth weight (VLBW) infants received human milk to the time of discharge. Formula feeding was begun at about age 3 months and continued to age 1 year. Solid foods were introduced at age 5 months. Iron drops were given at age 2 months and, by 2½ months, infants received about 2 mg of iron per kg daily as ferrous salt up to about age 1 year. After age 3 months the formula was supplemented with 12 mg of iron per L. The total supplement of iron from age 3 months was about 4 mg/kg daily.

Average weight rose from 892 gm at birth to 3,240 gm at age 4 months and 8,100 gm at age 15 months. Hemoglobin values were not significantly related to growth rate at age 4 or 9 months. The lowest hemoglobin concentration occurred later than in larger preterm or term infants. A total of 77 red blood cell or whole blood transfusions were given. Six infants received no transfusions, whereas 9 received four or more. Transfusions in the first 2 months were unrelated to the hemoglobin concentration at age 3 months or later.

Even VLBW infants appear to be able to accommodate their gastrointestinal absorption of iron to the high level needed. Infants weighing less than 1 kg have undergone many laboratory studies but have compensated for the blood loss quite well, without need for transfusions. Subsequent hemoglobin concentrations have been maintained at values similar to those in infants given transfusions. Supplementation with iron can effectively prevent iron deficiency in VLBW infants.

► [Dr. Peter R. Dallman, Professor of Pediatrics, School of Medicine, University of California at San Francisco, comments:

"Very low birth weight infants have an extraordinarily rapid rate of growth, with as much as a fivefold increase in weight during the first 3 postnatal months and up to a 12-fold increase by 15 months of age. This involves enormous iron needs, not only for growth, but also to compensate for having missed the period of greatest transplacental iron transport. The study of Siimes and Järvenpää shows that the iron needs of such infants are adequately met by 4 mg iron/kg of body weight per day, started at about 2 months of age. Of necessity, this iron intake is twice the amount that previously was suggested in a study of larger preterm infants with a birth weight between 1,000 and 2,000 gm.

"It is advisable to wait as long as 2 months before starting iron administration. One reason is that the postnatal fall in concentration of hemoglobin and the neonatal

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(9–4) J. Pediatr. 101:277–280, August 1982.

iron stores (though small) supply sufficient iron for red blood cell production during this period. Another reason is that delaying iron administration decreases the risk of aggravating hemolysis due to vitamin E deficiency in very low birth weight infants; such infants have marked malabsorption of vitamin E during the first postnatal months

"The improved survival of very low birth weight infants has only been achieved by intensive attention to the details of their care. Fortunately, management of their iron status now turns out to be a relatively simple matter."] ◄

9–5 **Erythrocyte Differential Count in Newborn Infants.** Alvin Zipursky, Esther Brown, Janice Palko, and Elizabeth J. Brown developed a simple technique for accurately and reproducibly quantitating red blood cell shapes in blood samples. The three-dimensional shape of erythrocytes is evaluated by light microscopic examination of glutaraldehyde-fixed cells. Capillary blood collected in heparin or in edetate is mixed with phosphate buffer and fixed with glutaraldehyde solution. The red blood cell suspension then is mixed with glycerol and prepared for microscopy. Studies were done in 53 healthy adults of both sexes and in 31 term neonates in the first 3 days of life. Also, 52 premature infants weighing less than 1,500 gm were studied in the first 6 weeks of life, excluding those requiring respiratory assistance.

Fixation in 1% glutaraldehyde consistently produced a large number of knizocytes, and a concentration of 0.15% therefore was used. A two-stage fixation procedure was adopted. A wide variety of cell shapes was observed. Most adult cells were disk-shaped or bowl-shaped (Table 1). Disks were significantly more frequent in adult blood than in neonatal blood, whereas bowl-shaped cells were more common in newborn infants. Both forms were comparably frequent in term and premature infants. Differential counts are given in Table 2. In adults it was unusual to find cell types other than disks, bowls, and knizocytes, which may be artifactual. Term infants more often had irregularly shaped cells (Table 3), and these were especially evident in premature infants. Echinocytes were most frequent in premature infants, in whom they may occur in very high numbers.

This technique visualizes erythrocytes in three dimensions and permits determination of cell shape distribution in a given blood sample.

TABLE 1.—DISK-SHAPED AND BOWL-SHAPED ERYTHROCYTES IN ADULTS AND NEWBORN INFANTS

	No. Studied	Discs*	Bowls*
Adults	53	75.4 ± 14.5	18.3 ± 3.6
Newborn Infants			
Full-term	29	42.9 ± 13	40.6 ± 14.8
Premature	38	40.8 ± 12.3	31.6 ± 13

*Mean ± standard deviation.

(Courtesy of Zipuraky, A., et al.: Am. J. Pediatr. Haematol. Oncol. 5:45–51, Spring 1983.)

TABLE 2.—ERYTHROCYTE DIFFERENTIAL COUNT IN ADULTS AND NEWBORN INFANTS

	Median (5%-95%)*		
	Adults	Full-Term†	Premature‡
Number studied	53	31	52
Discs	78 (42-94)	43 (18-62)	39.5 (18-57)
Bowls	18 (4-50)	40 (14-58)	29 (13-53)
Disc/bowls	2 (0-4)	2 (0-5)	3 (0-10)
Spherocyte	0 (0-0)	0 (0-1)	0 (0-3)
Echinocyte	0 (0-3)	1 (0-4)	5.5 (1-23)
Acanthocyte	0 (0-1)	1 (0-2)	0 (0-2)
Dacrocyte	0 (0-1)	1 (0-3)	1 (0-5)
Keratocyte	0 (0-1)	2 (0-5)	3 (0-7)
Schizocyte	0 (0-1)	0 (0-2)	2 (0-5)
Knizocyte	1 (0-4)	3 (0-8)	1 (0-6)
Others	1 (0-4)	3 (0-7)	4 (1-11)

*All values are expressed as a median plus the 5% to 95% range because the distribution of most values was non-Gaussian.

†Twenty-nine ABO compatible; 1 AB (mother A); 1 AB (Mother B).

‡Includes both ABO compatible and incompatible infants.

(Courtesy of Zipursky, A., et al.: Am. J. Pediatr. Haematol. Oncol. 5:45–51, Spring 1983.)

TABLE 3.—ERYTHROCYTES IRREGULARLY SHAPED IN ADULTS AND NEWBORNS

	Acanthocytes	Keratocytes	Schizocytes
Adults (53)	8*	32	2
Full-term infants (31)	52	68	26
Premature infants (52)	38	92	85

*The figures represent the percentage of subjects studied in whom 1 or more cells of a particular type were found in a 100-cell erythrocyte differential count. For all three cell types, significantly fewer adults than newborns had irregularly shaped erythrocytes. ($\chi^2 = 13.8$; $P < .001$)

(Courtesy of Zipursky, A., et al.: Am. J. Pediatr. Haematol. Oncol. 5:45–51, Spring 1983.)

Three-dimensional evaluation will aid the study of red blood cell morphology in hematologic diseases of newborn infants.

▶ [Even though I would suspect that the information contained in this article will be put to little use by most people in practice, the work itself is a masterpiece of thoughtful data accumulation. Anyone who has looked at the blood smear of newborn infants knows that the red blood cells are quite a bit different than those in older children. Zipursky et al. have volunteered to do a job that no one else seemed willing to do, that is, to carefully catalog each expected morphological red blood cell finding in the newborn smear. If one really becomes a good aficionado of the newborn smear, one can use this information to tell normal from abnormal. I would keep this report around. If you collect things long enough, eventually they will have some value.—J.A.S., III] ◀

9–6 **Red Blood Cell Destruction Caused by a Micropore Blood Filter.** A new disposable woven stainless steel micropore filter requiring only a small primary volume for initial loading recently became available. William F. Schmidt III, Haewon C. Kim, Natale Tomassini, and Elias Schwartz (Children's Hosp. of Philadelphia) recently encountered two children who developed hemoglobinemia and hemoglo-

(9–6) JAMA 248:1629–1632, Oct. 1, 1982.

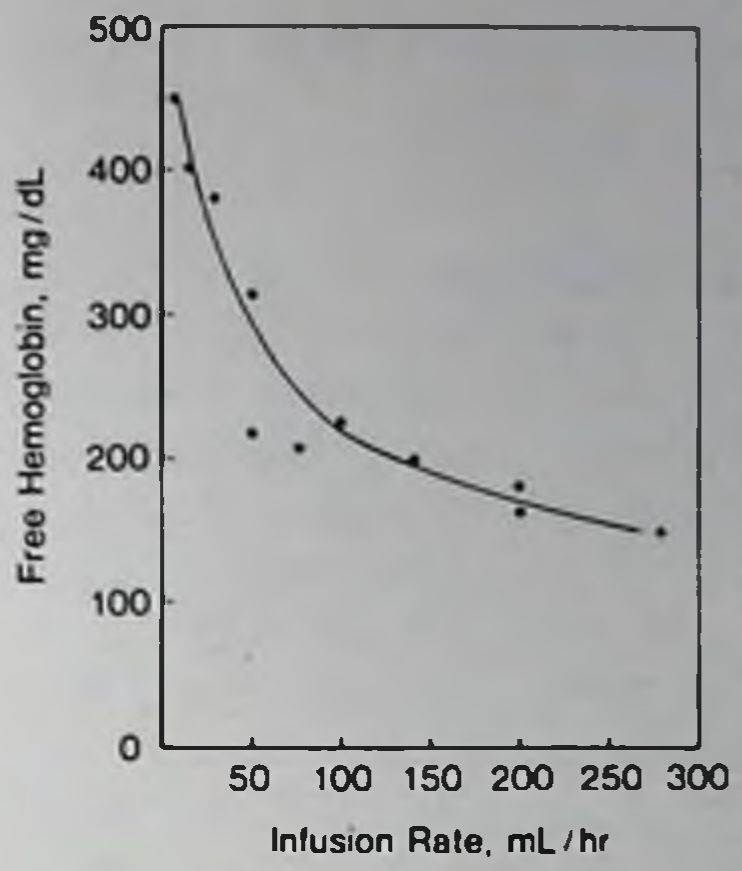
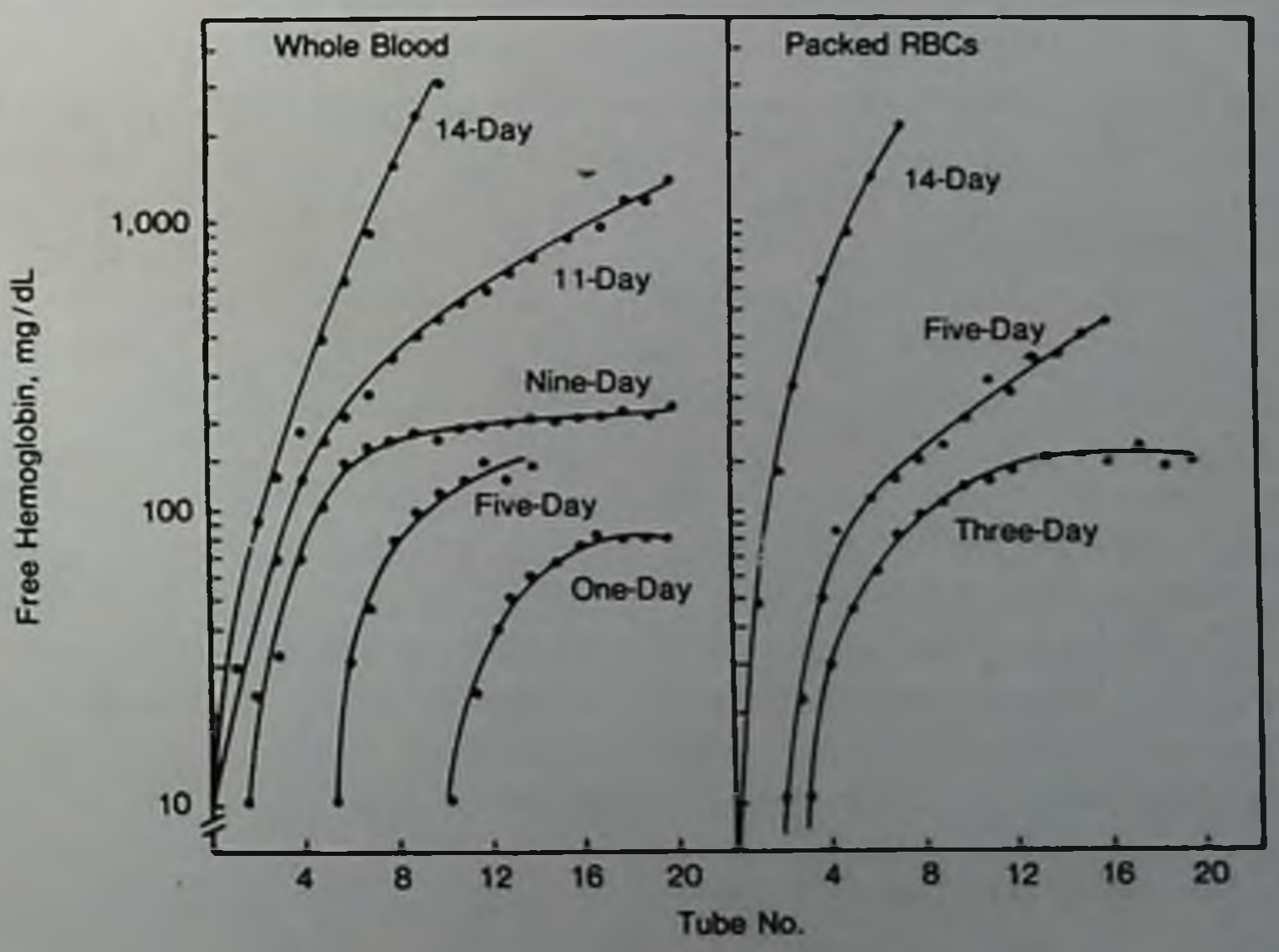


Fig 9–2.—Effect of infusion rate on filter-induced hemolysis. Differences in plasma hemoglobin between test and control samples after infusion of 10-ml aliquots of 10-day-old blood through separate filters are shown. A new filter was used for each 10-ml aliquot. Results shown are mean values of two separate experiments. (Courtesy of Schmidt, W. F., III, et al.: JAMA 248:1629–1632, Oct. 1, 1982; copyright 1982, American Medical Association.)

binuria after receiving whole blood through woven stainless steel micropore filters. One child had a plasma hemoglobin of 200 mg/dl. Filter-induced hemolysis therefore was quantified experimentally under standard conditions.

When aliquots of the same blood given to one of the patients were hand-pushed through a micropore filter, resistance increased after 15 ml were passed, and gross hemolysis occurred. Substantial hemolysis was observed at all infusion rates (Fig 9–2). Hemolysis increased as the rate of filtration declined. The influence of the age of stored red blood cells on filter-induced hemolysis is shown in Figure 9–3. Simi-

Fig 9–3.—Effect of red blood cell (*RBC*) age on filter-induced hemolysis. Blood was stored in citrate, phosphate, dextrose, and adenine. Aliquots were collected sequentially through single filter for total volumes up to 40 ml. Each tube contained either 2 ml of filtered whole blood or 1 ml of filtered, packed RBCs plus 1 ml of physiologic saline added after filtration. Free hemoglobin concentration values presented on logarithmic ordinate. Infusion rate was 200 ml/hour. (Courtesy of Schmidt, W.F., III, et al.: JAMA 248: 1629–1632, Oct. 1, 1982; copyright 1982, American Medical Association.)



lar results were obtained with blood stored in citrate, phosphate, dextrose (CPD)-adenine and blood stored in CPD alone. The calculated maximum pore size was about 30 × 60 μm. There are about 15,000 such pores per 4-sq cm surface area.

Problems may arise in using the woven stainless steel micropore filter in infants and small children, where slow transfusion speeds are usual. Patients given long-term red blood cell transfusion therapy should not have blood given through microaggregate filters without first checking for red blood cell damage by the filter. Administration of damaged red blood cells would add to the patient's iron burden without providing optimal red blood cell survival. The manufacturer currently recommends that stored blood be filtered by attaching the filter to a unit of blood and drawing the blood into a syringe with negative pressure.

▶ [The concept of micropore filtration was first introduced into this country over 2 decades ago. Today there is still considerable controversy over the benefit of these filters, even for patients who have to receive massive transfusions. Their purpose is to remove microaggregates in blood. These are composed principally of platelets, white blood cells, and fibrin strands. With the storage of blood, microaggregates increase both in number and in volume and have been implicated in clinical pulmonary insufficiency and histologic pulmonary embolization in human beings receiving massive transfusions of blood. The red blood cell really gets "up tight" when it has to pass through these filters. The result of this type of red blood cell anxiety is a broken up red blood cell that results in hemoglobinemia and hemoglobinuria.

I can't tell you whether to use micropore filters of this type or not. If you do, you should at least be aware of the phenomenon described by Schmidt et al. I semiapologize for using the phrase "up tight" in the preceding paragraph when referring to red blood cells. I would be willing to bet that you do not know how this two-word combination first entered the jargon of our literature. Most people take it to mean individuals who are high-strung. In fact, it refers precisely to the illicitation of the cremasteric reflex at the times of stress. Thus, technically it should not be applied to the red blood cell and, for that matter, is applicable to only half the members of our society (for another study of a slightly different nature on blood transfusions in the neonate, see the report by Humphrey, M. J., et al.: *J. Pediatr.* 101:605, 1982, which shows that attempting to dilute red blood cell transfusions and giving fresh red blood cell transfusions does nothing to decrease the hemolysis of red blood cells that are given through small-bore needles of the 25-gauge variety).—J.A.S., III] ◀

9–7 **Intrauterine Fetal Transfusions: Winnipeg 1982.** During 1964–1978, the Winnipeg Rh Laboratory performed 611 intrauterine transfusions on 257 fetuses and saw survival rates increase from 30% in 1964 to 1965, to 59% in 1966–1969, and to 70% in 1970–1977. The incidences of hydrops fetalis at intrauterine transfusion were 35%, 23%, and 30%, respectively, but the hydropic fetal survival rates improved dramatically, from 7% to 33% and to 50% in the three periods.

John M. Bowman and Frank A. Manning discuss the 117 intrauterine transfusions performed on 45 fetuses from 1978 to mid-1982, stressing problems with epidural catheter-induced hemolysis early in the period and the possible effect on Rh perinatal mortality after introduction of real-time scan ultrasonography in 1980. Indications for intrauterine transfusion, epidural catheter placement techniques, transfusion volume formulas, and transfusion intervals for the nonhydropic fetus were unchanged from the earlier study.

(9–7) Obstet. Gynecol. 61:203–209, February 1983.

Perinatal survival after fetal transfusion from 1978 to mid-1980 was 52% (11 of 21 transfused), which was worse than in the preceding 12 years. It was discovered that the manufacturer had narrowed the side hole opening diameters of the epidural transfusion catheter, which caused donor red blood cell hemolysis and hydrops fetalis. Catheter-induced red blood cell hemolysis was directly responsible for 3 perinatal deaths in this period and probably contributed to 2 others. The problem was corrected by removal of the catheter tip with side holes, allowing free donor red blood cell egress through the open end of the catheter.

Of the 24 fetuses undergoing 64 transfusions from mid-1980 to mid-1982, after the catheter-induced red blood cell hemolysis problem had been corrected, 22 (92%) survived, including all 16 nonhydropic and 6 of 8 hydropic fetuses. This dramatic improvement in survival was also due to routine use of real-time ultrasonography at intrauterine transfusion, which was begun in 1980. Ultrasonography allowed more accurate and less traumatic catheterization of the fetal peritoneal cavity, aided in assessing the condition of the hydropic fetus after intrauterine transfusions, and showed where edema and ascites were increasing or decreasing, thus helping selection of the most appropriate interval for the next tranfusion.

Other factors contributing to improved fetal survival included withdrawal of the 16-gauge Tuohy needle after the catheter had been threaded into the fetal peritoneal cavity, and use of very tightly packed donor red blood cells (hematocrit of 88–92 rather than 70–75). Methods of managment that are not recommended include exchange transfusion of the severely affected fetus by hysterotomy and cutdown on a fetal blood vessel, direct vascular transfusion of the severely affected fetus, and promethazine hydrochloride administration to the severely immunized pregnant woman.

With meticulous prenatal care, amniotic fluid ΔOD_{450} measurements beginning at 20½ weeks' gestation, and intrauterine transfusion carried out under ultrasound guidance beginning as early as 22½ weeks' gestation if necessary, most infants can be salvaged. Intensive plasma exchange, as an adjunct to these measures and begun at 12–14 weeks' gestation, should be reserved for the pregnant woman with a history of hydropic fetal death before 28 weeks' gestation.

▶ [The group in Winnipeg, Manitoba, has been on the forefront of the Rh stories now for some years. Here, they summarize their experience with intrauterine transfusions to salvage babies who presumably would be lost from hydrops fetalis. Their numbers are most impressive, showing that as many as 90% of these babies requiring intrauterine transfusions can be managed successfully. Why these investigators are so successful is obviously a credit to their skill in performing this technique at a time when most centers are seeing ever-decreasing numbers of pregnancies with this problem. One of the reasons their babies do so well is that about one half of the pregnancies were managed with intrauterine transfusions before 26 weeks' gestation.

In the past few years, other methods of managing the severly immunized mother and the affected fetus have been proposed. Some of these have been discussed in prior YEAR BOOKS. Apparently these authors from Canada are not enthusiastic about any of them. They feel that exchange transfusion of the severely affected fetus by hysterotomy and cutdown on a fetal blood vessel should be abandoned because of the very poor survival rates with the use of this technique. Likewise (as commented on in the 1982 YEAR BOOK, p. 262), they do not feel that direct visualization of a fetal

vessel and direct intravascular transfusion is likely to be of additional benefit either. The results of the latter approach seem significantly worse than that of intraperitoneal fetal transfusions in the hands of people experienced in doing them. Some have recommended using promethazine hydrochloride in severely immunized pregnant women (Charles, A. G., et al.: *Obstet. Gynecol.* 60:627, 1982). This drug will block the reticuloendothelial system of the neonate and decreases the immune clearance of sensitized red blood cells The authors from Canada also remarked that this drug significantly depresses fetal and neonatal T lymphocyte function, with the potential risk of increased infection during the newborn period. Although the latter has never been documented, the authors may well have a point when their own success rate is so high. They do indicate that intensive plasma exchange in severely immunized pregnant women may be helpful in a restricted sense. They recommend reserving this very rigorous approach to the woman who has had a prior hydropic baby before 28 weeks' gestation. Under these circumstances, they start plasmapheresis of the mother at 12–14 weeks' gestation. This technique is used to reduce the antibody titer of the mother to sufficiently low levels that survival of the fetus is permitted until the point where intrauterine transfusions are feasible. The authors could not comment on the technique of giving red blood cell stroma orally to severely sensitized pregnant women (Bierme, S. J., et al.: *Lancet* 1:604, 1979).

I have thought that the end of the Rh story was coming to a fast conclusion. The handwriting seemed on the wall. Apparently the handwriting was a forgery, because we still see a lot that we need to learn and do about this time-honored disorder.—J.A.S., III] ◀

9–8 **Meningitis in Patients With Sickle Cell Anemia: Normocellular Cerebrospinal Fluid at Initial Diagnosis.** Sreedhar P. Rao, Emily Schmalzer, Mary Kaufman, and Audrey K. Brown (SUNY, Downstate Med. Center) reviewed the cerebrospinal fluid (CSF) findings in children with bacterial meningitis with and without sickle cell anemia (hemoglobin SS). The investigation was prompted by the discovery of 3 SS children with positive findings in CSF cultures for *Streptococcus pneumoniae* but with normocellular CSF. Thirty-six episodes of bacterial meningitis occurred in 29 children with sickle cell anemia between 1956 and 1978; findings were compared with those in 47 episodes occurring in children without sickle cell anemia seen from 1976 to 1978. Most children in both groups were younger than age 3 years at the time that meningitis was diagnosed.

The causative organisms are shown in the table. *Streptococcus pneumoniae* predominated in the patients with sickle cell anemia, and *Hemophilus influenzae* type B predominated in the group without

CEREBROSPINAL FLUID FINDINGS IN MENINGITIS PATIENTS WITH AND WITHOUT SICKLE CELL ANEMIA*

	No. of Pts.	No. of Episodes	Causative Organism	Number	CSF WBC Count Not Elevated
Non-sickle cell patients	24	24	*Hemoph. Influ.*	19	0
			Strep. Pneumo.	3	1
			Group B Strep.	1	0
			Neisseria Meningitides	1	0
Sickle cell patients	18	21	*Strep. Pneumo.*	20	5
			Hemoph. Influ.	1	1

*Nonhemoglobinopathy meningitis: range of cerebrospinal fluid white blood cells, 0–27,000/cu mm; mean, 4,330/cu mm. Sickle cell patients with meningitis: range, 0–3,500/cu mm; mean, 1,160/cu mm.

(Courtesy of Rao, S., et al.: Am. J. Pediatr. Hematol. Oncol. 5:101–103, Spring 1983.)

(9–8) Am. J. Pediatr. Hematol. Oncol. 5:101–103, Spring 1983.

anemia. One third of the anemic patients had normal CSF leukocyte counts, with less than 5 mononuclear cells/cu mm and no polymorphonuclear leukocytes. Two of the 6 had positive findings on Gram stains of the CSF. Four had positive blood culture results at the time of initial lumbar puncture. Four patients had no signs of meningeal irritation. Pleocytosis was found in all 3 patients who were restudied after 24–48 hours. Only 1 nonanemic child with meningitis had normocellular CSF.

Several episodes of bacterial meningitis in children with sickle cell anemia were associated with normocellular CSF, and similar cases appear in the literature. A lack of evidence for pleocytosis may result in diagnostic and therapeutic delay. Spinal taps may be done earlier in the course of febrile illness in sickle cell patients, and it also is possible that a more sluggish inflammatory response contributes to the findings. Patients with sickle cell anemia and clinical features of meningitis (e.g., high fever with vomiting, lethargy, or seizures) should be treated as having meningitis regardless of the CSF leukocyte count until the culture results become available.

9–9 **Clinicopathologic Characteristics of Septicemia in Sickle Cell Disease.** Between 1972 and 1980, 210 patients with sickle cell disease have been followed up at the Children's Hospital Medical Center in Cincinnati. Jeffrey S. Lobel and Kevin E. Bove reviewed the medical records of the 22 patients (10.5%) who had an episode of bacterial septicemia (table). In the group with hemoglobin SS, the attack rate was 13.3%. *Streptococcus pneumoniae* accounted for 73% of infections. Only 2 of the 22 patients had been immunized with polyvalent pneumococcal vaccine; 1 had *Moraxella* sepsis and 1 had *S. pneumoniae* type 15, a serotype not included in the vaccine. Associated infection included meningitis with *S. pneumoniae* in 5 patients, 2 of whom died, pneumonia with *Moraxella,* and acute pyelonephritis with *Escherichia coli*. Sixteen patients were between 10 and 27 months old.

The duration and type of symptoms before hospitalization were diverse. In 9 cases (including 2 fatal ones), onset was sudden and the patient was seen within 12 hours, usually with high-grade fever, lethargy, gastrointestinal tract symptoms, and pain in the extremities. In the other 13 cases, including 4 fatalities, these symptoms were also common; however, onset was more gradual, with 1 to 7 days' duration of symptoms. Temperature was more variable and upper respiratory tract symptoms were most common.

All patients who died had progressive shock and died within 48 hours. Mean duration from onset of fever to death was 24 hours (range, less than 6 to 56 hours). Hyponatremia and metabolic acidosis were found in 4 of the 5 fatal cases evaluated before death. Results of autopsy showed massive hemorrhagic necrosis of the adrenal glands in 3, with focal adrenal hemorrhage in the other 3 patients. In 5, adrenal sinusoidal microthrombi were present. In 3 patients, microthrombi in multiple sites were interpreted as histologic evidence of

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(9–9) Am. J. Dis. Child. 136:543–547, June 1982.

OCCURRENCE OF SEPTICEMIA IN 210 PATIENTS WITH SICKLE CELL DISEASE, 1972 TO 1980

Organism	Hemoglobinopathy				
	SS	SS-α-Thalassemia	SC	SC_{Harlem}	Total
Streptococcus pneumoniae	13(5)*	1	1	1 (1)	16 (6)
Haemophilus influenzae	2†	0	0	0	2
Salmonella	2‡	0	0	0	2
Moraxella	1	0	0	0	1
Escherichia coli	1	0	0	0	1
Total	19(5)	1	1	1 (1)	22 (6)

*Numbers in parentheses indicate deaths.
†One, type b; 1, not typed.
‡Both *Salmonella heidelberg*.
(Courtesy of Lobel, J. S., and Bove, K. E.: Am. J. Dis. Child. 136:543–547, June 1982; copyright 1982, American Medical Association.)

disseminated intravascular coagulation. All fatalities were secondary to pneumococcal infection.

Because it is impossible to exclude septicemia in a febrile young patient with sickle cell disease, parenteral antibiotic therapy should be started expectantly when these patients have either high or moderate fever. Stress dosages of corticosteroids should be initiated at the first sign of circulatory insufficiency.

▶ [This article and the preceding one teach us a lot about infections in patients with sickle cell disease that we may not have appreciated previously. The finding of normocellular cerebrospinal fluid (CSF) in one third of patients with meningitis and sickle cell disease is astounding. It shakes our confidence in the usual screening test that we perform for the presence or absence of meningitis. Fortunately, most of the children with these findings still would be salvaged under the umbrella of a more generalized approach to fever in "sicklers." As Lobel and Bove point out, practically any fever in a child with sickle cell disease can be a reflection of septicemia and should be regarded as such with respect to starting parenteral antibiotic therapy. If you follow this rule, you are not likely to miss the child who also has meningitis, but with a normal CSF cell count. The CSF culture will come back in 1 or 2 days and be positive and you already will have had the patient on antibiotics just because of the high index of suspicion of septicemia. I realize that this may mean many hospitalizations, but with our present understanding the reliability of markers to exclude septicemia is relatively poor. Thus, we will continue to see overtreatment of fevers under these circumstances.

There is still no satisfactory way to reduce the incidence of infectious complications predictably in patients with sickle cell disease. No study has been designed satisfactorily that documents a protective effect of orally administered penicillin as a prophylactic in children with impaired splenic function. This is not to say that penicillin should not be used prophylactically, but, rather, that if you choose to go this route, you should realize that you don't have much backing you up. The greatest problem that we have seen with the prophylactic use of penicillin is the overconfidence on the part of parents that this will protect their children from something disastrous. I personally have seen pneumococcal septicemia develop after splenectomy in a child who was verified to have been taking her prophylactic oral amoxacillin therapy. The pneumococcal vaccine may not be of much help either. Certainly, there are well-described cases now of children who have developed pneumococcal infection with strains of organisms that were included in the pneumococcal vaccine they had received. This, too, is not meant to say that pneumococcal vaccine should not be given. It certainly should be administered to all patients with sickle cell anemia. It

just is not 100% effective in anybody's hands. As we are aware, the pneumococcal vaccine has only a modest ability to produce antibody in children with sickle cell anemia who are younger than age 2. This, or course, is one of the greatest risk periods for infection in these patients. There has been rather high resistance among private physicians to give pneumococcal vaccine (Patriarca, P. A.: *Public Health Rep.* 97:406, 1982); the reason for this resistance is not entirely clear.—J.A.S., III] ◀

9–10 **Newborn Sickle Cell Screening: Benefits and Burdens Realized.** Peter T. Rowley and Donna J. Huntzinger (Univ. of Rochester) attempted to determine how 17 newborn infants who were identified by sickle cell screening in the Rochester, New York, area benefited from identification. Nine had a diagnosis of sickle cell anemia, 4 had hemoglobin SC disease, 1 had sickle cell β-thalassemia, and 3 had homozygous hemoglobin C disease. Twelve of the families had provided proper care for their children, and 6 children had received pneumococcal prophylaxis. Some parents, however, did not understand the recurrence risk. In 3 instances, genetic counseling may have threatened the parental relationship by focusing attention on the identity of the father. Two physicians interpreted the request for a second blood sample to confirm the diagnosis as meaning that the preliminary result was unreliable.

States mandating screening for sickle cell disease must provide individual case follow-up. An attempt should be made to inform parents of the mandatory program at or before the time of testing. In addition, guidance should be provided to physicians in their role of counseling parents about a disease before symptoms have appeared. Parents require the exact diagnosis in writing, and the physician must provide a specific recurrence risk for other offspring of the same union. Unless the parents have decided not to have more children, the physician should suggest that each be tested for an abnormal hemoglobin and, if none is found, for β-thalassemia trait. Parents planning to have more children should be informed about prenatal diagnosis for sickle cell disease, including the recently developed amniotic fluid cell DNA method.

▶ [Prenatal or antenatal diagnosis of sickle cell hemoglobinopathies is now feasible (Boehm, C. D., et al.: *N. Engl. J. Med.* 308:1054, 1983). The diagnosis can be performed with the use of techniques to define DNA polymorphisms located so near the β-globin gene that they are inherited along with that gene and therefore serve as a marker of the disease. Despite the feasibility of this approach, the technique is only just emerging out of the experimental stage and is still available in only a limited number of medical centers because of the sophisticated medical and laboratory skills required for performance of the procedures. On the other hand, neonatal testing (involving the use of cord blood samples and hemoglobin electrophoresis) is currently feasible and has been recommended by a number of authors for routine implementation, especially for hospitals serving populations at risk for sickle cell disease. The rationale for early detection of sickle cell disease is to identify those persons in whom medical surveillance and early treatment of infections can reduce morbidity and mortality. Clearly, this early detection is a legitimate endeavor even though there is still no definitive cure for sickle cell disease. Additional benefits include development of information that makes it possible to provide counseling for the parents and screening for other members of the family. Early diagnosis also facilitates the use of prophylactic measures such as administration of antibiotics and pneumococcal vaccine at the appropriate time. Moreover, early diagnosis and longitudinal follow-up studies can provide information that ultimately will be helpful to parents, patients, and phy-

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(9–10) Am. J. Dis. Child. 137:341–345, April 1983.

sicians in acquiring a better understanding about the heterogeneity and other characteristics of the clinical course of this disease. Also, early detection of a first born child with sickle cell disease permits parents to be informed of the genetic characteristics of this disorder in case they wish to enter into subsequent prenatal diagnosis discussions.

Admittedly, the procedure of neonatal detection of sickle cell disease poses possible hazards to the family, such as misdiagnosis, exposure of nonpaternity, and development of grief, guilt, and anxiety. For this reason, some centers have adhered strictly to voluntary screening after informed consent. This is not true in the state of New York, where all newborns at risk now have been screened. Obviously, when states mandate screening for sickle cell disease, this should be done part and parcel with careful follow-up. All the screening in the world will not help a newborn with sickle cell disease unless the information is gotten back to the parents in a meaningful way. P. T. Rowley et al. have analyzed the benefits and burdens of newborn sickle cell screening (*Am. J. Dis. Child.* 137:341, 1983). They found both benefits gained and burdens realized. It is easy for a state legislature to sign a bill putting these procedures in place. It is more difficult to be certain that they are carried out.—J.A.S., III] ◀

9–11 **Genetic Defect in the Binding of Protein 4.1 to Spectrin in a Kindred With Hereditary Spherocytosis.** Hereditary spherocytosis is considered to be a disorder of the red blood cell membrane, but the precise molecular defect has not been identified. Indirect evidence suggests that the genetic defect lies in the erythrocyte membrane skeleton, a submembranous meshwork of proteins responsible for membrane shape and structural stability. To test this premise, Lawrence C. Wolfe, Kathryn M. John, John C. Falcone, Ann M. Byrne, and Samuel E. Lux (Boston) systematically assayed the interactions of spectrin, the major skeletal protein, in 6 kindreds with autosomal dominant hereditary spherocytosis.

In 1 of these kindreds, enhancement of spectrin-actin binding by protein 4.1 was reduced, due to a 39 ± 4% decrease (mean ± SD) in the binding of normal protein 4.1 by spectrin, in 4 members with the disorder. The defective spectrin was separated into two populations by affinity chromatography on immobilized normal protein 4.1. One population (41 ± 2%) lacked the ability to bind 4.1, but the other functioned normally.

Indirect evidence suggests that the genetic defect in hereditary spherocytosis lies in the red blood cell membrane skeleton, but studies have shown that, with rare exceptions, the composition of red blood cell membranes in these patients is normal. However, the study found a qualitative defect in 1 of 6 kindreds (4 of 16 patients) tested, in that 40% of the spectrin lacked the ability to bind normal protein 4.1 in the affected members of this family. Consequently, the protein 4.1-stimulated binding of spectrin to F-actin was greatly reduced.

The membrane skeleton is the major determinant of membrane stability, and protein 4.1 enhances the critical spectrin-actin interaction that ties the skeleton together; consequently, defective spectrin-actin binding should weaken the membrane and promote membrane fragmentation.

The present investigations show that hereditary spherocytosis is a biochemically heterogeneous disorder. In addition to diminished binding of protein 4.1 by spectrin, the association of hereditary spherocy-

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(9–11) N. Engl. J. Med. 307:1367–1374, Nov. 25, 1982.

tosis with partial spectrin deficiency, inextractable or poorly extractable spectrin, and absent protein 4.2 have been reported.

▶ [The red blood cells of patients with hereditary spherocytosis are flawed. Evidence suggests that the genetic defect in this disorder lies in the red blood cell membrane skeleton. In order to understand what this article is telling us, we have to review for a second a little bit about the structure of the red blood cell membrane. The structural stability of the red blood cell membrane is almost entirely determined by the membrane skeleton, a filamentous meshwork of proteins lining the inner membrane surface. The skeleton is composed predominantly of four proteins: spectrin, actin, protein 4.1, and ankyrin. Spectrin itself is a very flexible molecule. It interacts with the other three major proteins to hold the red blood cell membrane together. Didn't you think it was miraculous how the membrane tucked itself into a biconcave disk? In more detail, spectrin fastens to ankyrin, which tethers the skeleton to the membrane by means of its connection to protein 3, an integral membrane protein that spans the lipid bilayer structure of the red blood cell membrane. Spectrin establishes lateral connections within this meshwork. It may do this by binding to short filaments of actin. The latter interaction is enhanced greatly by the association of protein 4.1 with spectrin near the spectrin-actin binding site. Now that we all understand how the red blood cell membrane holds itself together, what these investigators demonstrated in several families was that this interaction of spectrin-actin binding by protein 4.1 was reduced. They speculate that this then was responsible for the peculiarities of shape and survival of the red blood cells of these patients with hereditary spherocytosis.

It is likely that hereditary spherocytosis is not a single diagnostic entity and that it is caused by a rainbow of different biochemical disorders that have in common the ability to cause the red blood cell to form into a sphere. What the authors discuss above may be only one part of the spectrum of that rainbow. We will keep you informed of other colors of that rainbow as the story unfolds.—J.A.S., III] ◀

9–12 **Severe Hemolytic Anemia in Black Children With Glucose-6-Phosphate Dehydrogenase Deficiency.** Deficiency of erythrocyte glucose-6-phosphate dehydrogenase (G-6-PD) is inherited on an X-linked recessive basis and occurs commonly in African and American black, Mediterranean, and Far Eastern populations. Reduction in enzyme activity may predispose to hemolysis because of the red blood cell's inability to tolerate oxidative stress. During a 3½-year period, Kevin Shannon and George R. Buchanan (Univ. of Texas Health Sci. Center at Dallas) studied 14 hospitalized black G-6-PD-deficient children with moderate to severe hemolytic reactions.

The vast majority (13/14) were boys and were younger than age 30 months. Initial hemoglobin values in 8 children ranged from 4.0 to 8.5 gm/100 ml. Nine patients needed blood transfusions. Eleven of the 14 episodes occurred with infection (5 bacterial, 6 viral); children with viral syndromes tended to have more severe hemolysis. Naphthalene was responsible for 3 episodes, but oxidant drugs were implicated in no instances.

Heinz body preparations, obtained shortly after admission in 6 children, were positive in 4. Findings on the peripheral blood smears of most subjects included irregular, dense, misshappen erythrocytes with asymmetric distribution of hemoglobin and an adjacent membrane-bound clear zone ("eccentrocytes," Fig 9–4). Polychromasis and nonspecific anisocytosis and poikilocytosis also were seen commonly. All patients made an uneventful recovery.

(9–12) Pediatrics 70:364–369, September 1982.

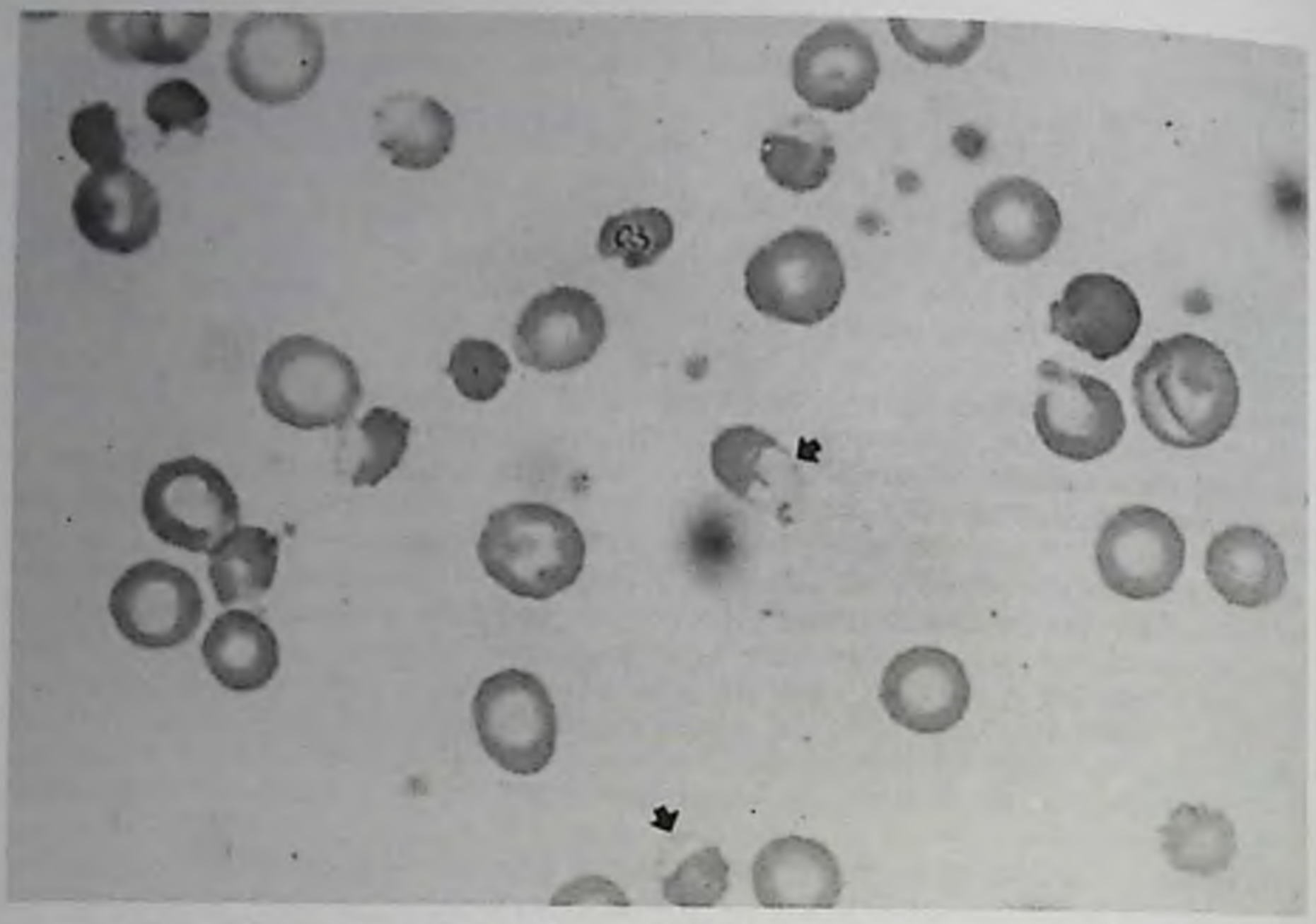

Fig 9–4.—Peripheral blood smear showing typical "eccentrocytes" *(arrows)*, dense cells with asymmetric distribution of hemoglobin and a clear zone usually bound by cell membrane. Wright-Giemsa; ×650. (Courtesy of Shannon, K., and Buchanan, G. R.: Pediatrics 70:364–369, September 1982. Copyright American Academy of Pediatrics 1982.)

Hemolytic reactions in the black G-6-PD-deficient child induced by oxidative stress may be severe (particularly in young infants), are most commonly associated with infection and are often characterized by distinctive erythrocyte morphology. Because older cells containing less G-6-PD are destroyed preferentially, the surviving young erythrocytes in the anemic subject shortly after hemolysis may have normal activity by the qualitative G-6-PD screen or even by quantitative assay. The degree of reticulocytosis may distinguish G-6-PD-deficient children with normal screens after a significant hemolytic episode. When G-6-PD deficiency is suspected in a patient with a normal screen, studies of the mother of a boy or both parents of a girl may be done to clarify the diagnosis. Alternatively, the child's red blood cells may be fractionated by centrifuging and the populations selectively assayed for G-6-PD activity.

► [Although this article doesn't give us any truly new information, the clinical spectrum of hemolysis due to G-6-PD deficiency has not been described recently in the pediatric literature. This is the value of this article. What we see is that very significant anemia can be associated with hemolysis in G-6-PD deficiency. This is a well-known characteristic of G-6-PD-deficient cells in persons of Mediterranean ancestry. It is somewhat less common in patients with the black variant of G-6-PD. The reason for this milder form of presentation is that the youngest red blood cells of black persons with G-6-PD deficiency still have residual enzyme that protects those cells. Nonetheless, a significant fall in the hemoglobin level can occur in black children before they reach this protective level of young red blood cells that contain enzyme. This study also reiterates the value of examining the peripheral blood smear for the typical morphological findings noted in Figure 9–4. It additionally stresses the lack of utility of a G-6-PD screen in order to diagnose this problem if the patient is actively hemolyzing. All you would be testing is the youngest cells that have normal enzyme activity, and

the screening test itself therefore will be normal. You must perform an assay for the enzyme activity in order to be more certain of the diagnosis. These data also stress the importance of avoiding chemical oxidant substances. Recently, there was a rash of Heinz body hemolytic anemia described in a group of otherwise normal neonates as a result of the use of a phenolic disinfectant in the nursery. Presumably, if there had been any infants in that nursery who had G-6-PD deficiency, they would have been in very serious trouble (Vitkun, S. A., et al.: *Pediatrics* 71:352, 1983).

Finally, this year saw disappointment as far as vitamin E is concerned. A couple of years back, L. Corash et al. (*N. Engl. J. Med.* 303:416, 1980) found that high-dose vitamin E therapy given to patients with Mediterranean-type G-6-PD deficiency would result in reduced chronic hemolysis. Not leaving well enough alone, G. J. Johnson et al. (ibid. 308:1014, 1983) repeated this study and claimed to have demonstrated that high-dose vitamin E therapy does not decrease rapid hemolysis secondary to G-6-PD deficiency. Well, now we have what looks like an even draw. Two articles on the same subject that reach different conclusions is sort of like the story of a man and his watches. A man with one watch knows what time it is. A man with two watches is never really sure. For an excellent review of medical uses of vitamin E, please see the article by J. G. Bieri et al. (ibid, p. 1063).—J.A.S., III] ◄

9–13 **Role of Neutrophil Antigen NA1 in an Infant With Autoimmune Neutropenia.** Several antigens specific for human neutrophils have been characterized by reactivity with serum from patients with isoimmune neonatal neutropenia or autoimmune neutropenia or from multiparous women. Antibodies reactive with neutrophil antigen NA2 are found most often in serum from infants with chronic neutropenia. Prema R. Madyastha, Catherine U. Kyong, Charles P. Darby, Jr., Petrina V. Genco, K. Ramananda Madyastha, Armand B. Glassman, and H. Hugh Fudenberg (Med. Univ. of South Carolina) evaluated an infant with persistent neutropenia caused by an autoantibody with anti-NA1 specificity. Reactivity of the autoantibody was associated with the reduction in circulating neutrophils.

The infant was a girl, aged 14 months, with persistent neutropenia. Diarrhea developed at age 10 months, lasted 2 to 3 months, and subsided after a change in diet. Absolute neutrophil counts were 410 to 935/cu mm, but there were no recurrent or serious pyogenic infections. The patient's serum reacted with neutrophils from her peripheral blood, from normal donors, and from her mother, all these having NA1, but not with neutrophils from NA1-negative donors, including the father. The autoantibody was detected by capillary agglutination and by direct immunofluorescence, but not by complement-dependent cytotoxicity testing. The serum of the mother lacked antibody. Three serial studies showed good correlation between appearance of the circulating autoantibody and peripheral neutrophil counts.

This case and previous reports suggest a possible relation between NA1 antigen and the susceptibility of NA1-positive infants to autoimmune neutropenia. The patient was not treated for neutropenia, and the decline in autoantibody activity over 10 months of study suggests that the antibody was of short duration. Studies of autoantibody specificity in similar patients may elucidate the nature of the neutrophil antigens that predispose infants to chronic neutropenia.

► [Dr. Larry Boxer, Professor of Pediatrics and Director of Pediatric Hematology/Oncology, C. S. Mott Children's Hospital, Ann Arbor, Michigan, comments:

"Neutropenia exists in adults and school-age children when circulating neutro-

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(9–13) Am. J. Dis. Child. 136:718–721, 1982.

phils number less than 1,500/cu mm mature and band forms. Individual patients may be characterized as having mild neutropenia with counts of 1,000 to 1,500/cu mm, moderate neutropenia with counts of 300 to 1,000/cu mm, and severe neutropenia with counts generally below 300/cu mm. This stratification is useful for predicting the risk of infections, because only the patients with severe neutropenia have increased susceptibility to life-threatening infections. Neonatal isoimmune neutropenia, analogous to Rh hemolytic anemia, is the most convincing example of a disease involving antineutrophil antibodies. Maternal sensitization during gestation to fetal neutrophil antigens results in an IgG antibody that crosses the placenta and destroys the infant's neutrophils, resulting in neutropenia. Infected infants frequently develop fever after a few days of life. Cutaneous infections predominate, usually secondary to *Staphylococcus aureus* and less frequently *Escherichia coli* or β-hemolytic *Streptococcus*. Respiratory tract or urinary tract infections or septicemia have been reported infrequently. This order is self-limiting, which coincides with the expected half-life of maternal IgG in the infant's serum. Study of isoimmune neutrophil antibody has led to the identification of neutrophil-specific antigen, which have been classified by using *N*, which signifies 'neutrophil specificity,' followed by a single letter of the alphabet that represents different loci, i.e., *NA*, *NB*. The numbers that follow these two letters represent different alleles, e.g., *NA1*, *NA2*, etc. The treatment of isoimmune neonatal neutropenia consists of antibiotic therapy appropriate for life-threatening infection. Plasma exchange to remove the offending antibody also might be useful; this exchange could be followed by infusion of maternal neutrophils known to lack the antigen to which the antibody is directed.

"Unlike isoimmune neonatal neutropenia, autoimmune neutropenia has been much more difficult to diagnose. Many of the conventional assays that have proved useful in establishing the diagnosis of isoimmune neonatal neutropenia, such as agglutination, have proven unsatisfactory in establishing the diagnosis in autoimmune neutropenia. The most reliable methods for establishing the diagnosis of autoimmune neutropenia have utilized methods that directly measure IgG on this surface of the sensitized neutrophil. Once the diagnosis of autoimmune neutropenia has been established, treatment of patients involves the judicious use of appropriate antibiotics for bacterial infection and a trial of prednisone therapy at 1 to 2 mg/kg/day over 2 to 3 weeks for patients with severe neutropenia who are having recurrent infection. In one half of the reported cases of children and adults with autoimmune neutropenia, corticosteroid therapy has resulted in a normal neutrophil count. Splenectomy has been tried in a few patients, but appears to be of only transient benefit in some and may further predispose patients to a loss of effective means for dealing with life-threatening bacterial infections. The roles of other modes of therapy, such as plasmapheresis, intravenous γ-globulin, and immunosuppressive therapy, in the treatment of autoimmune neutropenia remain unproved because control studies have not been conducted.

"Finally, I suspect that autoimmune neutropenia in infancy, as detailed in this report, may be a self-limiting disorder, much like childhood immune thrombocytopenia. Personal communication with Dr. Parviz Lalezari, who has studied a number of these patients, would indicate this to be the case. However, we must await the report of a large series of patients for verification."] ◀

9-14 **Prenatal Prediction of Thrombocytopenia in Infants of Mothers With Clinically Diagnosed Immune Thrombocytopenia.** Management of the pregnant patient with immune thrombocytopenia is complicated by the unavailability of the fetal platelet count. Because transplacental passage of antiplatelet antibodies mediates infant thrombocytopenia, measurement of maternal platelet-associated IgG might predict infant outcome. John G. Kelton, Martin J. Inwood, Robert M. Barr, Sidney B. Effer, David Hunter, William E. Wilson, David A. Ginsburg, and Peter J. Powers (Hamilton, Ont.) related the maternal platelet count and platelet-associated IgG level to the in-

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(9-14) Am. J. Obstet. Gynecol. 144:449–454, Oct. 15, 1982.

fant's platelet count in 41 pregnancies in 38 patients clinically diagnosed as having immune thrombocytopenia.

Of 39 live-born infants, 15 were thrombocytopenic at delivery. Maternal platelet-associated IgG was predictive of infant platelet count, but maternal platelet count was not; only 1 of 18 pregnancies in mothers who were thrombocytopenic at delivery with normal platelet-associated IgG resulted in a thrombocytopenic infant, whereas 11 of 12 thrombocytopenic mothers with elevated platelet-associated IgG had thrombocytopenic infants.

Five infants died in utero between 18 and 28 weeks' gestation, but there were no neonatal deaths and there was no significant morbidity in the live births. In many thrombocytopenic infants, the platelet nadir did not occur until several days after delivery. The 1 maternal death was not due to thrombocytopenia.

Measurement of platelet-associated IgG in mothers with immune thrombocytopenia during pregnancy can be used to predict infant thrombocytopenia, but it does not predict the severity of the thrombocytopenia.

▶ [I don't know that we've had enough experience with attempting to predict the presence of thrombocytopenia prenatally in infants of mothers with a clinical diagnosis of immune thrombocytopenia. The ability to measure antiplatelet antibodies has taken us a giant step forward in achieving this goal, however. We see in this article that when a mother has no demonstrable antibody, then we should be able safely to conclude that the baby will be unaffected. If the mother does have antibody, then the baby will be at risk for passively acquired platelet antibody, and the potential for thrombocytopenia is quite real, although not predictable in terms of its severity. Unfortunately, there are not many centers that have good assays for platelet antibody, and it may be some time before we see wide application of this technique.

If a baby is born with passively acquired antibody against his or her platelets, we certainly are tempted to use high-dose intravenous IgG therapy if that baby is thrombocytopenic. Although no data on the use of intravenous IgG in the immediate neonatal period are available, there is ample evidence to suggest that this relatively recently released product is helpful in managing older children and adults with autoimmune thrombocytopenia. It is thought that IgG in large doses will block the reticuloendothelial system. This would decrease the clearance of antibody-coated platelets (Newland, A. C.: *Lancet* 1:84, 1983; and Mueller-Eckhardt, C., et al.: *N. Engl. J. Med.* 308:287, 1983). No one knows what giving IgG might do to the immune system of the neonate, so all of us are anxiously awaiting the courageous person who goes ahead and tries this in a newborn. When the story of IgG first appeared in abstract form and in the permanent literature, I thought it would turn out not to be on the best seller list. Clearly, its effects are reproducible in many investigators' hands. It may take a little while to see some of the controversy develop. A one-sided story is a little like watching touch football. The story of IgG for immune thrombocytopenia would be a bit more interesting if it were roughed up a little more.—J.A.S., III] ◀

9–15 **DDAVP: Useful Alternative to Blood Components in Moderate Hemophilia A and von Willebrand's Disease.** The vasopressin analogue 1-deamino-8-D-arginine vasopressin (DDAVP) has been used widely in Europe as an alternative to blood products in treatment of mild hemophilia A and von Willebrand's disease. It results in a rapid twofold to threefold increase in all components of the factor VIII system when given intranasally or intravenously. A. Indira Warrier and Jeanne M. Lusher (Detroit) examined the effects of DDAVP in 31 patients with von Willebrand's disease, 7 patients with mild to

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(9–15) J. Pediatr. 102:228–233, February 1983.

BASELINE AND PEAK VIII:C VALUES IN SUBJECTS WHO WERE OPERATED ON AFTER DDAVP

Subject	*Diagnosis*	*Procedure*	*Baseline VIII:C (U/ml)*	*Peak VIII:C (U/ml)*
1	von Willebrand disease	Dental extractions	0.03	0.42
2	von Willebrand disease	Dental extractions	0.36	1.02
3	von Willebrand disease	Dental extractions	0.37	1.05
4	von Willebrand disease	Tonsillectomy	0.37	1.03
5	von Willebrand disease	Tonsillectomy	0.30	1.30
6	von Willebrand disease	Nasal polypectomy	0.41	1.05
7	von Willebrand disease	Tonsillectomy	0.24	0.53
8	Hemophilia A	Minor oral surgery	0.02	0.13

(Courtesy of Warrier, A. I., and Lusher, J. M.: J. Pediatr. 102:228–232, February 1983.)

moderate hemophilia A, and 3 normal subjects. Two patients with von Willebrand's disease had severe involvement. The intranasal dose was 2–4 μg/kg, and the intravenous dose of DDAVP was 0.2 or 0.3 μg/kg.

Most subjects had a marked rise in factor VIII activity after intranasal DDAVP administration. Intravenous DDAVP administration led to a marked, sustained rise in all components of the factor VIII

system both in patients with von Willebrand's disease and in those with hemophilia A. Prolonged bleeding times were normal after intravenous DDAVP injection in patients with mild or moderate von Willebrand's disease. The results of using DDAVP rather than cryoprecipitate to obtain hemostasis at operation in 8 patients, 7 with von Willebrand's disease and 1 with hemophilia A, are given in the table. Use of DDAVP was effective in treatment of bleeding episodes in 4 patients. No adverse effects resulted from administration of DDAVP by either route.

Treatment with DDAVP has been successful in patients with von Willebrand's disease or hemophilia A in whom a short-term increase in factor VIII activity has been necessary. The situations include early, acute hemarthroses and such procedures as tonsillectomy and tooth extraction. The agent is not hemostatically effective in all patients with von Willebrand's disease. Patients with hemophilia A and factor VIII activities of 0.05 to 0.20 unit per ml seem to be ideal candidates for DDAVP treatment if a threefold rise in activity lasting several hours will suffice.

▶ [Hemophilia A and von Willebrand's disease are hereditary hemorrhagic disorders due to complete or partial deficiency of factor VIII activity. Hemophilia A is a sex-linked recessive problem resulting from reduced factor VIII coagulant activity, and von Willebrand's disease is an autosomally inherited heterogeneous group of bleeding disorders, which, in its most common form, is manifested by reduced factor VIII coagulant activity as well as a deficiency or absence of von Willebrand's factor, important for normal platelet action. The present treatment of these diseases consists of replacement of the missing plasma factors, usually with purified factor VIII concentrates. Factor VIII concentrate usually is given in the form of cryoprecipitate for von Willebrand's disease, and either as cryoprecipitate or more concentrated forms of factor VIII for hemophilia A. All factor VIII preparations potentially are contaminated with hepatitis virus, and recently the possibility that the acquired immunodeficiency syndrome (AIDS) may be transmitted by factor VIII preparations has been raised.

Desamino-8-D-arginine vasopressin (DDAVP) or desmopressin, is an analogue of the naturally occurring hormone, vasopressin. However, DDAVP is free of vasoactive effects. This drug has been observed to increase factor VIII coagulant activity by severalfold when administered to patients with von Willebrand's disease or to patients with mild factor VIII deficiency of the hemophilia A type. This marked, but transient, increase perhaps could eliminate the need for replacement with factor VIII preparations in patients undergoing surgical procedures and possibly could be used in the treatment of recurrent bleeding episodes. Warrier and Lusher have shown us that the drug can be used with some margin of safety for these purposes.

The manufacturers of DDAVP must be delighted by the reception that this drug has received. It was marketed solely to help care for patients with centrally mediated diabetes insipidus. Now it can be used to treat coagulation disorders. Some people are still using it to help treat nocturnal enuresis, as discussed in prior YEAR BOOKS. The stuff is not cheap, but with regard to congenital bleeding disorders, the toxicities are so minimal compared to getting AIDS or hepatitis that this route seems well worth pursuing if the clinical condition of the patient warrants the use of this pharmacologic agent to stimulate an increased amount of factor VIII in the circulation.—J.A.S., III] ◀

9–16 **Anti-inhibitor Coagulant Complex (Autoplex) in Hemophilia Inhibitor Patients Undergoing Synovectomy.** Surgical synovectomy has been contraindicated in hemophilic patients with inhibitors because of potential difficulty in achieving hemostasis, but the availability of activated prothrombin-complex concentrates has improved

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(9–16) Pediatrics 71:631–633, April 1983.

the management of these patients, especially those with high inhibitor values. Raymond J. Hutchinson, John A. Penner, and Robert N. Hensinger used the activated product Autoplex to treat 2 inhibitor patients who had severe arthropathy of one knee and underwent elective surgical synovectomy. Hemostasis was achieved perioperatively in both, and neither had clinical signs suggesting consumptive coagulopathy or thrombosis. Both patients required further treatment for recurrent bleeding in the postoperative period. One patient has not rebled in 16 months since operation. The other has rebled several times, but much less often than before operation.

Surgical synovectomy can reduce the frequency of recurrent joint bleeding in hemophilic patients and the attendant morbidity. Autoplex permitted such surgery in 2 boys with inhibitors, without excessive operative bleeding. Both tolerated the procedure, although both required red blood cell transfusions postoperatively and further treatment with Autoplex. Neither developed thrombocytopenia, hypofibrinogenemia, or clinical evidence of hypercoagulability. The prothrombin and partial thromboplastin times were shortened and the platelet counts declined, but there were no associated clinical problems. Activated prothrombin-complex concentrate can be recommended to control bleeding during and after operation in this setting. A dose of 40–60 units per kg is given every 6–12 hours for 5 days, followed by 25–35 units per kg every 8–12 hours for another 5 days. The use of ϵ-aminocaproic acid is contraindicated.

▶ [The development of an inhibitor in patients with hemophilia is one of the most potentially disastrous complications that can occur. These inhibitors are antibodies against the factor VIII molecule. They result in a very poor response to replacement with factor VIII infusions when hemophiliacs require these for bleeding problems. About 15% of all hemophiliacs will develop an inhibitor sometime during their lifetime. What to do about these inhibitors has been controversial. In some patients the inhibitor levels will decline gradually with no rhyme or reason. In other patients the administration of factor VIII acts as a stimulant to the production of more factor VIII inhibitor. In these patients it may be necessary to avoid giving standard preparations of factor VIII altogether. Some patients with low amounts of inhibitor can have replacement with very large quantities of factor VIII concentrate, and the amount of factor VIII that is not bound up by the inhibitor will often control the bleeding problem. One also can use factor IX concentrates to help manage patients with factor VIII inhibitors. In some instances the patient will respond to factor IX concentrates because these contain small amounts of activated factors below the factor VIII step in the coagulation schema. They therefore tend to bypass the inhibitory step in coagulation. Unfortunately, various factor IX preparations vary widely in their ability to manage patients with factor VIII inhibitors, so that we must rely on the relatively recent introduction of the anti-inhibitor coagulant complex concentrates that came onto the market about 3 years ago. These are preparations that have been activated directly and that bypass the inhibitor step in the coagulation scheme. They are not without risk in the sense that they are thrombogenic and therefore must be used with great care. For a long time after the introduction of these activated complexes, clinicians involved in the care of hemophiliacs were reluctant to use them on a completely elective basis for operations such as synovectomies. Now we see that someone has bitten the bullet (as have other investigators by now). If used with great care, the activated complex can nurse a patient through the postoperative period without untoward side effects.

The two leading preparations of activated complex are Autoplex, as used in this study by Hutchinson et al., and a preparation called "Feiba." Feiba is the abbreviation for "factor VIII inhibitor bypassing activity." All seems to be working well with these new agents right now. Let's hope there are no snafus (did you know that this is the

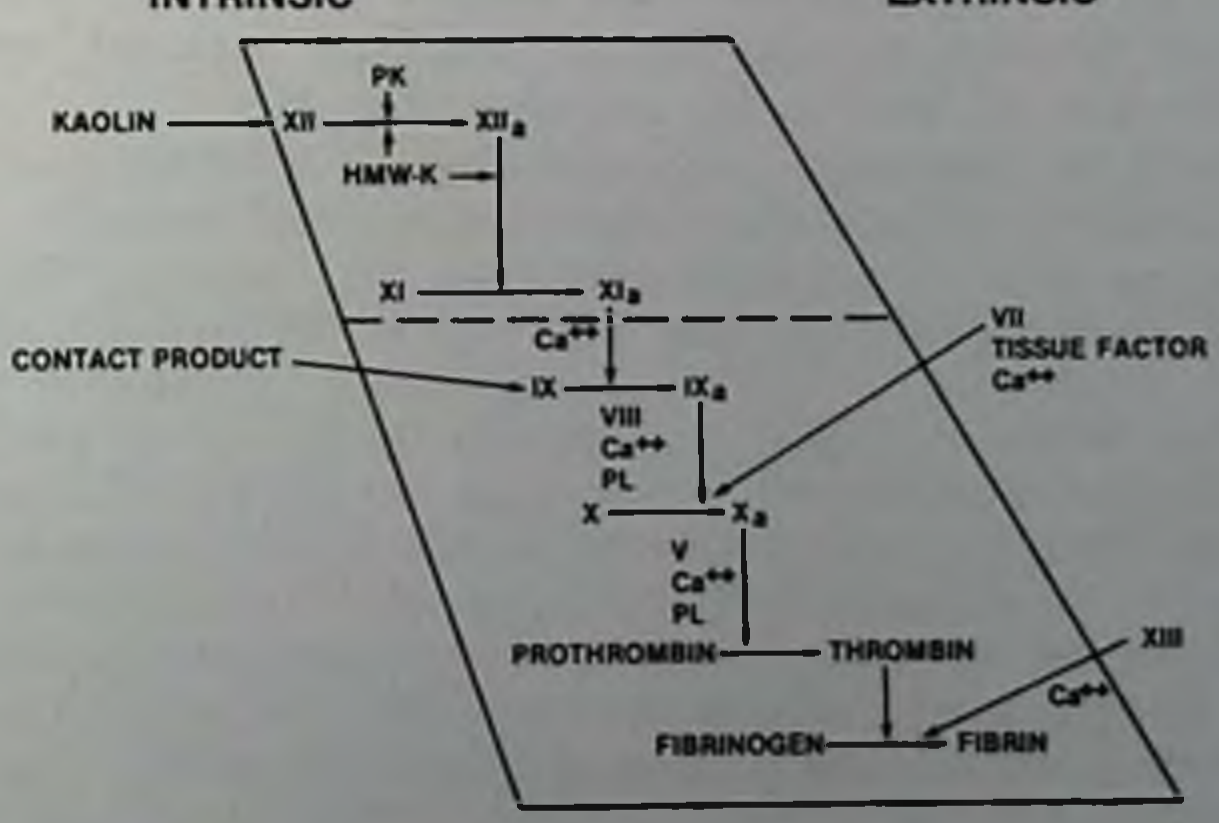
military term for, "Situation all fouled up?" Snafu is the minor degree of "fubar," which means, "fouled up beyond all recognition." How about that!—J.A.S., III] ◀

9–17 **Simple Screening Test for Evaluating Prolonged Partial Thromboplastin Times in Newborn Infants.** Newborn infants have significantly prolonged partial thromboplastin times (PTTs) despite vitamin K administration. Maureen Andrew and Margaret Karpatkin (New York Univ.) used a PTT performed with contact product rather than kaolin to determine whether contact factors or vitamin K-dependent factors are responsible for the prolonged PTT in neonates. Studies were done in 48 infants aged 6 months or younger, 35 premature infants, 6 infants with disseminated intravascular coagulation (DIC), 4 children with hemophilia, and 13 with deficiencies of factors XI, XII, PK, and HMW-K. Four children receiving coumadin and 7 receiving heparin also were evaluated, as were 39 children with a variety of clinical states who were studied preoperatively and 54 normal adults. Addition of contact product corrects the PTT of plasma deficient in factor XI or any of the factors that participate in activation of factor XI (Fig 9–5).

The mean PTT of controls was shorter when contact product was used in place of kaolin. The PTT shortened to control values in children with contact-factor deficiencies when contact product was used in testing. In term and premature infants, the mean PTT was shortened to within 3 and 9 seconds of control, respectively. In children with DIC, those receiving coumadin or heparin, and with hemophilia, the mean PTT with contact product remained at least 25 seconds over control. Low levels of factors XII and XI were confirmed in the premature infants studied.

A PTT done with contact product rather than kaolin is a useful screening test in neonates, distinguishing between physiologically low levels of contact factors and pathologic states that lengthen the

Fig 9–5.—Simplified representation of coagulation pathway. The large box includes all factors measured by PTT. The broken line separates the four contact factors *(XII, XI, PK,* and *HMW-K).* The activating agents, kaolin and contact product, are depicted where they initiate clotting. (Courtesy of Andrew, M., and Karpatkin, M.: J. Pediatr. 101:610–612, October 1982.)



(9–17) J. Pediatr. 101:610–612, October 1982.

PTT. The test can be done rapidly in any laboratory. A normal result often precludes the need for specific coagulation factor assays.

▶ [Dr. Bertram Lubin, Director of Medical Research and Chief of Hematology/Oncology, Children's Hospital Medical Center, Oakland, California, comments:

"Evaluation of the newborn (and particularly the premature infant) for bleeding disorders is oftentimes difficult. These patients frequently have complex medical problems, including chronic hypoxia, acidosis, and septicemia, that may alter hemostasis. In addition, although many of these infants have been given vitamin K, hepatic synthesis of vitamin K-dependent factors may be limited. Finally, it is unusual for a sick newborn infant, especially a premature one, not to receive transfusions of blood products. Taken together, these factors make the precise diagnosis of a clotting disorder quite difficult. Nevertheless, due to the high incidence of hemorrhagic tendencies and the consequences of intracranial hemorrhage, in particular, it is imperative that appropriate procedures become available to identify infants at risk of such bleeding tendencies.

"Standard coagulation tests (prothrombin time, partial thromboplastin time, clotting time) are prolonged in the newborn, and more so in the premature infant, when compared to adult values. This article describes a simple screening test for evaluating prolonged PTTs in newborn infants. By performing PTT with contact product instead of kaolin, Doctors Andrew and Karpatkin were able to exclude contact factor deficiency as a cause of prolonged PTT in newborn infants. Furthermore, their study demonstrated that low biologic activities for factors XI, XII, PK, and HMW-K (the contact factors) are often responsible for prolonged PTT in infants.

"Doctors Andrew and Karpatkin recommend that the first step in evaluating a prolonged PTT in the newborn is to repeat the test using contact material rather than kaolin. If the PTT is corrected, the need to measure a series of clotting factors is eliminated. Preparation of the contact material is quite simple and it can be stored for an extensive period. Because deficiencies of contact factors do not appear to be associated with clinical bleeding in the newborn, this rather simple procedure can save time, money, and effort and potentially improve patient care.

"As the authors clearly demonstrate, the PTT done with contact material rather than kaolin is abnormal in clinical conditions associated with significant bleeding. Indeed, it seems reasonable to screen all prolonged PTTs using contact material prior to further investigation even in older patients. Except for the rare case of factor XI deficiency, a normal PTT performed with contact material excludes all clinically relevant coagulant factor deficiencies."] ◀

9–18 **Successful Treatment of Skeletal Hemangioma and Kasabach-Merritt Syndrome With Aminocaproic Acid: Is Fibrinolysis "Defensive"?** Hemangioma located in bone or soft tissue can produce serious complications such as disordered hemostasis and bleeding or local organ impairment. James A. Neidhart and Ralph W. Roach report the case of a patient with diffuse skeletal hemangiomatosis, incapacitating bone pain, and coagulopathy.

White youth, 19, had had a pathologic fracture of the left proximal femur at age 13. X-ray film showed a mixed osteoblastic and osteolytic lesion of the proximal femur with no other abnormalities. At operation, the lesion was interpreted as hemangioma; the surgical specimen showed normal bone. Subsequently, mild chronic low back pain and slowly progressive hip pain required therapy with analgesics. The platelet count was 80,000/cu mm, and treatment with prednisone for 2 months failed to increase the platelet count or to alleviate pain. Referred to Ohio State University Hospitals, Columbus, he was found to have moderate limitation of motion of the left hip and mild tenderness over the left greater trochanter. Hemoglobin level was 15.2 g/dl, hematocrit value 44%, reticulocyte count 2%, white blood cell count 6,000/cu mm with normal differential, and platelet count 46,000/cu mm. Radiologic

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(9–18) Am. J. Med. 73:434–438, September 1982.

studies, when compared with films obtained 6 years earlier, showed much progression. Table 1 presents the coagulation parameters as related to methods of treatment.

The patient was hospitalized because of incapacitating pain. Infusion x-ray study of the lesion demonstrated multiple vascular channels communicating across the joint space; the aspirated blood showed no bone marrow elements; in Table 2. Pain was not relieved by administration of 12 tablets per day of results of coagulation studies on hemangioma and peripheral blood are shown acetaminophen with oxycodone, nor by 1,200 rad over 6 days to L3 and L4, the left hemipelvis, and the left upper femur. Eight weeks after irradiation, the patient had become bedridden due to painful restriction of hip motion. Two months after completion of radiotherapy, aminocaproic acid administration was begun at 3 gm orally, 3 times a day. A week later, when no adverse effects were observed, the dose was increased to 3 gm, 4 times a day. After 3

TABLE 1.—SERIAL MEASUREMENT OF COAGULATION PARAMETERS AS RELATED TO METHODS OF TREATMENT

	Hospitalization Arteriography (11/14/80–12/6/80)	Radiation (12/18/80–12/24/80)	Aminocaproic Acid (2/28/81–4/9/81)			No Treatment (4/10/81–1/7/82)		
Platelet count × 10^{-3}*	94.0–212.0	212.0–172.0	172.0–238.0			257.0–286.0		
Coagulation profile (date)	11/21/80	...	2/18/81	3/13/81	3/20/81	4/10/81	5/22/81	1/7/82
Prothrombin time (nl 9–11.3 sec)	13.7	...	10.9	11.8	11.1	10.9	10.2	10.0
Partial thromboplastin time (nl 24.0–38.0 sec)	38	...	34.9	34.0	32.2	32.6	30.0	30.5
Fibrinogen (nl 177–369 mg/dl)	110	...	>177	155	>177	>177	ND	200
Fibrin split products (nl ≤ 10 g/dl)	80	...	>40	>20	>10	Negative	>10	Negative
Fibrinolytic activity†	‡	...	‡	ND	‡	nl	nl	§
Analgesic requirement (acetaminophen with oxycodone [tablets/day])	10–14	...	14–16	16	10	2	0	0

ND, not done; *nl*, normal.
*First and last value for treatment period.
†Normal activity defined as lysis of an euglobulin clot in more than 60 minutes.
‡Greatly increased.
§Minimally increased.
(Courtesy of Neidhart, J. A., and Roach, R. W.: Am. J. Med. 73:434–438, September 1982.)

TABLE 2.—COMPARISON OF HEMANGIOMA AND PERIPHERAL BLOOD

	Peripheral Blood	Hemangioma Blood
White blood cell count	4,900/mm^3	8,600/mm^3
Platelet count	144,000/mm^3	60,000/mm^3
Fibrinogen	137 mg/dl	52 mg/dl
Factor VIII	86%	16%
Fibrin split products	>40 g/ml	>320 g/ml

(Courtesy of Neidhart, J. A., and Roach, R. W.: Am. J. Med. 73:434–438, September 1982.)

weeks of therapy with aminocaproic acid, there was dramatic alleviation of pain and eventual disappearance of laboratory evidence of fibrinolysis. Aminocaproic acid therapy was discontinued and the patient remained free of symptoms and coagulopathy.

The efficacy of an antifibrinolytic agent as treatment for the Kasabach-Merritt syndrome challenges widely held concepts regarding pathophysiology of the disease. Aminocaproic acid is not an innocuous drug. It has the theoretic potential to induce fatal thrombosis in patients with consumption coagulopathy. Only after conventional treatments had failed and the condition probably had become life-threatening was the described treatment instituted.

▶ [Hemangiomas are common childhood tumors and can present initially in adults as well. These lesions are often cosmetically displeasing and can cause considerable disability, pain, or even death due to mass effect, congestive heart failure, hemorrhage, or coagulopathy. Kasabach and Merritt initially described the association of hemangioma with systemic bleeding, thrombocytopenia, and prolonged coagulation times. This was more than 40 years ago. Subsequent reports have documented deposition of fibrin and platelets within the distorted blood vessel walls of these hemangiomas. Apparently the massive surface area of these blood vessels will trigger coagulation and a picture of disseminated intravascular coagulation. Historically, the fibrinolytic component of this process is thought to have been secondary to localized coagulation and therefore protective against systemic coagulation, thus "defensive" in nature. In other words, substances are released that break down the fibrin clots and therefore prevent massive coagulation throughout the body. What Neidhart and Roach are postulating is that fibrinolysis is actually primary in this process. That is to say, that patients with hemangiomas primarily produce lytic substances that can cause massive bleeding. If the latter concept is correct, then an agent that blocks the lysis of fibrin could be used to reverse this process. One such agent is Amicar (aminocaproic acid).

Obviously, these are two diametrically opposed theories as to what is going on. The use of Amicar in the former case could be tragic, but it could be lifesaving in the latter. Somehow or other, these investigators got up the gumption to go ahead and use Amicar and found that it worked. They are truly courageous for having done this, but I cannot honestly say that one case a series makes. For this reason, I will reserve judgment as to whether or not their approach was indeed correct. M. A. Koerper et al. used what seemed to be a safer approach and achieved the same results when they gave patients with this same problem aspirin and dipyridamole as antiplatelet-trapping agents. The drugs interfere with normal platelet function and presumably would block deposition of platelets within the hemangiomas (*J. Pediatr.* 102:311, 1983). These two drugs under these circumstances would be expected to have very little in the way of side effects.

In fairness to Neidhart and Roach, investigators in Sweden (Astedt, B., et al.: *Acta Obstet. Gynecol. Scand.* 61:479, 1982) found that the fibrinolytic inhibitor tranexamic acid was helpful in producing regression of a hemangioma in a 21-year-old patient who also had thrombocytopenia.

The best treatment of hemangiomas is to leave them alone if they are not causing any problem. The relative roles of radiation therapy, the pharmacologic agents reported above, steroids, etc., etc., are difficult to evaluate, at best, because of the infrequent occurrence of the Kasabach-Merritt syndrome. Given the option of all choices, I would elect for moving from the most benign forms of therapy initially to the more complex ones if satisfactory resolution of the problem is not achieved.—J.A.S., III] ◀

9–19 **Disseminated Intravascular Coagulation Fibrinolytic Syndrome Following Head Injury in Children: Frequency and Prognostic Implications.** An association between severe brain injury and clinical bleeding abnormalities has been reported by many workers. Michael E. Miner, Howard H. Kaufman, Steven H. Graham, Floyd H. Haar, and Philip L. Gildenberg (Univ. of Texas, Houston) examined 87 consecutive head-injured children prospectively for clotting abnormalities. Twenty patients had penetrating injuries, 14 had mass lesions, and 53 had diffuse injuries. Injuries were considered to be severe, with pathologic posturing, in 37 patients, moderate in 29, and mild in 21. Children with disseminated intravascular coagulation (DIC) were treated with fresh-frozen plasma, concentrated platelet packs, and cryoprecipitate. Those with isolated coagulation defects were not treated.

Clotting studies were abnormal in 86% of patients with penetrating injuries, 75% of those with mass lesions, and 58% of those with diffuse injuries. A stronger correlation was found with the severity of injury. The most common abnormality was in fibrin-split products. Disseminated intravascular coagulation was documented in 32% of patients and was related directly to the severity of brain injury. It also correlated with mortality. Overall mortality was 25%; it was 54% in patients with DIC and 12% in the others. Severly injured patients had a 3.5-fold higher mortality when DIC was present, and mortality in the moderately injured group was 2.7 times higher when DIC was present.

Abnormal clotting was the rule in children with head injury in this series, and one third of patients had DIC. An impressive relationship between DIC and mortality is evident in children with moderate or severe head injury. Deaths may result from diffuse microvascular fibrin deposits that plug small vessels and cause increased brain damage and multiple-organ failure. Alternatively, abnormal clotting could be an epiphenomenon that merely reflects the severity of brain injury. It is possible that DIC is a treatable effect of head trauma, and that appropriate treatment will reduce mortality.

▶ [There is enough evidence that brain injury causes disseminated intravascular coagulation that every neonate and older child who sustains an injury to the brain substance should be screened for this problem. J. Phenninger et al. (*Z. Kinderchir.* 37:53, 1982) described infants and 3 children with clinically manifested generalized bleeding due to a consumptive coagulopathy after severe head injury. Despite the most intense support, all of these patients died due to severe brain swelling. They suggest, and I think quite correctly, that abnormal bleeding in a comatose, head-injured patient with laboratory findings compatible with disseminated intravascular coagulation appears to be an expression of a very severe injury with a poor outcome. B. Dalens et al. showed a similar coagulopathy after brain injury in neonates (*J. Pediatr.* 102:166, 1983).—J.A.S., III] ◀

(9–19) J. Pediatr. 100:687–691, May 1982

9–20 **Effects of Acetylsalicylic Acid Ingestion on Maternal and Neonatal Hemostasis.** Acetylsalicylic acid crosses the placenta after maternal ingestion and has been associated with hemostatic abnormalities in both full-term and premature infants. Marie J. Stuart, Steven J. Gross, Haim Elrad, and Janet E. Graeber (SUNY, Upstate Med. Center, Syracuse) examined the effects of aspirin on maternal and neonatal hemostasis in a prospective case-control study of mothers taking aspirin within 10 days of delivery. Thirty-four control mother-infant pairs were compared with 10 pairs in which 5–10 gm of aspirin were ingested by the mother within 5 days before delivery, 7 in which the mother took 5–15 gm from 6 to 10 days before delivery, and 7 in which ingestion was documented during the immediate postpartum period only.

Only 1 control pair showed hemostatic abnormality. Six of 10 mothers taking aspirin within 5 days before delivery and 9 of their 10 infants had a bleeding tendency. No clinical bleeding occurred when aspirin was ingested 6–10 days before delivery. Four of 7 mothers who ingested aspirin in the postpartum period had impaired hemostasis. Maternal bleeding was confined to excessive intrapartum or postpartum blood loss. Infants exhibited petechiae over the presenting part, hematuria, a cephalhematoma, subconjunctival hemorrhage, and bleeding from a circumcision site. Four infants whose mothers used aspirin within 5 days before delivery had profuse petechiae over the presenting part.

Aspirin should be avoided during pregnancy. If the mother has ingested aspirin within 5 days before delivery, the neonate should be evaluated for bleeding. Serious internal bleeding did not occur in the present full-term infants, but the risk of life-threatening hemorrhage may be increased in small premature infants.

▶ [This article stirred up quite a bit of controversy, as you might suspect. Aspirin has been around now for about 100 years and its therapeutic benefits to our society are well-known. The need to ingest aspirin during pregnancy, however, is practically nonexistent in almost all instances. With data such as presented above, I am convinced that until someone tells us otherwise, we should recommend that pregnant women avoid aspirin ingestion the way they should avoid alcohol and cigarettes. Perhaps a warning label should be attached to aspirin bottles informing pregnant women of this potential hazard. I hope that the YEAR BOOK OF OBSTETRICS AND GYNECOLOGY also abstracts this study. The information contained in it is just as important to the delivery man.—J.A.S., III] ◀

(9–20) N. Engl. J. Med. 307:909–912, Oct. 7, 1982.

10. Oncology

10–1 **Therapeutic Choices Made by Patients With End-Stage Cancer.** Ruprecht Nitschke, G. Bennett Humphrey, Charles L. Sexauer, Barbara Catron, Shirley Wunder, and Susan Jay (Oklahoma City) examined the usefulness of an approach designed to improve opportunities for children with malignant disease not responding to standard treatment and their parents to make an informed choice regarding continuation with an experimental, or phase II, drug. Children older than age 3 years are told initially that they have cancer that will result in death if not treated. Since 1974, children older than age 5 have been included in decision-making on further treatment. At the final-stage conference, the improbability of cure and imminence of death are discussed, and both the use of phase II drugs and supportive care are offered. The options are presented as objectively as possible, without mention of possible benefit to future patients from further experience with the drugs.

In 1974–1980, 43 patients, aged 6–20 years, participated in the final-stage conference. They understood that their health was deteriorating, and were able to decide on further treatment autonomously or with their families. Most children made the decision themselves: 28 chose supportive care, and 14, further chemotherapy. Most who selected supportive care participated in activities at home as much as they were able. Severe depression and behavioral problems were rare. The emotional status of the children varied widely. Reasons given for choosing supportive care included concerns about separation from home, intravenous therapy, and side effects.

This approach has helped patients and family members to communicate openly with one another. Children older than age 5 comprehended the finality of death and were able to make rational decisions about further treatment. Most children who selected supportive care tolerated the knowledge of impending death. Participation in phase II drug trials declined during the study period, for reasons that are not clear.

▶ [Olle Jane Z. Sahler, Assistant Professor of Pediatrics and Psychiatry, Department of Pediatrics, University of Rochester-Strong Memorial Hospital Medical Center, Rochester, New York, comments:

"A recent regulation from the Department of Health and Human Services (DHHS) (applicable to all research reviewed after June 6, 1983) requires the "assent" of the child as well as the consent of the parents or guardians for participation in any research protocol. Exceptions to this regulation include research involving normal educational practices, observation of public behavior, data collection confined to the study of existing documents, records, or specimens, or survey or interview procedures where the protocol has been reviewed but the assent requirement waived.

"Under the regulation, assent is defined as affirmative agreement to participate,

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(10–1) J. Pediatr. 101:471–476, September 1982.

and individual Institutional Review Boards are responsible for developing policies that adequately determine whether or not each child or all children under a particular protocol are capable of providing assent, considering age, maturity, and psychological state. Under some circumstances (for example, studies involving infants), the assent requirement would be waived because the child could not be "reasonably" consulted.

"During the development stage of the regulation, the proposed assent requirement drew a number of thoughtful commentaries regarding criteria for determining capability, since it generally is agreed that chronological age alone is an insufficient criterion. It is of interest that many commentators 'believed that the best protection for children would be thoughtful consideration of what information would be given by a competent group of scientists and lay persons together with the informed permission of parents' (*Fed. Register* 48 (no. 46):9817, Mar. 8, 1983).

"If the institutional review boards elect to approach the issue of deciding what information is most appropriate to provide to children through the mechanism of a panel of experts, most likely this group would include physicians, nurses, social scientists, lawyers, clergymen, ethicists, and educators. One of the items this group would, and should, grapple with is whether or not a discussion of the potential future benefit to society of investigational drug studies should be included in the course of necessary and sufficient disclosure to the child patients.

"It can be argued that it is much easier for a patient to make a choice that seems to reflect what he really wants, just for himself, when he does not have to carry a burden of guilt about having denied society the use of his mind or body as a laboratory. On the other hand, it can be argued that a truly informed choice can only be made when all the potential risks and benefits are considered. It can further be argued that the child himself may derive positive feelings about himself through a sense of helping others.

"To my mind, the most fascinating aspect of the study by Nitschke and co-workers is not that children as young as age 5 years are articulate enough to state what they want, or that children who have been living with cancer are aware of and, to a great extent, understand and accept death as a real possibility for them when treatment fails. These findings have, I think, been well documented in the literature. Rather, I am intrigued by the following statement from the investigators' report that has direct bearing on the issue of obtaining informed child assent: 'Because one patient agreed on therapy only to improve medical knowledge, although he resented it very much, the benefit for society by participating in a phase II drug study was not mentioned in subsequent (final stage) conferences' (p. 475).

"My hypothesis is that the decreased participation rate in phase II drug use during the study period reflects patient choices that were seen as maximally beneficial to one's self. For a variety of reasons, most of them theoretical at this point in time, the investigators plan to reintroduce the issue of altruism into their final-stage conferences with their patients. It will be of great interest to see if the participation rate in the drug studies again increases in response to discussing this issue. Should the investigators undertake a second study that monitors these patient responses, they will be able to provide us with some direct information regarding the value young children and adolescents place on social benefit as a motivating force for their behavior.

"The final question, then, is: Is it fair or unfair to place this particular issue before a terminally ill child? I hope the children will tell us."] ◄

10–2 **Selected Epidemiologic Observations of Cell-Specific Leukemia Mortality in the United States, 1969–1977.** Steve Selvin, Lynn I. Levin, Deane W. Merrill, and Warren Winkelstein, Jr. (Univ. of California, Berkeley) used a newly available data set that includes, for the first time, cell-specific leukemia mortality figures, to analyze age and sex distributions, time trends, and geographic patterns for leukemia mortality in the United States during 1969–1977. The statistics were assembled by the National Center for Health Statistics

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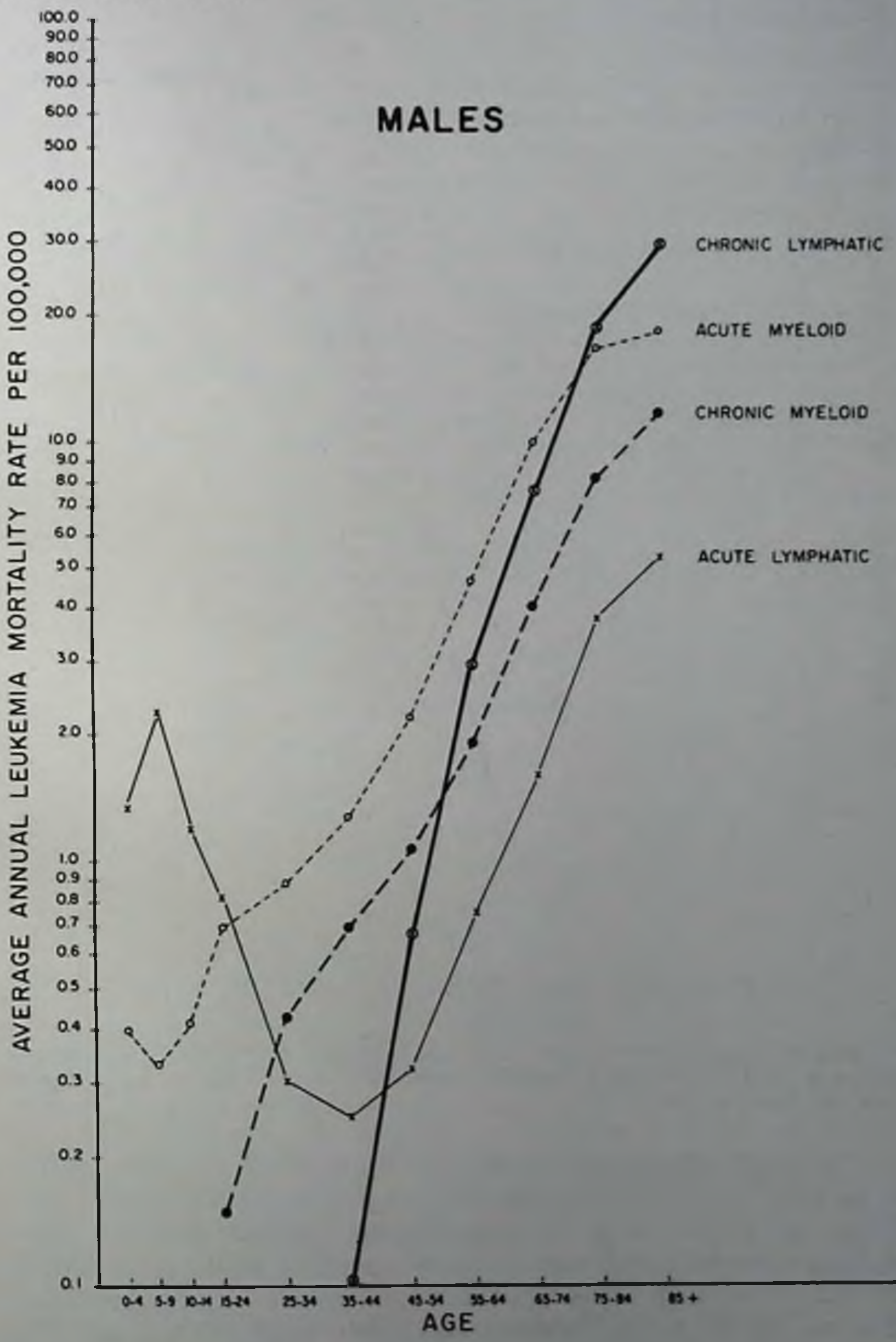
(10–2) Am. J. Epidemiol. 117:140–152, February 1983.

and from the Mortality Surveillance Project conducted at Johns Hopkins University. Lymphatic and myeloid cell types of both the acute and chronic forms were taken into account.

Average annual cell-specific leukemia mortality rates for white male and female populations are shown in Figures 10–1 and 10–2.

Fig 10–1.—Average annual cell-specific leukemia mortality rates per 100,000 for white male population in the United States, 1969 to 1977. (Courtesy of Selvin, S., et al.: Am. J. Epidemiol. 117:140–152, February 1983.)



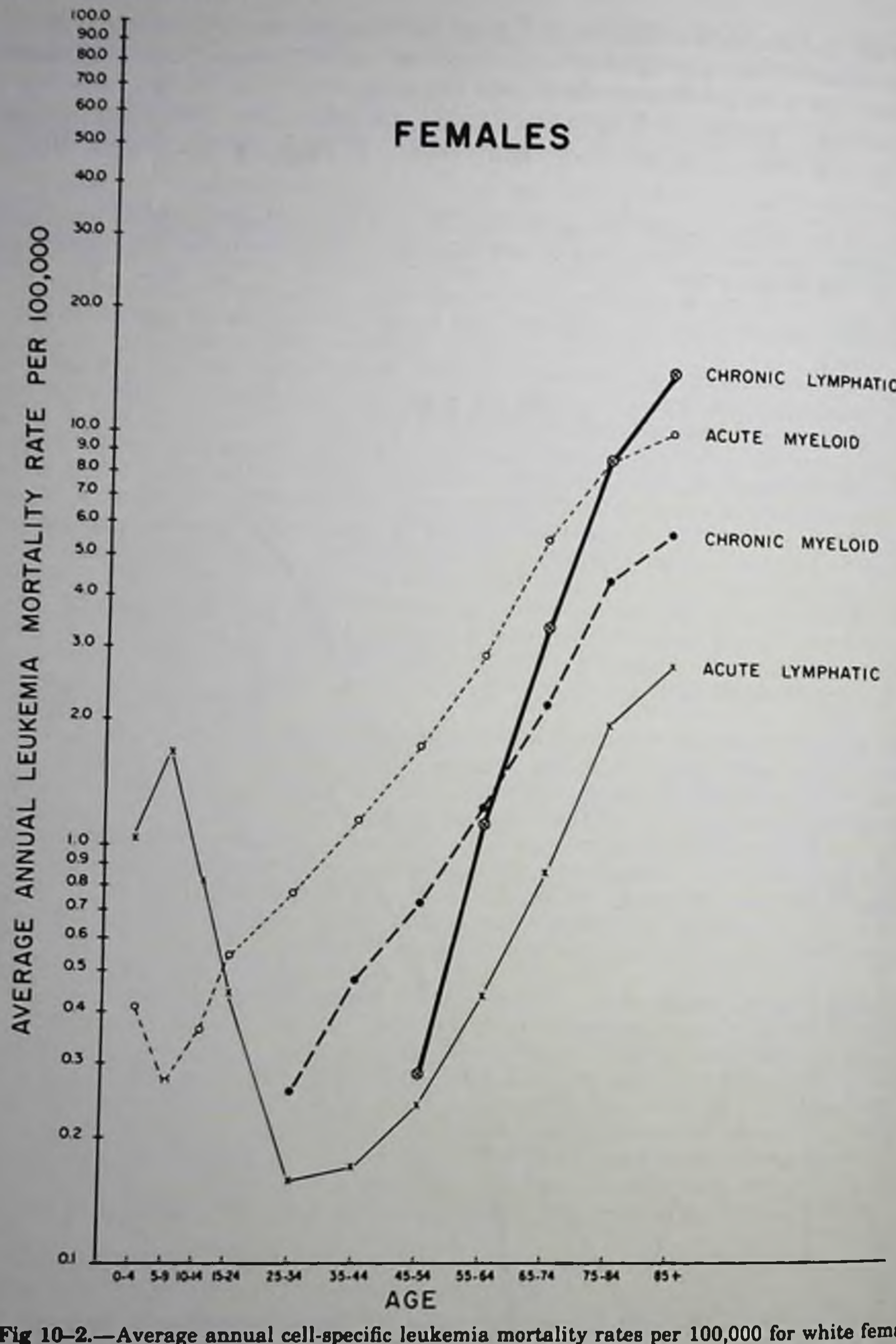


Fig 10–2.—Average annual cell-specific leukemia mortality rates per 100,000 for white female population in the United States, 1969 to 1977. (Courtesy of Selvin, S., et al.: Am. J. Epidemiol. 117:140–152, February 1983.)

Acute lymphatic leukemia showed a bimodal distribution with the first peak at ages 5–9 years and the lowest rates at ages 35–44 years, followed by a geometric increase. Acute myeloid leukemia had a small peak in childhood and a low at ages 5–9 years, followed by a geometric rise. Both chronic leukemias showed a geometric rise in rate after age 15 years. Females had lower rates in each age group,

with the highest sex ratio for chronic lymphatic leukemia. Mortality from acute lymphatic leukemia in adults fell by nearly 10% over the review period, whereas mortality from acute myeloid leukemia increased by nearly 20%. Geographic analysis indicated an association between acute lymphatic leukemia and acute myeloid leukemia in children, but no association between childhood and adult cell types. Acute and chronic cell types were associated with one another geographically in adults.

All cell-specific types of leukemia had higher mortality rates in male than in female populations in all age groups in this survey. The only reduction in mortality over time was in acute lymphatic leukemia. The failure of mortality to decline among other cell-specific types is consistent with what is known of treatment efficacy. Some findings support the view that childhood leukemias represent different etiologic entities, but the geographic observations make a common cause for the two cell types a possibility. That different histopathologic types do not vary together in adults suggests that each type has a particular constellation of risk factors.

▶ [This epidemiologic survey provides us with some information that I think we already knew. It also supplies us with some information that, although enlightening, is very troublesome. Most particularly, the geographic correlations between acute lymphocytic leukemia and acute myelogenous leukemia really do seem to make infectious or environmental risk factors much more likely in the triggering of malignant disease in our children. A similar geographic association was not found between adult and other childhood forms of leukemia and for most other adult diseases. This might suggest that some endogenous risk factors play a greater role in the onset of adult malignancy.

It may be worth spending a few lines updating some of the current thoughts about acute lymphocytic leukemia in children. All treatment centers probably now should use monoclonal-antibody phenotyping in this disease. You may be aware that with the onset of monoclonal-antibody technology, antibodies have been made against a variety of antigens on leukemic cells. These have been extraordinarily helpful in subclassification of the various forms of leukemia and for identification within specific types as well. J. Kersey et al. have shown, for example, that the presence of the common acute lymphocytic antigen (CALLA) is a very favorable prognostic factor. It has been known for some time now that having a T cell leukemia or a B cell leukemia was an extremely adverse prognostic factor (*Lancet* 2:1419, 1982). Testicular biopsies definitely should be done in all boys at the termination of chemotherapy. Boys with positive biopsies will require specific treatment of that disease plus a longer course of systemic chemotherapy. Pretreatment testicular biopsies, however, do not add much useful information. T. H. Kim found that prophylactic testicular irradiation in boys who have positive testicular biopsies when they are just starting chemotherapy does not seem to be warranted (ibid. 2:657, 1981). A testicular relapse occurring when the patient is not receiving therapy is not necessarily associated with a uniformly poor prognosis. K. Tiedemann et al. (*Br. Med. J.* 285:1614, 1982) found that if both testes are irradiated after testicular relapse and boys are treated with 2 years of chemotherapy, the survival rate will still be at least 50% several years subsequently. A. I. Freeman et al. (*N. Engl. J. Med.* 308:477, 1983) compared the use of 2,400 rad of cranial irradiation plus intrathecally administered methotrexate to treatment with intermediate-dose intravenously administered methotrexate plus intrathecally administered methotrexate as prophylaxis for involvement of the central nervous system and other "sanctuary" areas. One of the rationales behind the study was to determine if irradiation, with all of its consequent side effects, could be avoided in the treatment of this relatively common malignancy. These investigators found that although there was no difference in continuous complete remission in association with prophylactic therapy within the confines of the study, intermediate-dose methotrexate therapy conferred greater protection to the bone marrow in standard-risk patients and to the

testes in male patients, whereas cranial irradiation conferred greater protection to the central nervous system. They concluded that the use of intermediate-dose methotrexate therapy probably avoids the long-term toxicity to the central nervous system that is inherent in cranial irradiation.

We may be seeing a slightly different approach in the way that we maintain children on chemotherapy for treatment of acute lymphatic leukemia. S. Zimm et al. (ibid., p. 1005) found that plasma levels of 6-mercaptopurine were frequently unexpectedly low and variable after the standard oral route of administration. The investigators suggested that the current method of empirically determining the dose of maintenance chemotherapy is not the optimal one, and their suggestions may well lead to clinical investigation of a completely new way of administering maintenance drugs based on the unique pharmacokinetic responses of individual patients. There may be a changing view of whether routine bone marrow study should be done in follow-up of children who are receiving or who have stopped receiving chemotherapy for acute lymphatic leukemia. G. M. Komp et al. found little justification for performing "routine" bone marrow examinations. They did not seem to benefit the patient or to assist much in comparing treatment regimens for this disease (*J. Pediatr.* 102:395, 1983). This will be a difficult concept to swallow for many oncologists and parents as well. In closing this commentary, I would note that two new categories of occupational hazards may increase the risk of malignancy. A 10-fold increased risk of esophageal cancer has been found in a 13-year follow-up of vulcanization workers—and I thought vulcanization simply caused pointed ears, as is true of the Vulcan, Dr. Spock, on "Star Trek" (Norell, S., et al.: *Lancet* 1:462, 1983). Finally, there has been a definite suggestion of an increased risk of cancer among butchers (Johnson, E. S., et al.: ibid., p. 913). It would seem reasonable to me to examine the offspring of butchers also. The children of many "old-fashioned" butchers may have the same kind of exposures as their fathers. The White House isn't the only place where people have to live over the shop.—J.A.S., III] ◀

10–3 **Oral Antibiotic Prophylaxis in Patients With Cancer: Double-Blind, Randomized, Placebo-Controlled Trial.** Philip A. Pizzo, Kathleen J. Robichaud, Brenda K. Edwards, Cathie Schumaker, Barnett S. Kramer, and Alicia Johnson (Natl. Inst. of Health) investigated whether oral administration of trimethoprim-sulfamethoxazole plus erythromycin (TMP/SMX + E) could reduce the incidence of fever and infection in cancer patients becoming granulocytopenic during chemotherapy. A double-blind, randomized trial was conducted in 89 male and 61 female patients, aged 1 to 43 years (median, 17 years), undergoing 541 episodes of chemotherapy for acute leukemia (45 patients), lymphoma (34), or solid tumors (71). Therapy with TMP/SMX (10 mg/kg/day as TMP in two divided doses), or placebo, was begun immediately after completion of chemotherapy (about 5–8 days before the onset of granulocytopenia) and continued until granulocytopenia resolved or fever occurred. Patients were on study for up to 3 weeks if they received conventional or maintenance chemotherapy and for 4 or more weeks if they received induction or intensive chemotherapy. To permit the monitoring of toxicity and possible emergence of antibiotic resistance, patients received the same treatment (drug or placebo) for each episode of therapy, i.e., no crossover. No patient was isolated in laminar airflow rooms or received prophylactic antifungous agents, nonabsorbable antibiotics, or granulocyte transfusions. Compliance with the prescribed medication was prospectively rated as excellent in 60.6% of the episodes, good in 11.7%,

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(10–3) J. Pediatr. 102:125–133, January 1983.

poor in 11.1%, and unknown in 16.6%; compliance was better in the placebo than in the drug group ($P = .001$).

The overall incidences of fever or infection were 22% for the TMP/SMX + E group and 27% for the placebo group. When only episodes with excellent compliance and documented granulocytopenia were compared, the incidences of fever or infection were 18% for the drug group and 32% for the placebo group ($P = .009$), with bacterial infection occurring in 4% of drug recipients and 12% of placebo recipients ($P = .019$) and unexplained fever in 10.5% and 19.6%, respectively ($P = .037$). Patients with good or poor compliance showed no significant benefit from TMP/SMX + E, and patients with excellent compliance did best regardless of whether they received drug or placebo, suggesting that patient compliance is an important independent variable. The incidence of fever or infection was lower ($P = .037$) for patients with leukemia who showed excellent compliance and who received antibiotics than for patients with lymphomas or solid tumors.

Resistance to TMP/SMX was not observed. The incidences of drug-related rash were similar in both groups. Nausea, vomiting, and diarrhea occurred more often in the drug group, probably reflecting erythromycin toxicity. Administration of TMP/SMX appeared to cause more prolonged granulocytopenia.

Oral antibiotic prophylaxis apparently reduces the incidence of fever and infection in some granulocytopenic patients. However, benefits are modest and restricted to patients whose compliance is complete, and treatment is not without potential side effects.

10–4 **Fever in the Pediatric and Young Adult Patient With Cancer: A Prospective Study of 1001 Episodes.** During a 5-year period, all febrile Pediatric Oncology Branch patients (approximately 320/year) were evaluated by P. A. Pizzo, K. J. Robichaud, R. Wesley, and J. R. Commers (Natl. Inst. of Health). An average of 163 patients per year received chemotherapy for their underlying malignancy.

Fever was attributed to the malignancy only in nongranulocytopenic patients with evident tumor and no indication of infection who defervesced after initiation of tumor-specific therapy in conjunction with objective tumor regression. Fever was considered secondary to chemotherapy when it occurred during or within 12 hours of termination of chemotherapy and the patient defervesced during the following 24-hour period. Fever was judged to be secondary to blood product transfusion if the patient became febrile during or within 12 hours of the transfusion. Postoperative fever was defined when patients became febrile within 3 days of surgery and had no evidence of infection.

Virtually all granulocytopenic patients recently had received chemotherapy or blood product transfusions, and while many had evidence of active tumor, all febrile granulocytopenic patients were started on an empiric antibiotic regimen. During the 7-day period after initial evaluation, all patients were examined daily and then cat-

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(10–4) Medicine (Baltimore) 61:153–165, May 1983.

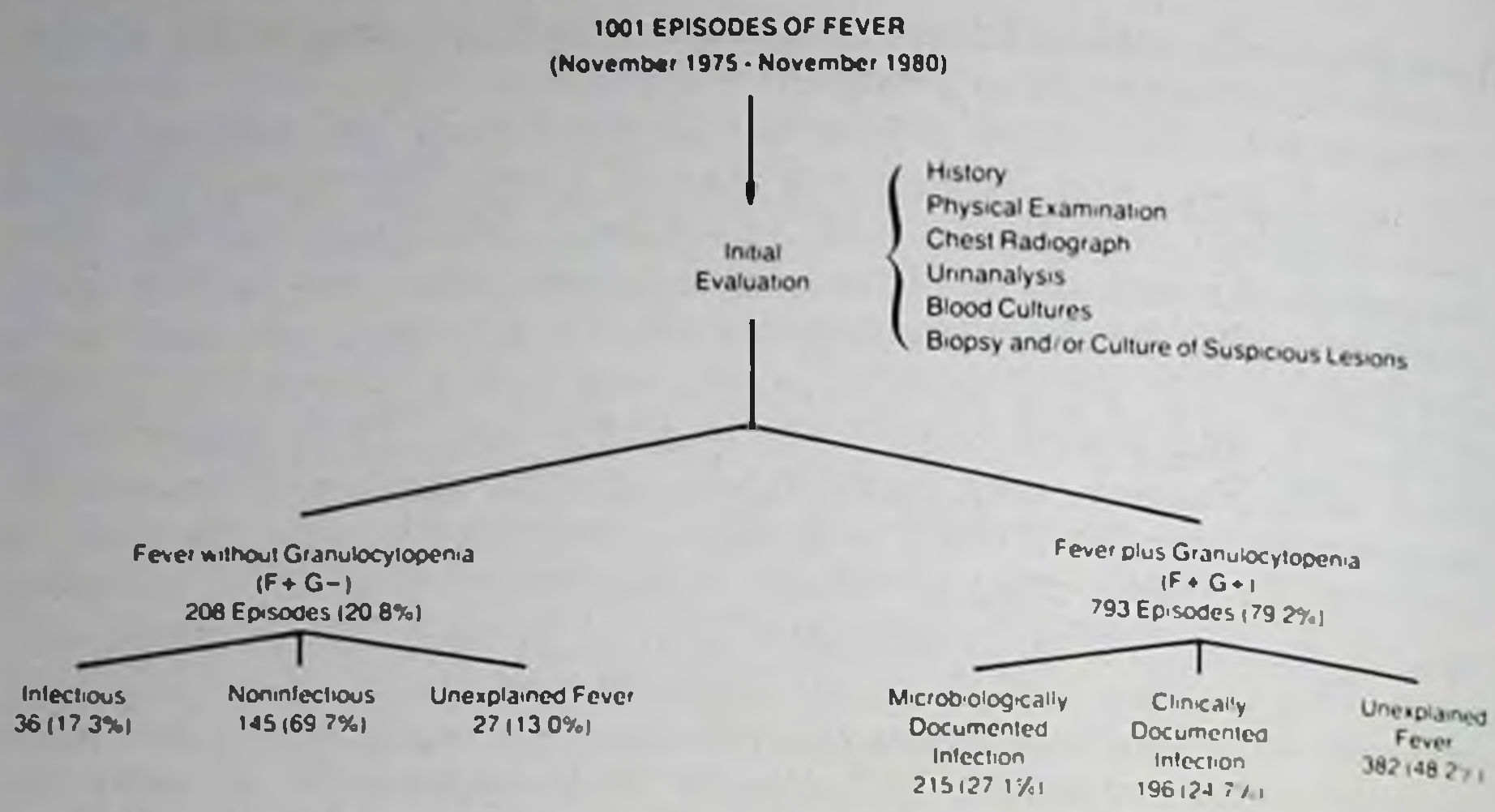

Fig 10–3.—Overall distribution of febrile episodes after initial evaluation according to patient's granulocyte count. (Courtesy of Pizzo, P. A., et al.: Medicine (Baltimore) 61:153–165, May 1982.)

egorized as having either a documented infection or fever of unexplained origin (FUO).

Figure 10–3 indicates that 208 (20.8%) fever episodes occurred when patients were not granulocytopenic, whereas 793 (79.2%) were associated with episodes of granulocytopenia. Of 208 episodes of fever, only 36 (17.3%) were of infectious etiology while patients were not granulocytopenic, but infection was discernible in 411 of 793 episodes (51.8%) occurring in association with granulocytopenia. Approximately 163 patients each year received cytotoxic chemotherapy regimens. The risk of developing a fever ranged from 31% for patients with acute lymphocytic leukemia to 68.8% for patients with metastatic neuroblastoma. While patients were nongranulocytopenic, the percentage of episodes of fever was higher for patients with solid tumors than for those with leukemia or lymphoma.

Infections of the respiratory tract or bloodstream accounted for 62.5% of all documented infections; 85% of all microbiologically defined infections were due to bacteria. Infectious complications occurred in half the high-risk FUO episodes when antibiotics were discontinued after 7 days of empiric therapy, indicating that undetected infections are of concern in patients with protracted granulocytopenia. Regardless of underlying malignancy or clinical presentation, initiation of empiric antibiotics in any granulocytopenic patient who is febrile continues to be necessary.

▶ [Dr. George Honig, of Children's Memorial Hospital, Chicago, and Dr. James Nachman, Department of Pediatrics, University of Chicago, comment:

"Current trends in the management of childhood cancer and leukemia continue in the direction of ever more intensive treatment regimens. Profound granulocytopenia, often with a protracted course, is a correspondingly frequent complication. The findings of Pizzo et al. emphasize that a large percentage of pediatric cancer patients who develop fever will have granulocytopenia (<500 neutrophils and band forms per μ1) and that more than 50% of these children will have documentable infections, most of which are bacterial in origin. In children, gram-positive organisms, mainly *Staphylococcus aureus*, have been isolated in approximately 50% of cases of docu-

mented bacterial infections, with *Escherichia coli* and *Pseudomonas* accounting for more than 75% of gram-negative isolates.

"There is general agreement that febrile neutropenic cancer patients require prompt administration of parenteral antibiotics. Most centers use an empirical triple-antibiotic regimen including a cephalosporin (cephalothin or cephapirin) primarily for gram-positive coverage and an aminoglycoside (gentamicin or amikacin) and a semisynthetic penicillin (carbenicillin, ticarcillin, piperacillin) for gram-negative organisms, including *Pseudomonas*. Antibiotic regimens of this sort have been shown to produce an 80% cure rate for bacterial infections in granulocytopenic patients. Newer cephalosporins and β-lactam antibiotics may make it possible to treat these patients effectively with only one or two antibiotics, but, as yet, insufficient clinical data are available to warrant their use for initial treatment in granulocytopenic patients.

"Our own experience has shown that febrile neutropenic patients whose disease is in remission have a very low likelihood of having bacterial infections, as compared with patients whose malignancy is newly diagnosed or those with recurrent disease. These and other observations have raised the question of whether all febrile granulocytopenic patients require this type of antibiotic treatment, in spite of clear evidence that this approach has greatly reduced mortality and morbidity. There is also controversy regarding the optimal duration of antibiotic therapy for febrile granulocytopenic patients who have negative cultures after 72 hours of treatment. In our experience, antibiotics can safely be discontinued after 72 hours if the patient's total granulocyte count is >1,000/μl or if the patient has been afebrile for more than 24 hours; there is no evidence in children that more prolonged antibiotic therapy will improve the outcome. Another controversy concerns the appropriate treatment for patients who remain febrile and granulocytopenic for more than 7 days. In the experience with adult patients, the addition of low-dose amphotericin B to the antibiotic regimen has been beneficial, and many pediatric centers are currently adopting this strategy.

"The trimethoprim-sulfamethoxazole saga also continues to unfold. This agent was initially used in patients with leukemia as prophylaxis against *Pneumocystis carinii* pneumonia. Several studies showed that this treatment lowered the incidence of *Pneumocystis* infections and, in addition, decreased the frequency of bacterial infections. It was even shown in one report that prophylactic trimethoprim-sulfamethoxazole lowered the frequency of nonspecific interstitial pneumonitis in children with leukemia, and it now seems clear that fever and infection can be significantly decreased in patients receiving this prophylactic treatment. However, as Pizzo and his colleagues point out, compliance is a very important factor. One possible objection to the use of trimethoprim-sulfamethoxazole in these patients is its potential for myelosuppression, presumably due to the folate antagonist effect of the sulfamethoxazole. However, when administered in trimethoprim doses of 5 mg/kg/day, we have not found this to be a significant problem. It is our current practice to administer trimethoprim-sulfamethoxazole to leukemia patients and to those with solid tumors who receive intensive intermittent chemotherapy."] ◀

10–5 **Risk Factors for Thyroid Abnormalities After Neck Irradiation for Childhood Cancer.** Exposure of the neck to external radiation increases the risk of development of both benign and malignant thyroid neoplasms, besides the risk of hypothyroidism. Michael M. Kaplan, Marc B. Garnick, Richard Gelber, Frederick P. Li, J. Robert Cassady, Stephen E. Sallan, William E. Fine, and Martha J. Sack (Boston) undertook thyroid evaluations in 95 patients who had received radiotherapy directed to the neck for childhood cancer 5 to 34 years previously. Age range at evaluation was 7 to 38 years. None of the patients was known to have abnormal thyroid function or had received thyroid hormone, and none had evidence of relapse of the primary cancer. The most common primary diagnosis was Hodgkin's

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(10–5) Am. J. Med. 74:272–280, February 1983.

disease. Over half the patients had received megavoltage irradiation. Eighty-three patients had also received chemotherapy.

At least one abnormality was found on measurement of thyrotropin (TSH) concentration and serum free thyroxine index and palpation of the thyroid in 61% of patients. Forty patients had elevated TSH concentrations. The risk of TSH elevation was increased independently by a thyroid radiation dose of 3,000 rad or greater and lymphangiography, and three fourths of patients with both risk factors had an elevation. Three of the 10 patients operated on for nodules had localized papillary thyroid carcinomas. The cancers presented, respectively, as a 1-cm nodule, two microscopic foci of cancer in a 2-cm nodule that also contained multiple small adenomas, and an incidental finding in a patient whose multiple neck nodules contained atypical malignant schwannoma, probably related to irradiation.

Three of 95 patients in this survey who received neck radiation exposure for childhood cancer had localized papillary thyroid carcinomas. The frequency of palpable thyroid abnormalities increased with follow-up after exposure, but was unrelated to the serum TSH concentration or the radiation dose. The possibility that TSH suppression with thyroxine could reduce the occurrence of subsequent thyroid neoplasia in such patients merits investigation.

▶ [Exposure of the neck to external radiation increases the risk of subsequent benign and malignant neoplasms, and hypothyroidism as well. This has been understood for some time now. Nonetheless, there have been precious little data giving precise details about this relationship. What Kaplan et al. are telling us is that there is over a 60% probability that something will go wrong with the thyroid after it has received exposures to moderate or greater amounts of radiation. This study shows a clear, direct relationship between thyroid radiation dose in the range of 1,000 to 5,000 rad and the likelihood of thyroid functional damage. When it comes to Hodgkin's disease, this risk is even greater because of the probability that patients with this diagnosis would have undergone lymphangiography also. Lymphangiography prior to radiation therapy carries a theoretic risk of increased damage to the thyroid gland from radiation. This is because the iodide released from contrast material can inhibit thyroid hormone biosynthesis and secretion within a few days, thereby causing increased thyrotropin secretion and subsequent stimulation of thyroid cell division when radiation is given subsequently. In addition to the subnormal thyroxine levels, elevated TSH levels, and palpable thyroids that are seen in most patients eventually, patients receiving 3,000 or more rad to the thyroid who underwent diagnostic lymphangiography were at particularly extraordinary risk not just for functional abnormalities, but for the development of nodules in the thyroid. Most of the functional abnormalities appear to be nonprogressive 5 years after radiation therapy, but the nodules and risk of malignancy had no limit on their development. From this study, one can conclude that careful biochemical screening of thyroid function is necessary for approximately 5 years, whereas physical examination for detection of thyroid malignancy would be necessary indefinitely. It is not known whether it would be possible to prevent either of these two complications by routine use of thyroid hormone suppression beginning shortly after radiation exposure.

Many types of hazards are associated with irradiation received during childhood. As one example, between 1950 and 1960, about 20,000 Israeli children were treated for tinea capitis by x-ray therapy as part of a large public health campaign to eradicate the disease (Ron, E., et al.: *Am. J. Epidemiol.* 116:149, 1982). These children received an average dose of irradiation of approximately 130 rad. On follow-up, the irradiated children had lower examination scores on IQ testing, fewer of these children completed grade school, and a slightly higher risk of mental retardation also was seen. The amount of radiation used to treat central nervous system leukemia on a prophylactic basis, as is commonly practiced in the United States is approximately

20 times as high. Here, too, follow-up data are becoming more and more ominous. H. A. Moss et al. (*Am. J. Med.* 71:47, 1981) showed that the IQ of patients treated with prophylactic central nervous system irradiation was 98.6, compared with 112.5 for sibling controls. P. K. Duffner et al. (*Cancer* 51:233, 1983) evaluated 10 children who had had posterior fossa intracranial tumors treated with irradiation and chemotherapy in order to determine their neurologic status. Long-term follow-up showed that all the children had dementia, learning disabilities, or evidence of intellectual retardation. Cranial irradiation as part of the management of acute lymphocytic leukemia also can cause growth retardation (Wells, R. J., et al.: *Am. J. Dis. Child.* 137:37, 1983). All these problems are only part of the concerns that many parents have about treatment of malignancy. Most parents of children with these disorders are also aware of the increased incidence of secondary malignancies. V. Mike et al. (*Lancet* 2:1326, 1982) showed that the risk of a secondary malignancy in a survivor of childhood cancer was increased 10-fold 5 to 15 years after the diagnosis of the first malignancy.

You may complain that these comments are really not comparing apples with apples when making broad statements about radiation of so many different disorders. It just strikes me that a rem is a rem is a rem. Whatever the source, given enough of the same type, the effects may turn out to be quite similar. This is the reason why you see people worried about children sitting close to television monitors while using home computers (Nashel, D. J., et al: *N. Engl. J. Med.* 307:891, 1982). It is also the reason why so many mothers were arrested last summer in Romulus, New York, protesting at a site suspected of being the distribution point for cruise missiles.—J.A.S., III] ◀

10–6 **Age-Related Probability of Development of Hereditary Medullary Thyroid Carcinoma.** Hereditary medullary thyroid carcinoma (MTC) is inherited as an autosomal dominant trait; data are consistent with 100% penetrance. Measurement of plasma calcitonin concentrations after provocative calcium or pentagastrin stimulation has proved useful in early diagnosis. To determine the age-related risk of conversion from a negative to a positive provocative test, Robert F. Gagel, Charles E. Jackson, Melvin A. Block, Zoila T. Feldman, Seymour Reichlin, Bruce P. Hamilton, and Armen H. Tashjian, Jr., studied 445 members of 11 kindreds with multiple endocrine neoplasia IIa with sequential tests.

Of 159 family members with a 50% risk at birth of developing MTC, 38 converted from a negative to a positive test result (mean age of conversion, 15 years; median age, 12 years) during the 11 years of the study. The diagnosis of C cell hyperplasia or microscopic MTC was confirmed by histologic techniques in all patients except 1, in whom operation has not yet been performed. By age 25 years, 90% of the group had converted.

By use of methods previously described for determining the age-related probability for developing Huntington's chorea, a method is presented for determining the probability of development of MTC. The probability that a person with a negative test result will develop disease is predicted to equal $(1 - p_h)/(2 - p_h)$, where p_h is the proportion of individuals who have developed disease by age h. A person at risk whose test result was negative had the following probability of converting to a positive test result at a later date: age (years)/probability, 0/0.5; 5/0.49; 10/0.41; 15/0.25; 20/0.16; 25/0.10; 30/0.05; and 35/0.

Screening for hereditary MTC should begin by age 5 years and be

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(10–6) J. Pediatr. 101:941–946, December 1982.

continued at regular intervals until age 35. Testing should occur with greatest frequency between ages 5 and 20 years. It is believed that annual testing should be undertaken in the pediatric population. The age-at-onset data are only for hereditary MTC, which begins at an earlier age than sporadic MTC.

▶ [Medullary thyroid carcinoma is associated with the syndrome of multiple endocrine neoplasia type II. The endocrinologic aspects of this are discussed in Chapter 11, "Endocrinology," in this volume of the YEAR BOOK. As this article indicates, this form of malignancy is inherited as an autosomal dominant trait. Thus, half the offspring of an affected parent will demonstrate this malignancy. What this study does is to show us that pediatricians must be aware of this risk because some patients will develop the malignancy during childhood. In fact, the average age of conversion was by 15 years.

What one would obviously like to do is to be able to detect which half of the population risk group a particular child would be in. We now see that measurement of plasma calcitonin concentrations after provocative calcium or pentagastrin stimulation has proved useful in early diagnosis. Without question, these children should be examined at regular intervals and by a few years of life should start having plasma calcitonin studies performed. Medullary carcinoma of the thyroid is not as benign as other forms of thyroid malignancy, and careful surveillance will pay off in the long run.—J.A.S., III] ◀

10–7 **Cancer in Neonates: Experience at Children's Hospital of Philadelphia** is reviewed by Gordon B. Gale, Giulio J. D'Angio, Antonia Uri, Jane Chatten, and C. Everett Koop (Univ. of Pennsylvania). The occurrence of cancer in the first month of life is of the same order as during any other 4-week period of childhood. Of the 22 patients with malignant lesions, 11 (50%) had neuroblastomas of which 2 were widely metastatic; there were 3 infants each with teratoma, sarcoma, and leukemia and 1 infant each with Wilms' tumor and parotid carcinoma. For the 21 patients for whom follow-up data of at least 18 months are available, the survival rate is 41%.

Of the 10 neonates treated with complete excision of tumor, 8 are alive without evidence of disease; only 1 died of cancer (pulmonary metastases); and 1 died of unknown causes. Of 8 patients with solid tumors not totally excised, 7 died. All 3 infants with leukemia died within 18 months. Of the 5 patients with solid tumors who received chemotherapy, only 2 are long-term survivors; both had all gross tumor removed operatively. None of the neonates treated with radiation are long-term survivors. There were no deaths that could be attributed to surgery, radiation therapy, or chemotherapy.

Surgery plays a major role in the therapy of solid tumors in neonates. At this time of rapid growth, development, and maturation of all organs and tissues (especially the brain, liver, bones, kidneys, and pulmonary parenchyma), routine adjuvant chemotherapy or radiation therapy are contraindicated because of the known and anticipated long-term morbidities associated with these treatments. The exception may be the neonate with a completely removed sacrococcygeal teratoma, when chemotherapy in addition to surgery may be helpful. In the presence of metastatic disease, nonresectable tumor, or a hematologic malignant process, chemotherapy is indicated. Vincristine, cyclophosphamide, and actinomycin D are useful in soft tissue sarco-

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(10–7) Pediatrics 70:409–413, September 1982

mas and in teratomas. For leukemias, methotrexate, 6-mercaptopurine, prednisone, and vincristine are used. The chemotherapist must be aware of the limitations of the physiology of the neonate to absorb, biotransform, distribute, and excrete chemotherapeutic agents. Irradiation, an oncogen, produces deformities in children, and meticulous technique must be used to deliver the lowest dose known to be effective. Cranial irradiation may have especially grave consequences for the neonate.

Surgical excision is the treatment of choice for solid tumors whenever possible. When anticancer drugs are used, dose reduction and careful monitoring of toxicities are needed. Radiation therapy should not be used electively.

▶ [The dilemma facing the surgeon, the oncologist, and the radiotherapist caring for a newborn with cancer is how to apply those treatments that offer the best chance for long-term survival without producing severe damage to rapidly growing and maturing organs. Cancer in the newborn is obviously not a common problem; however, when it occurs, even sophisticated research centers have had to grapple with trying to decide whether this, that, or the other therapy will be not only effective but safe. The data from Philadelphia tell us what oncologic diseases we should expect to see in the newborn and what treatments may be applied to them.

We can see from the data that neuroblastoma constitutes the major neoplasia of early infancy. Although this tumor is not one that any of us will diagnose every day, some have considered it sufficiently common to recommend early infancy screening. A report from Japan (Sawada, T., et al.: *Am. J. Dis. Child.* 136:710, 1982) shows how this can be done. In Japan, 3-month-old infants receive a physical examination at local health centers under the "Child Health Survey." At this time, their parents are given "a vanillylmandelic acid (VMA) screening set" for early detection of neuroblastoma. Essentially, this involves putting a sample of urine on filter paper and mailing it to a central laboratory where a VMA spot test is done. The procedure of this test is the same as for the LaBrosse's spot test, discussed in the 1980 YEAR BOOK OF PEDIATRICS. This formal screening was recommended because of the incidence of neuroblastoma, 1 in 20,000 (estimated), in Japan. As admirable as this appears, there seem to be many problems with this type of mass screening of young infants for neuroblastoma. Among 78,000 children in Japan who were screened, there were almost 3,000 false positive tests that required retesting. Of this number, a fairly significant percentage again were false positive. Of the original group of 78,000 the expected 4 children were found to satisfy the projected incidence figures; however, 1 child missed by the screening program was later found by physical examination to have neuroblastoma. As sensitive as this screening test was (detecting 80% of cases), the specificity was miserably low, at only 0.13%. For every child with neuroblastoma who was picked up, over 700 sets of parents presumably were subjected to the trouble and anxiety of a retest in order to discard false positive results. The pros and cons of this type of mass screening of neuroblastoma are debated in letters to the editor that followed the original presentation of the data of Sawada et al. (If this is of interest to you, please see *Am. J. Dis. Child.* 137:304, 1983.) I would tend to think that we as pediatricians can do more by careful physical examinations at routine office visits to detect malignancy than all of these screening tests combined. Once you are beyond the hospital physical examination of the newborn and the first follow-up visit, the probability of picking up congenital formations is practically negligible. I would think that the major reason for doing such complete follow-up examinations as we are trained to do is primarily to detect just these sorts of problems that can result in death from malignancy.—J.A.S. III] ◀

10–8 **Management of Hodgkin's Disease in Children and Adolescents.** Beverly Lange and Philip Littman (Univ. of Pennsylvania) reviewed the management of Hodgkin's disease in 66 children and ad-

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(10–8) Cancer 51:1371–1377, Apr. 15, 1983.

olescents seen between 1970 and 1980. The 40 boys and 26 girls had a median age of 12.5 years. Nodular sclerosing disease was present in 51 patients. Thirty-four patients underwent staging laparotomy. Radiotherapy alone consisted of 3,600 to 4,000 rad of 6-meV therapy, given over 3 to 4 weeks, per region. Chemotherapy usually included cyclophosphamide, Oncovin, prednisone, and procarbazine (COPP). Five patients received CCNU (1-[2-chloroethyl]-3-cyclohexyl-1-nitrosourea), Velban, prednisone, and procarbazine, and 5 received doxorubicin in place of procarbazine. Four patients received AVBD (doxorubicin, Velban, bleomycin, and DTIC [dimethyl triazeno imidazole carboxamide]) because of failure to respond to COPP. Radiotherapy was given after six courses of chemotherapy to patients with bone marrow involvement.

Sixteen pathologically staged patients received potentially curative radiotherapy. All 11 with stage I or stage IIA disease survived, and 70% survived without relapse. Three of 5 patients with stage IIB to stage IVB disease survived, but all relapsed. The 50 patients scheduled for combined-modality therapy were followed up for a median of 52 months. Seventeen patients with stage IA and stage IIA disease had an actuarial survival at 40 months of 100% and a relapse-free survival rate of 86%. The 33 with stage IIB to stage IVB disease had respective rates of 86% and 60% at 5 years. Complications of treatment included hypothyroidism in 6 patients and skeletal deformities in 6. Two patients have developed benign tumors in irradiation fields, but no second malignancies have been detected.

These and other results warrant the omission of staging laparotomy when combined-modality treatment of Hodgkin's disease is planned. Morbidity from this treatment is high, and it may be reasonable to consider reducing or even eliminating radiotherapy if more effective chemotherapy is used. Three courses of MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) and three of AVBD therapy, or even fewer courses of each, might provide better disease control than either combination used by itself. A search for less toxic combinations should continue, and use of supplemental hormonal therapy to prevent thyroid and gonadal damage should be investigated.

► [We seem to have reached a plateau with regard to the long-term outlook for children who have been diagnosed as having Hodgkin's disease. This is not to say that there won't be evidences of gradual improvement in survival data, just that the magnificent improvements of the past 20 years will be difficult to exceed. What you see in this study by Lange and Littman are evidences of a fine tuning of therapeutic modalities that already exist. These investigators recognized the morbidity of staging laparotomy, large-field irradiation, and chemotherapy. Recognizing this, they attempted to adjust therapy according to the age and disease stage of the patients to achieve maximal control of disease with minimal morbidity. Specifically, they omitted staging laparotomy for any patient who was to receive chemotherapy and recommended combination chemotherapy and radiation therapy for all prepubertal patients and those at risk of relapse when treated with radiation alone. This approach eliminated the risk of postsplenectomy sepsis. They increased the role of chemotherapy, hoping that a reduction in radiation dosage would reduce problems with growth and postirradiation hypothyroidism. They have no long-term evidence yet to support the latter point. The results are similar to those of others and appear to justify omission of staging laparotomy when combined-modality therapy is planned. In fact, these data

are so clear that practically no one argues for staging laparotomy anymore if chemotherapy is going to be used. The idea here is that chemotherapy, because it is truly a total-system approach, will take care of any splenic disease if it exists. Obviously, the decision gradually to retrench on the use of radiation therapy is not one that comes easily, either for the oncologist or the radiotherapist.

There is one situation, however, in which everyone agrees that radiation may pose a great hazard in patients with Hodgkin's disease. These are patients with Hodgkin's disease who also happen to have ataxia-telangiectasia. Children with ataxia-telangiectasia are known to have a defect in the repair of radiation-induced cellular damage, which is manifested in affected individuals by extreme tissue response after therapeutic doses of ionizing radiation. As you may know, patients with ataxia-telangiectasia have a 40 to 100 times increased risk of developing a lymphoproliferative malignancy. Thus, the association of ataxia-telangiectasia and Hodgkin's disease in a child is not rare, and each time this situation arises, any role for radiation therapy quickly diminishes (Pritchard, J., et al.: *Cancer* 50:877, 1982).

Every now and then we still see some attempt to link infectious mononucleosis with Hodgkin's disease. For once and for all (maybe?), it seems that the Epstein-Barr virus (EBV) plays no role in the causation of Hodgkin's disease. T. C. Shope, et al. show that patients with Hodgkin's disease have no greater incidence of prior infection with this virus that causes infectious mononucleosis (*Am. J. Dis. Child.* 136:701, 1982). They did find that those patients who had Hodgkin's disease and who previously had been infected with EBV did have extraordinarily high antibody titers against the virus. Presumably, this greater production of antibody relates to the known immunoregulatory defects associated with Hodgkin's disease. There are occasional patients who have EBV infection who will acquire Hodgkin's disease. Only in very rare circumstances do these two disorders act in a significantly related way. In 1 instance in which they did, a boy aged 6 developed EBV infection that evolved gradually into a full-blown picture of Hodgkin's disease. This case was unusual, as the boy had a sister, aged 9, in whom the same situation developed. Parenthetically, the mother of these children was diagnosed as having a non-Burkitt-type undifferentiated lymphoma that proved rapidly fatal. Whether any of this relates to the X-linked recessive lymphoproliferative syndrome is questionable. Dr. John Sullivan discusses the latter disorder in his comment to article 10–10.—J.A.S., III] ◄

10–9 **Bone Marrow Transplantation for Non-Hodgkin's Lymphoma in Children and Young Adults: A Pilot Study.** Maura O'Leary, Norma K. C. Ramsay, Mark E. Nesbit, Jr., David Hurd, William G. Woods, William Krivit, Tae H. Kim, Philip McGlave, and John Kersey (Univ. of Minnesota, Minneapolis) report the use of allogeneic bone marrow in 10 patients with Burkitt's lymphoma or relapsed T cell lymphoblastic lymphoma who had histocompatible donors. Each received a conditioning regimen of cyclophosphamide, total-body radiation, cytosine arabinoside, and bis-chloro-nitroso-urea (CRAB) before bone marrow transplantation. Six patients had Burkitt's lymphoma with wide dissemination, and 4 had T cell lymphoblastic lymphoma and had failed to respond to conventional treatment. Seven patients were in remission at the time of marrow transplantation. The CRAB conditioning protocol was given over 6 days, and bone marrow was administered 1 day after irradiation. Patients then received prophylaxis against graft-versus-host disease, with methotrexate alone or combined with prednisone and antithymocyte globulin.

One patient died of sepsis and heart failure in the pretransplant period. Five of the 9 who received transplants are alive after 18–73 months; the median follow-up is 29 months. Engraftment occurred a

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(10–9) Am. J. Med. 74:497–501, March 1983.

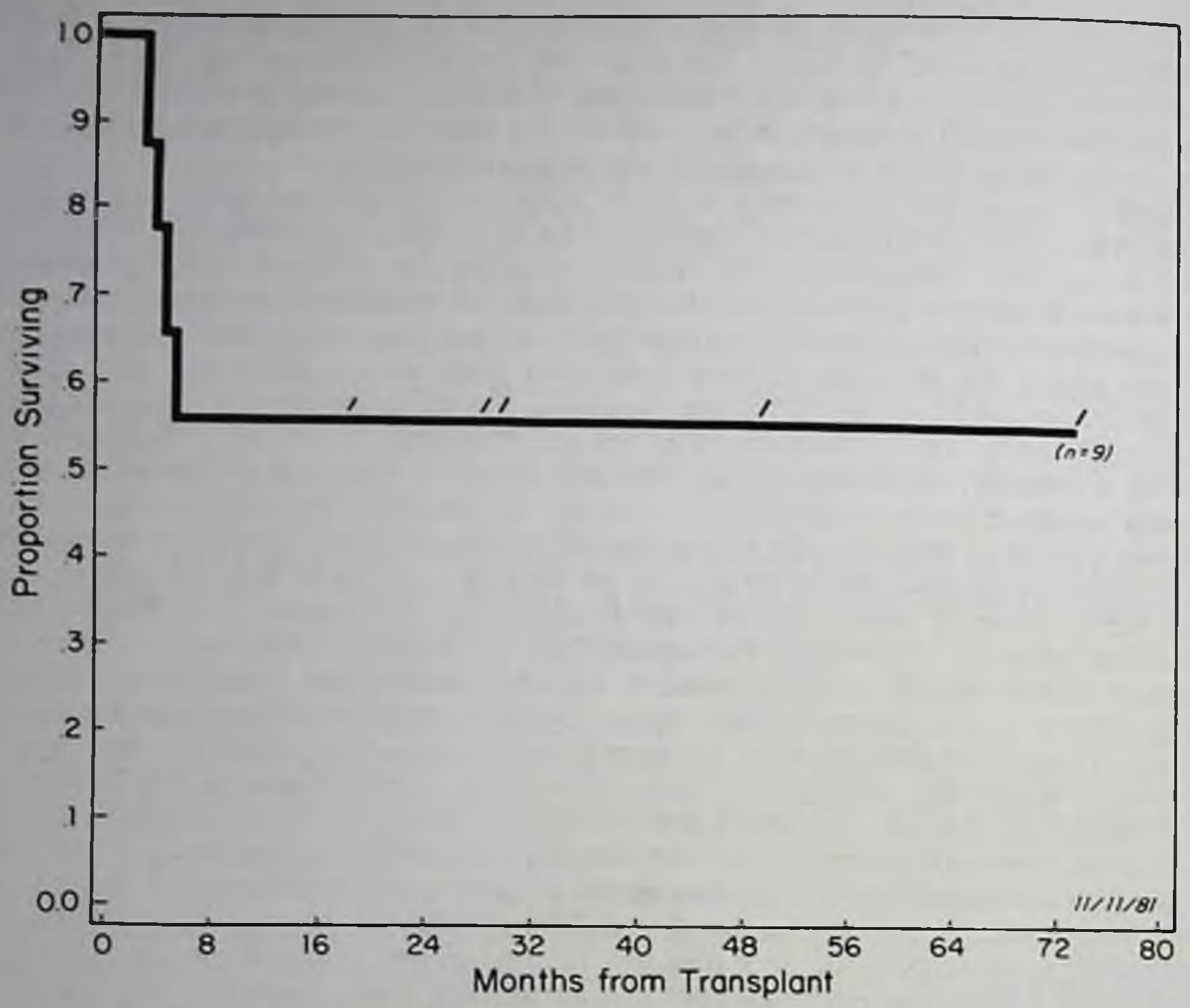

Fig 10–4.—Disease-free survival after bone marrow transplantation in patients with non-Hodgkin's lymphoma. (Courtesy of O'Leary, M., et al.: Am. J. Med. 74:497–501, March 1983.)

median of 20 days after transplantation. The overall estimated disease-free survival from the time of transplantation by the life-table method is 56% at 73 months (Fig 10–4). Three patients with Burkitt's lymphoma and 2 with T cell lymphoma have survived. Complications included interstitial pneumonitis in 3 patients, which was the primary cause of death in 1 instance, and congestive heart failure in 2 patients. Graft-versus-host disease developed in 4 patients, and this was a major contributing cause of 1 death. Two patients have chronic graft-versus-host disease.

Bone marrow transplantation provides an alternative to conventional chemotherapy for patients with poor-risk non-Hodgkin's lymphoma. All surviving patients presently are at home with unmaintained remissions. Further study of bone marrow transplantation in both children and young adults with poor-risk non-Hodgkin's lymphoma is warranted.

▶ [Recent advances in the treatment of childhood non-Hodgkin's lymphoma have produced improvements in survival. Aggressive chemotherapy regimens have produced a 3-year relapse-free survival of over 60% in non-Hodgkin's lymphoma. One of the best treatment programs today is a 10-drug regimen that has a name that is quite fanciful to most nononcologists. It is called the "LSA_2-L_2 protocol." This multi-drug regimen originally was developed at Memorial Sloan-Kettering Hospital in New York City. The recent data concerning the use of this drug (Anderson, J. R., et al.: *N. Engl. J. Med.* 308:559, 1983) are so excellent that there is no question concerning the fact that the LSA_2-L_2 protocol is the gold standard by which all other first-line treatments are being compared. Despite this rather optimistic series of statements, many children with non-Hodgkin's lymphoma do relapse. Those at particularly high risk for

relapse have disseminated Burkitt's lymphoma or T cell lymphoblastic lymphoma at diagnosis. In fact, the outlook for these two varieties of non-Hodgkin's lymphoma is so poor that O'Leary et al. chose to perform bone marrow transplants immediately in these patients. The preliminary data from the transplantations suggest a greater than 50% survival at 2 years in this small group of patients. Without question, this is worthy of further follow-up.

Bone marrow transplantation as part of the management of acute leukemias in children is much farther along. Initially, bone marrow transplants were used only in end-stage patients. Now patients with acute lymphatic leukemia who have relapsed are having transplantations while in a stable remission. The Seattle Transplant Group is suggesting transplantation as the procedure of choice for children with acute myelogenous leukemia as soon as they achieve their first remission. Obviously, using a perfectly matched family member for the source of the donor marrow is restricted to those patients who have such a donor. Usually this averages to only 1 child in 4. For this reason, we are now seeing more and more in the way of autologous bone marrow transplantation. With this procedure, bone marrow is taken from the child while the child is in remission, and any unseen malignant cells are "purged" from the bone marrow using a variety of monoclonal antibodies. While this is going on, the patient is having total body radiation and systemic chemotherapy and is salvaged with a transfusion of his or her own bone marrow. For a stunning review of the current status of bone marrow transplantation in leukemia, see the article by George Santos (*Yale J. Biol. Med.* 55:477, 1982).

Finally, if you read the above article by O'Leary et al. carefully, you will see that prior to marrow transplantation, the patient received a conditioning regimen consisting of cyclophosphamide, total body irradiation, cytosine arabinoside, and bis-chloro-nitroso-urea. As the article indicates, all this can be abbreviated to "CRAB." It certainly is fortunate that these investigators chose the bis-chloro-nitroso-urea in favor of procarbazine. If the latter drug had been used, the corresponding abbreviation for the new combination would not have made it through any human experimentation committee that I know of.—J.A.S., III] ◀

10–10 **Epstein-Barr Virus-Induced Diseases in Boys With the X-Linked Lymphoproliferative Syndrome (XLP): Update on Studies of the Registry.** Immunodeficient persons such as male patients with XLP are vulnerable to Epstein-Barr virus (EBV)-evoked diseases. David T. Purtilo, Kiyoshi Sakamoto, Vanessa Barnabei, Janet Seeley, Thomas Bechtold, Geraldine Rogers, Joanne Yetz, Shinji Harada, and the XLP Collaborators (Univ. of Nebraska) reviewed data on 100 subjects with XLP in 25 kindreds.

The overlapping occurrence of the major phenotypic expressions of XLP is shown in Figure 10–5. Seventy-five subjects exhibited the infectious mononucleosis phenotype, 41 alone. Seventeen subjects had infectious mononucleosis and aplastic anemia. All died within a week of pyogenic infection or hemorrhage. Nineteen subjects had infectious mononucleosis complicated by hypogammaglobulinemia, and 35 subjects, including 9 with mononucleosis, had malignant lymphoma. Twenty-six lymphomas arose in the ileum. Fifteen subjects had malignant lymphoma only. Eleven had hypogammaglobulinemia alone. The overall mean survival after diagnosis of XLP was 29 months. Morbidity in survivors consisted chiefly of pharyngitis with intermittent fever and chronic bronchitis. In the 15 survivors studied, serum immunoglobulin concentrations varied widely, ranging from hypergammaglobulinemia to agammaglobulinemia. Antibody responses to EBV-specific antigens were deficient. Mothers of affected boys showed abnormally elevated titers of EBV antibodies.

(10–10) Am. J. Med. 73:49–56, July 1982.

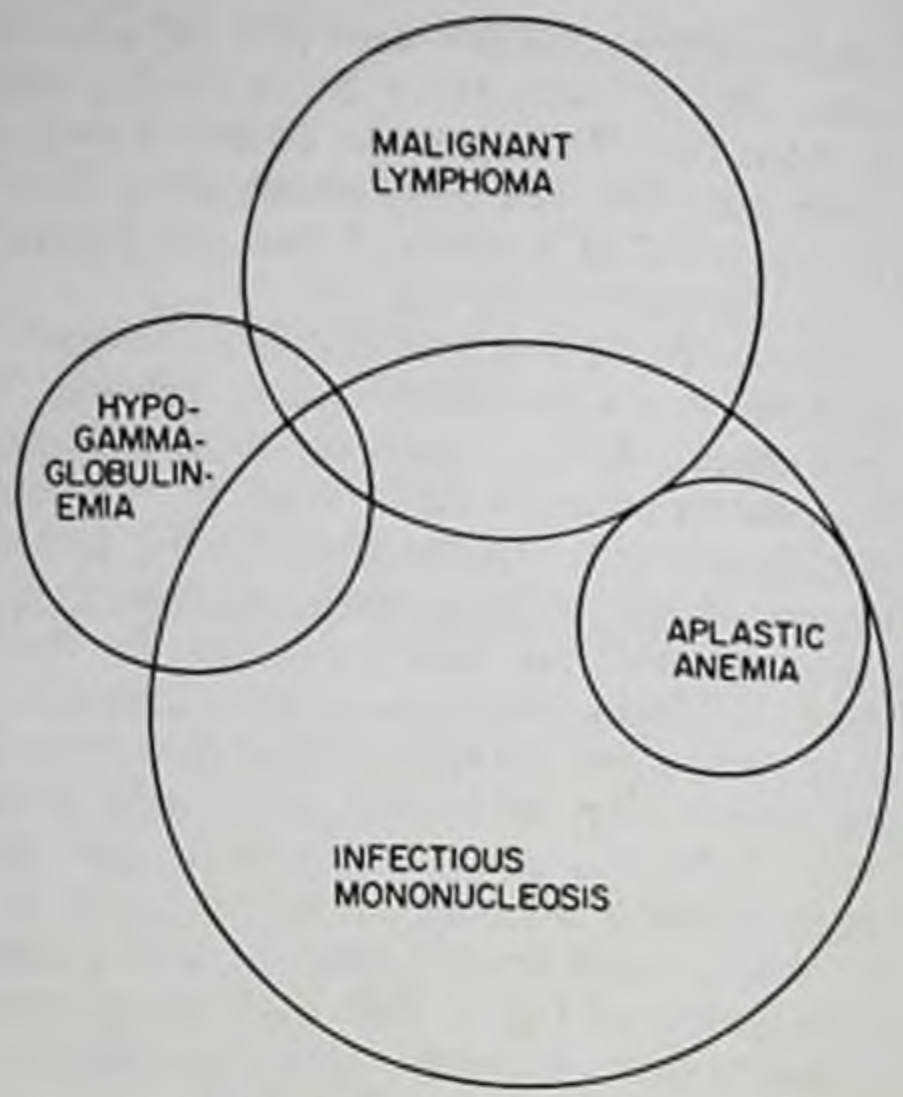

Fig 10–5.—Venn diagram displaying relative frequency of four major phenotypes of XLP. Overlapping of circles indicates simultaneous occurrence of phenotypes. (Courtesy of Purtilo, D. T., et al.: Am. J. Med. 73:49–56, July 1982.)

Persons of both sexes with XLP phenotypes should be evaluated for immunodeficiency to EBV. Those with inherited or acquired immunodeficiency may be susceptible to life-threatening EBV-induced diseases. Boys with the most marked immune defects may die rapidly of infectious mononucleosis, whereas activation of suppressor T cells could result in the hypogammaglobulinema phenotype. Those with more subtle immune defects may develop a chronic polyclonal B cell hyperplasia that can convert to monoclonal lymphoma under immunoselective pressures.

▶ [Dr. John Sullivan, Associate Professor, Department of Pediatrics, University of Massachusetts Medical Center, Worcester, comments:

"This article represents an expansion of the series of patients first described in 1980 by Hamilton et al. (*J. Pediatr.* 96:669–673). The number of patients investigated has increased from 57 to 100. From these extensive studies, it is clear that approximately 60%–80% of males with XLP will die during the acute phase of EBV infection with symptoms compatible with infectious mononucleosis. Most of those who survive their initial encounter with EBV will develop more global immune defects typical of common variable immunodeficiency (acquired immune deficiency). Of extreme interest is the fact that 25%–35% of all males with XLP will develop a lymphoproliferative disorder that is pathologically indistinguishable from lymphoma. However, unlike a true lymphoma, some of these are polyclonal B lymphocyte proliferative disorders.

"Purtilo and colleagues note that 25% of XLP patients studied in their retrospective survey had completely normal medical histories prior to infection with EBV. These data are consistent with our prospective studies of 2 males in one well-characterized kindred. Both of these males had normal immunologic function prior to EBV infections and both succumbed to fatal infectious mononucleosis. Comprehensive immunologic studies that are in press in the *Journal of Clinical Investigation* suggest that the immunologic defect in XLP may be excessive killer cell activity triggered by EBV-infected B lymphocytes. These killer cells were shown to have cytotoxic activity against autologous (self) hepatocytes and fibroblasts. These data suggest that regulation of the normal cytotoxic T cell response triggered during acute EBV infection may be deficient in XLP, leading to destruction of hepatocytes and possibly to the immune system itself, resulting in a global immune defect in those who survive their initial infection.

"Therapy of life-threatening EBV infections remains an important problem for clinical researchers. Acyclovir appears not to be effective in limiting proliferation of EBV-

infected B lymphocytes (Sullivan, J. L., et al.: *Am. J. Med.* 73:262–266, 1982). Immunosuppressive agents alone or in combination with acyclovir also do not appear to be effective. Trials with interferon are under way."] ◄

10–11 **Cat-Scratch Disease Simulating Malignant Lymphoma.** Cat-scratch disease is a benign, self-limited disorder that commonly causes regional adenopathy in children. Atypical variants have been described, most commonly the oculoglandular form. Ruth E. Luddy, John C. Sutherland, Barbara E. Levy, and Allen D. Schwartz (Univ. of Maryland, Baltimore) report a case of this variant in which a parotid biopsy suggested malignancy.

Girl, 6, developed lethargy, erythema and tearing of the eyes, followed in a week by progressive left temporal swelling adjacent to the eye. Examination showed a tender left periorbital swelling, two tender left temporal masses, several enlarged nodes, and an enlarged parotid gland (Fig 10–6). A parotid biopsy showed a dense infiltrate of histiocyte-like cells, some of them multinucleated, and vascular proliferation with focal and diffuse hemorrhages. A panel of pathologists concluded that the most likely diagnosis was histiocytic lymphoma. Studies for malignancy were negative. The orbital lesion became larger, but subsequently all lesions became smaller and nontender. The patient was found to have played with cats, and two cat-scratch tests were positive. A granuloma was found in the left palpebral conjunctiva. All lesions had resolved 5 months after the onset of symptoms, and the child has been well since then.

The pathologic findings in this case were strongly suggestive of histiocytic malignancy, but, fortunately, the mass lesions began resolving during evaluation, and the oculoglandular form of cat-scratch disease was diagnosed. The microscopic appearances of nodes from these cases are not pathognomonic, and occasional patients with nonmalignant adenopathy may have received unnecessary treatment. Reports

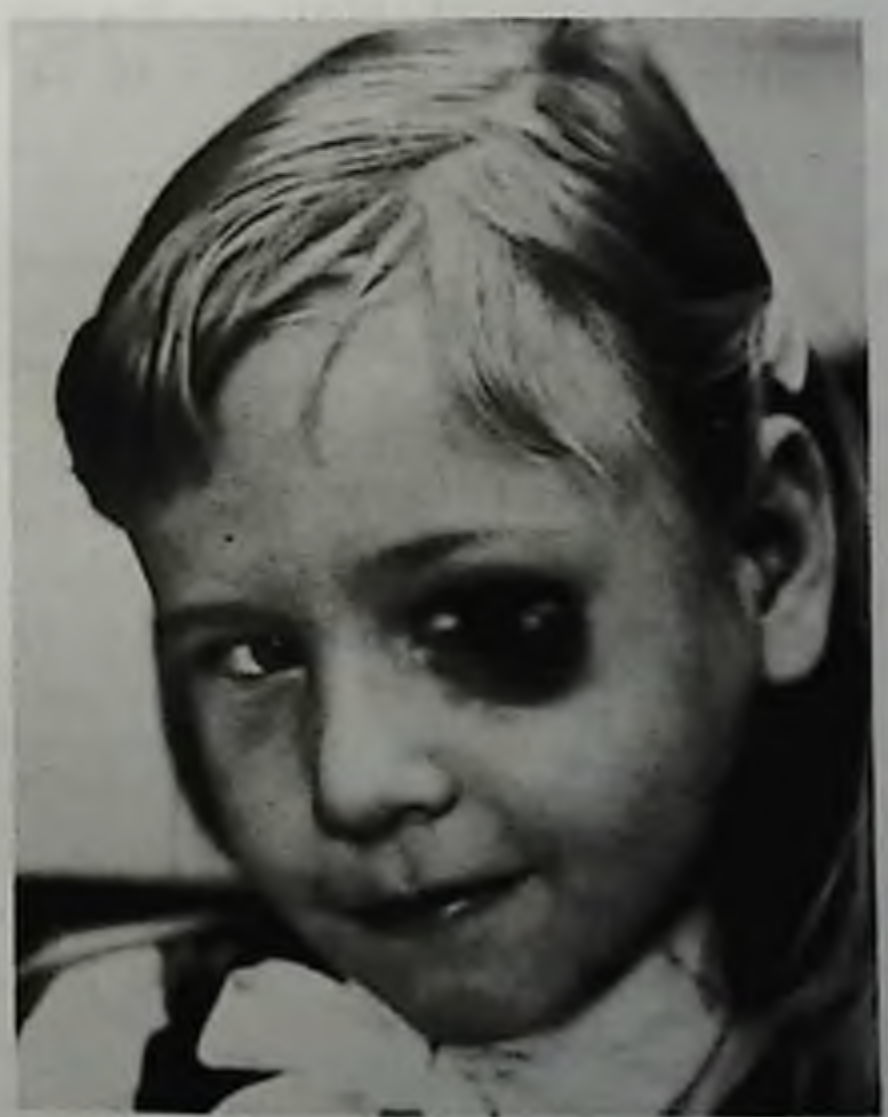

Fig 10–6.—Photograph taken at the peak of periorbital discoloration and swelling. (Courtesy of Luddy, R. E., et al.: Cancer 50:584–586, Aug. 1, 1982.)

(10–11) Cancer 50:584–586, Aug. 1, 1982.

of cases of lymphoma undergoing spontaneous regression may in some instances represent nonmalignant lymphadenopathy.

▶ [We have commented previously on the difficulty of distinguishing between cat-scratch disease and malignant lymphoma. There is no pathognomonic finding in the nodes of children who have cat-scratch disease. On occasion, multinucleated giant cells of the Langhans type may simulate the Reed-Sternberg cells found in Hodgkin's disease. It is likely that occasional cases of nonmalignant lymphadenopathy have resembled lymphoma so closely that the patients received unnecessary treatment.

The easiest way in the world that I know of to solve having to be faced with these diagnostic dilemmas is to find a new ingredient for ketchup (which in many parts of the world is spelled "catsup"—get the idea?).—J.A.S., III] ◀

10–12 **Suprasellar Tumors in Children: Review of Clinical Manifestations and Managements.** Duk Il Sung (Columbia-Presbyterian Med. Center, New York) reviewed the records of the 45 boys and 53 girls with suprasellar tumors treated during 1950 to 1975. The tumors included 43 optic chiasma gliomas (anterior lesions in 36 cases and posterior lesions in 7), 43 craniopharyngiomas, and 12 germ cell tumors.

Most anterior chiasma gliomas developed during the preschool years, nearly all posterior chiasma gliomas and germ cell tumors developed in the early second decade, and most craniopharyngiomas developed between ages 6 and 10 years. The most common manifestation in the 98 children was progressively decreased visual acuity or visual field deficit, or both (table).

Of the 98 children, 16 died of tumor within 5 years of treatment (4 within 4 weeks), 12 died of recurrent or persistent tumor more than 5 years after treatment, 6 were lost to follow-up after 5 years, and 64 (65.3%) are alive. The respective absolute 5-year and 10-year survival rates are 91.7% and 72.4% for anterior chiasma gliomas, 85.7% and 40% for posterior chiasmal gliomas, 72% and 31% for germ cell tumors, and 82.9% and 71.9% for craniopharyngiomas. Half of the 64 survivors returned to active, normal lives; these include 36% of 22

Clinical Findings in 98 Children With Suprasellar Tumors*

Findings	Anterior chiasmal gliomas No. of pts (%)	Posterior chiasmal gliomas No. of pts (%)	Germ cell tumors No. of pts (%)	Craniopharyngiomas No. of pts (%)
Diminished VA and/or VF	34 (94)	6 (86)	10 (83)	22 (54)
Diabetes insipidus	0	5 (71)	9 (75)	3 (7)
Growth retardation	2 (6)	1 (14)	4 (33)	14 (33)
Growth acceleration	3 (8)	1 (14)	0	0
Sexual precocity	3 (8)	2 (28)	2 (17)	0
Delayed puberty	0	1 (14)	3 (25)	4 (10)
Symptoms of ↑ ICP	6 (16)	2 (28)	5 (42)	23 (54)
Neurofibromatosis	11 (31)	0	0	0

*VA: visual acuity; VF: visual field; ICP: intracranial pressure; pts: patients.
(Courtesy of Sung, D. I.: Cancer 50:1420–1425, Oct. 1, 1982.)

(10–12) Cancer 50:1420–1425, Oct. 1, 1982.

survivors with anterior chiasma gliomas, 75% of 4 with posterior chiasma gliomas, 80% of 5 with germ cell tumors, and 52% of 33 with craniopharyngiomas.

Long survival with reasonably good quality of life was found in most children with germ cell tumors or posterior chiasma gliomas irradiated with 5,000 rad in 6 weeks using fields extended to include the entire ventricular system and sella turcica, children with craniopharyngiomas treated with total resection when the tumor was limited to the suprasellar area, and children with craniopharyngiomas treated with combined surgery and postoperative irradiation (5,500 rad in 6 weeks without extended fields) when the lesions could not be resected totally. More passive-dependent, immature responses due to persistent residual mass after irradiation were noted in most children with anterior chiasma gliomas, although these children have survived long. Noncalcified craniopharyngiomas responded better to irradiation than did tumors with calcification.

10–13 **Intracranial Tumors in the First Year of Life.** R. Jooma and B. E. Kendall (London) investigated a total of 1,296 children for intracranial tumor between 1953 and 1981. In 107 children (8%), symptoms appeared before age 1, but a preoperative computed tomography (CT) scan was available only for 29, and histologic verification was not available for 4, leaving 25 patients suitable for study. The average number of such infants was 3.17/year in the 23 years prior to the introduction of CT scanning, whereas in the subsequent 6-year period the figure rose to 4.83/year. The proportion of supratentorial tumors rose from 52% to 76% after the introduction of CT. Vomiting and alteration in psychomotor development were the most common presenting symptoms; macrocrania was present in 88%. The histologic types and results of surgery are shown in the table. Overall, 19 (76%) of the tumors were supratentorial and 6 (24%) were infratentorial.

RESULTS OF SURGERY FOR EACH TUMOR TYPE

Tumor type and location	No.	Autopsy verified	Surgery verified	Operative mortality	Case mortality and postoperative time	Alive and postoperative time
Supratentorial						
Astrocytoma	7	1	6	1	4 years	6 m, 18 m, 3 years, 5 years
Primitive glial tumour	2	1	1	1		
Choroid plexus papilloma	4		4	1		1 year, 1 year, 2 years
Ependymoma	3	1	2		5 years, 5 years	
Teratoma	1	1				
Tuberous sclerosis	1		1			1 m
Craniopharyngioma	1		1		6 m	
Infratentorial						
Astrocytoma	3		3			1 year, 4 years, 5 years
Primitive glial tumour	1	1				
Ependymoma	1		1	1		
Medulloblastoma	1		1			3 years
Total	25	5	20	4	4	12

(Courtesy of Jooma, R., and Kendall, B. E.: Neuroradiology 23:267–274, September 1982; Berlin-Heidelberg-New York: Springer.)

(10–13) Neuroradiology 23:267–274, Sept. 1982.

The histologic diagnoses were not greatly dissimilar to neoplasmas of later childhood, with gliomas comprising 76% of the series. The single medulloblastoma is at variance with other studies where the incidence has been 15%–30%. The absence of dermoid cysts is perhaps surprising, but the incidence of verified dermoid cysts shown by CT in our series started at age 2. Just over half the tumors were apparent at age 6 months, and there was no clear change in the distribution of pathology between these cases and cases manifest only during the second 6 months of life.

Many tumors were large and well-defined, suggesting rapid expansive rather than infiltrative growth. The CT features generally corresponded to macroscopic appearances. Soft tumors were often of low density, and firm tumors tended to be of a density equal to or higher than brain substance.

The operative mortality of 20% is in line with the experience of others, and all but 1 death was in the neonatal period.

▶ [Dr. Ronald Dubowy, Assistant Professor of Pediatrics, State University of New York at Syracuse, comments:

"Central nervous system (CNS) tumors account for almost 20% of all malignancies in children. Progress in the treatment of brain tumors has not been as rapid as in other childhood cancers, yet there have been recent advances in therapy that can be of great help to at least some of these patients. There are many obstacles to the cure of brain tumors. These include difficulties in early diagnosis and anatomical staging, the great variability in response to treatment as a function of tumor location and histology, the toxicity of radiation to the brain and spinal cord, the problem of natural and acquired drug resistance, and, not least of all, historical general reluctance among physicians to use aggressive multimodality therapies as have been applied so successfully to other childhood tumors.

"The report by Jooma and Kendall points out the delay in diagnosing tumors in infants in the pre-CT era. We must remind ourselves that CT technology, yielding immeasurable advantages in early diagnosis and thorough delineation of anatomical involvement, has only been widely available within the past 10 years. Doctor Sung's review of suprasellar tumors in children illustrates the heterogeneity of tumors even within this limited anatomical area. Many of the more common pediatric tumors, such as astrocytomas and ependymomas, have very different prognoses depending on location (supratentorial vs. infratentorial) and histologic grading (benign vs. malignant). This variability makes evaluation of any one treatment all the more difficult.

"The truly significant progress to date in treating brain tumors has been in the appreciation of optimal surgical and radiotherapeutic technique and is best exemplified by how we presently deal with cerebellar meduloblastoma. This tumor was virtually uniformly fatal after surgery alone. We now know that complete resection always should be attempted and that the entire craniospinal axis should be irradiated, with a dose of greater than 5,000 rad given to the tumor bed. Children treated in this manner now show a 5-year survival rate of over 50% in many series. Long-term morbidity, however, remains a problem and includes intellectual deficits, endocrine deficiencies, and impaired spinal growth.

"There are three distinct roles for chemotherapy in children with CNS tumors: (1) as treatment for the child who has relapsed following irradiation, (2) as adjuvant therapy along with surgery and irradiation, and (3) as primary postsurgical therapy alone in very young patients for whom curative doses of irradiation would lead to excessive morbidity. There is no question that chemotherapy can shrink recurrent tumors, even inducing complete responses in some. Cangir et al. (*Med. Pediatr. Oncol.* 4:253, 1978) reported on the favorable results with the combination MOPP, nitrogen mustard, vincristine, procarbazine, and prednisone, which originally was developed for use in Hodgkin's disease. Khan et al. (*Cancer Treat. Rep.* 66:2013, 1982) described the activity of *cis*-platinum in a similar mixed group of patients. These drugs, along with other active compounds such as methotrexate and the nitrosoureas, provide the oncologist

with a diversified armamentarium. The insurmountable blood-brain barrier seems to be a myth.

"Less conclusive however, are the results regarding the utility of adjuvant chemotherapy in terms of increasing long-term disease-free survival. In a large European cooperative study (the SIOP group), adjuvant vincristine and CCNU seemed to produce increased survival in high-risk patients with medulloblastomas over that seen with surgery and radiation alone. A similar drug regimen tested by the Children's Cancer Study Group in medulloblastoma failed to show added benefits. Currently, MOPP adjuvant therapy is being evaluated by the Pediatric Oncology Group. The optimists among us feel that effective adjuvant drug combinations eventually will be found for medulloblastoma, ependymoma, and other tumors, but the problem of patient accrual rate will have us wait some time for conclusive data to be obtained.

"The morbidity of CNS irradiation in infants has led some investigators to use chemotherapy in these patients with the hope that irradiation can be delayed at least until an older age. This concept is very exciting, but results are still too preliminary to allow definite conclusions.

"The specialty of neuro-oncology is coming into its own as a true interdisciplinary endeavor. As long as the pessimists and therapeutic nihilists are kept out, there is every reason to expect great progress in the years ahead."] ◄

10–14 **Rhabdomyosarcoma in Childhood: Analysis of Survival in 98 Cases.** Jay L. Grosfeld, Thomas R. Weber, Robert M. Weetman, and Robert L. Baehner (Indiana Univ.) reviewed factors influencing survival in a series of 98 infants and children treated at a pediatric cancer center for rhabdomyosarcoma between 1955 and 1978. Twenty-one patients were younger than age 2 years. The disease-free survival rate was highest in the youngest group. Eleven patients had localized disease that was completely resected, whereas 15 had grossly resected disease but involved nodes or microscopic residual disease. Thirty-four patients had gross residual disease, and 38 presented with metastatic disease. Overall disease-free survival at 2 years was 37%. Sites of disease are shown in Figure 10–7. Survival has improved over time for patients with genitourinary, orbital, paratesticular, head and neck, and extremity tumors, but has remained poor for pa-

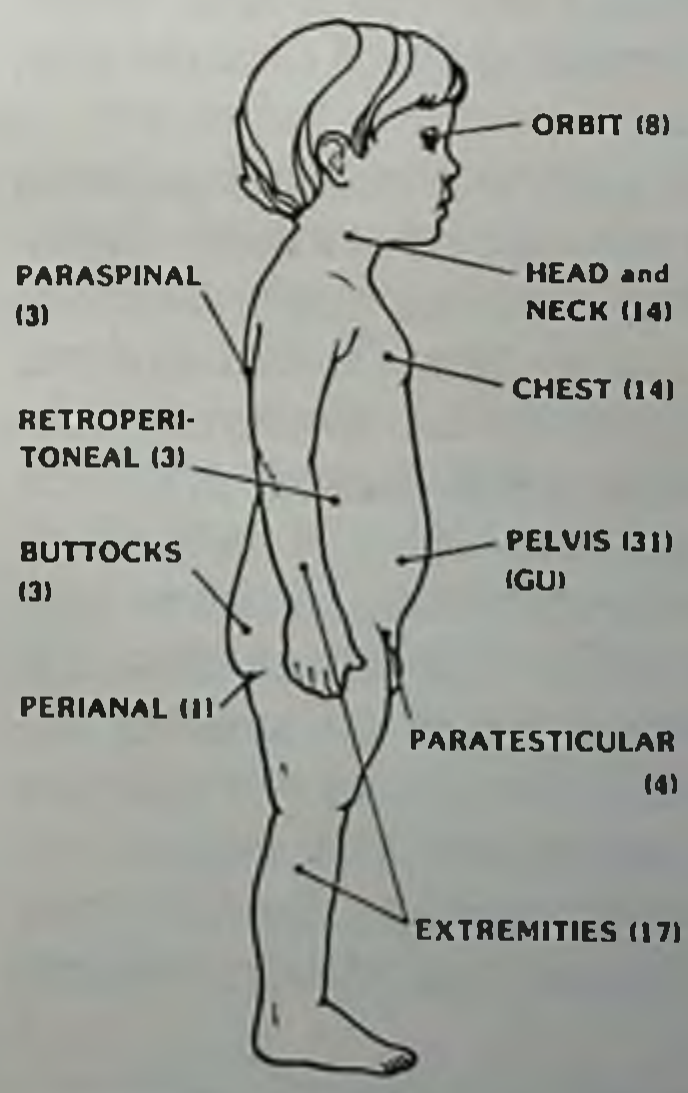

Fig 10–7.—Sites of primary occurrence in 98 infants and children with rhabdomyosarcoma. Genitourinary tract tumors, e.g., pelvic, were most common (31 cases). (Courtesy of Grosfeld, J. L., et al.: J. Pediatr. Surg. 18:141–146, April 1983.)

(10–14) J. Pediatr. Surg. 18:141–146, April 1983.

tients with primary disease of the chest wall, retroperitoneal space, buttocks, and paraspinal area.

Chemotherapy generally includes actinomycin D, vincristine, cyclophosphamide, and doxorubicin. Most patients with stage II to stage IV disease received local radiotherapy. Since 1972, when more systematic chemotherapy was made routine, 52% of patients have survived. Orbital lesions now are managed by aggressive radiotherapy directed to the orbit and chemotherapy, rather than by attempted orbital exenteration. Paratesticular lesions are managed by orchiectomy and high ligation of the spermatic cord, followed by retroperitoneal node dissection. All surviving patients have had tumors with an embryonal histologic pattern; those with alveolar and pleomorphic tumors have had an extremely poor prognosis.

The stage of disease at diagnosis is probably the most important prognostic factor in infants and children with rhabdomyosarcoma. The site of primary tumor is also important. Chemotherapy has failed to improve the outlook for patients with metastases and those who relapse. Emphasis should be on early diagnosis, refinements in therapy, and development of new chemotherapeutic agents. Long-term follow-up is needed to assess irradiation damage, treatment effects on growth and development, and occurrence of second neoplasms.

10–15 **Superior Vena Cava Syndrome in Childhood: Report of 10 Cases and Review of the Literature.** Philip Y. Issa, Emile R. Brihi, Yves Janin, and Michel S. Slim (American Univ., Beirut) reviewed experience with 10 consecutive children with superior vena cava obstruction, seen between 1966 and 1975, and 150 reports of the syndrome collected from the literature between 1951 and 1976. Most of the authors' patients were older than age 4 years. Average duration of symptoms was 1 month. Five patients had non-Hodgkin's lymphoma, 2 had Hodgkin's disease, and 1 had clinically suspected lymphoma. One patient each had a staphylococcal abscess and a cystic lymphangioma. The patients who survived and had their disease controlled are presently well.

Compression of structures in the superior part of the mediastinum is a rare but serious condition calling for prompt treatment. Lymphoma is the most common tumor producing superior vena cava obstruction in children. A brief preoperative course of radiotherapy can alleviate symptoms and permit safer thoracotomy for biopsy. A specific pathologic diagnosis must be made. Hodgkin's disease in children has a good prognosis with chemotherapy and low doses of radiotherapy. The causes of superior vena cava obstruction in children described in the literature are given in the table. The most common nonmalignant cause is the superior vena cava-to-right pulmonary artery anastomosis, when the pericardial baffle shrinks and impinges on the superior vena cava at the superior margin of the interatrial septum. The most common mediastinal tumor causing superior vena cava obstruction in childhood is malignant lymphoma. An increasing

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(10–15) Pediatrics 71:337–341, March 1983.

CAUSES OF SUPERIOR VENA CAVA OBSTRUCTION IN CHILDHOOD: REVIEW OF 150 CASES

	No. of Cases	
Mediastinal tumors	24	
Non-Hodgkin's lymphoma		16
Neuroblastoma		2
Ewing's sarcoma of rib		2
Hodgkin's disease		1
Malignant degeneration of bronchogenic cyst		1
Nonspecified malignant tumors		2
Ventriculoatrial shunt for hydrocephalus	8	
Congenital heart disease and cardiovascular surgery	106	
Mustard repair of transposition of great arteries		8
Superior vena cava to right pulmonary artery anastomosis		97
Repair of supradiaphragmatic total anomalous pulmonary venous connection		1
Mediastinal fibrosis	8	
Mediastinal histoplasmosis		7
Mediastinal granuloma		1
Miscellaneous	4	
Thrombosis of superior vena cava		3
Hydrocephalus		1
Total	150	

(Courtesy of Issa, P. Y., et al.: Pediatrics 71:337–341, March 1983. Copyright American Academy of Pediatrics, 1983.)

number of cases of mediastinal fibrosis have been found to be due to *Histoplasma capsulatum*.

Surgical reconstruction of the superior vena cava often fails. The best material for use in replacing the superior vena cava has been reported to be autologous vein.

10–16 **Superior Vena Cava Syndrome in Childhood and Adolescence: Review of the Literature and Report of 3 Cases.** Obstructions of the superior vena cava (SVC) occur rarely in children and adolescents. Y. Janin, J. Becker, L. Wise, K. Schneider, D. Schwartz, and H. So discuss data on 175 children and adolescents with SVC obstruction and various features of the SVC syndrome (SVCS). Three of their own patients with SCVS secondary to mediastinal tumor are described.

The most common causes of SVCS in childhood and adolescence (Tables 1 and 2) are iatrogenic, secondary to cardiovascular surgery for congenital heart disease (Mustard's operation and Glenn's procedure); ventriculoatrial shunting for hydrocephalus; and SVC catheterization for total parenteral nutrition, monitoring, and fluid administration. The two main primary causes of SVCS in childhood and adolescence are mediastinal tumors and mediastinal granulomas.

(10–16) J. Pediatr. Surg. 17:290–295, June 1982.

TABLE 1.—IATROGENIC CAUSES OF SUPERIOR VENA CAVA SYNDROME IN CHILDHOOD AND ADOLESCENCE

Cause	No. of Patients	References
Cardio-Vascular Surgery		
(A) Mustard's operation for transposition of the great arteries	41	26–38
(B) Glenn procedure for cyanotic heart disease with decreased pulmonary blood flow	6	39–41
Ventriculo-Atrial Shunting for Hydrocephalus	42	26, 27, 37, 39 42–56
Catheterization of the Superior Vena Cava		
(A) For total parenteral nutrition	27	57–66
(B) For monitoring and fluid administration	6	67

(Courtesy of Janin, Y., et al.: J. Pediatr. Surg. 17:290–295, June 1982.)

TABLE 2.—PRIMARY, NONIATROGENIC CAUSES OF SUPERIOR VENA CAVA SYNDROME IN CHILDHOOD AND ADOLESCENCE

Cause	No. of Patients	References
Mediastinal Tumors	37	11–19, 24, 25, 68–71*
Mediastinal Granuloma	8	72–76
Idiopathic Thrombosis of SVC	2	77, 78
Congenital Anomalies of the Cardiovascular System	4	
(a) Right-sided pericardial defect	1	79
(b) Total anomalous pulmonary venous return and stenosis of the junction between the SVC and the right atrium	1	80
(c) Supra-diaphragmatic total anomalous pulmonary venous connection	1	43
(d) Aneurysm of the SVC	1	81
Hydrocephalus	1	82
Local Giant Growth of the Thecal Bone	1	83

*Patients described in the present series.

(Courtesy of Janin, Y., et al.: J. Pediatr. Surg. 17:290–295, June 1982.)

Lymph node tumors account for 70% of the mediastinal tumors and half of these are lymphosarcomas.

Symptoms include headache, nausea, dizziness, fullness in the ears, mental lethargy, distortion of vision, syncope, hoarseness, stridor, stupor, respiratory distress, and, occasionally, chest pain, cyanosis, unconsciousness, and convulsions. Signs include dilatation of veins of the face, neck, upper extremities, and upper torso; skin with a cyanotic, flushed or violet hue; and suffusion and edema of the conjunctiva, with or without proptosis. All symptoms intensify when the patient bends forward or is recumbent. Although caval compression may by asymptomatic early in its course, complete blockage can develop suddenly nonetheless. A working diagnosis must be established at once so vigorous treatment to reduce the constricting masses can be started. Even when investigative procedures are not conclusive, therapy should begin without cellular diagnosis. Cervical mediastinal exploration is dangerous because manipulation of tissues around the SVC may prompt respiratory compromise or massive hemorrhage through injury to the dilated collateral veins. Tumor-induced SVCS can be relieved within 24–72 hours by rapid high-dose irradiation without producing radiation edema. With lymphoma, chemotherapy may be as effective. With lymphosarcoma, combined radiotherapy, chemotherapy, and steroids produced faster results than sequential use of the regimen. Because obstruction may be caused by thrombosis of the compressed SVC, anticoagulant should be added to the therapeutic regimen.

▶ [Two articles that deal with the superior vena cava syndrome in childhood and adolescence were selected for inclusion here in the YEAR BOOK. This was done to impress you doubly with the importance of this syndrome. As this second article states, the most common causes of the superior vena cava syndrome in childhood are iatrogenic, secondary to surgical procedures for heart disease or secondary to manipulation of the vena cava system in the chest for placement of shunts in patients with hydrocephalus or the presence of indwelling venous catheters for total parenteral nutrition. If you subtract out these causes, the next most common cause (and probably actually the most frequent) that you will run into in your practices is malignancy in the thorax. Bulky anterior mediastinal tumors that compress the trachea and the great vessels can lead to the superior mediastinal syndrome. Findings of this syndrome include syncope, dyspnea, orthopnea, stridor, and cyanosis. There also may be venous engorgement, edema of the head and neck, and increased intracranial pressure, all life-threatening. Many of these children will present in very significant distress because of compression of the trachea or the great vessels. Associated with masses causing these problems, there is great risk accompanying the use of anesthesia, and some investigators have suggested that vigorous treatment with either radiation therapy or corticosteroids should be instituted in symptomatic patients before a histologic diagnosis is obtained. Unfortunately, even a short course of corticosteroids or radiation can obscure a diagnosis, with potentially disastrous complications. Any oncologist worth his or her salt obviously would like to have a histologic diagnosis before being committed to a long course of blind therapy. For a thorough discussion of the pros and cons of the optimal way of going about getting a histologic diagnosis in children with symptomatic anterior mediastinal masses, see the fine report by S. Halpern et al. (*J. Pediatr.* 102:407, 1983).—J.A.S., III] ◀

11. Endocrinology

11–1 **Prognosis of Impaired Glucose Tolerance in Children With Stress Hyperglycemia, Symptoms of Hypoglycemia, or Asymptomatic Glucosuria.** Both asymptomatic and symptomatic disorders of glucose metabolism are heterogeneous in children. Arlan L. Rosenbloom and Sarah S. Hunt (Univ. of Florida, Gainesville) followed up 37 of an initial group of 68 subjects, aged 1½–20½ years: 3 with stress hyperglycemia, 21 with asymptomatic glucosuria, and 13 with symptoms suggestive of hypoglycemia. Seventeen met the National Diabetes Data Group criteria for impaired glucose tolerance.

Impaired glucose tolerance was found in 8 patients with glucosuria, 1 with hyperglycemia, and 8 with symptoms of hypoglycemia. Symptomatic insulin-dependent diabetes developed in 3 patients with glucosuria during the 14 months after initial testing. Compared with subjects with normal test results or those with impaired glucose tolerance who did not become insulin dependent, these 3 patients had more severe hyperglycemia or deficient insulin responses or both. Insulin responses relative to glycemia were age-related and did not distinguish the subjects with impaired glucose tolerance, except for those who became insulin dependent. Most subjects with normal test results but fewer than a third of those with abnormal test results had a history of diabetes in first- or second-degree relatives.

The 2-hour oral glucose tolerance test may be of use in assessing young persons with stress hyperglycemia or asymptomatic glucosuria to rule out abnormality or detect preclinical insulin-dependent diabetes. Patients with autonomic symptoms may exhibit transitory intolerance as a response to life stress; therefore, glucose tolerance testing is not warranted in the absence of other important symptoms or a family history of insulin-dependent diabetes. Such patients are currently being taught home blood glucose monitoring so that they or their parents can confirm that symptoms are not related to hypoglycemia.

▶ [Dr. Thomas Moshang, Jr., Associate Professor of Pediatrics and Director of the Endocrine Clinics, Children's Hospital of Philadelphia, comments:

"In this study, Rosenbloom and Hunt observed impaired glucose tolerance in a significant number of children who were evaluated by an oral glucose tolerance test (OGTT) because of asymptomatic glycosuria, stress hyperglycemia, or symptoms suggestive of hypoglycemia. Rosenbloom and Hunt suggested that the OGTT may be useful to rule out abnormalities or to detect patients with preclinical insulin-dependent diabetes mellitus. The problem is that often "abnormalities" cannot be ruled out because of the frequency of "impaired glucose tolerance." But what does "impaired glucose tolerance" mean? It almost certainly does not mean pre-diabetes mellitus (type I). In attempting to rule out an abnormality and then discovering "impaired glucose tolerance," one then has the difficult task of explaining to parents that the significance of the abnormal glucose tolerance test is not known.

(11–1) J. Pediatr. 101:340–344, September 1982.

"The OGTT is not necessary in order to diagnose insulin-deficient diabetes mellitus. Patients with incipient diabetes mellitus, such as the 3 patients of Rosenbloom and Hunt who developed symptomatic insulin-dependent diabetes within a short time after their OGTT, can be distinguished from patients with stress hyperglycemia, renal glycosuria, or drug-induced hyperglycemia by frequent blood glucose, urine glucose, and urine acetone monitoring. One of the most frequent reasons for referral of patients to endocrinologists is because of a possible abnormal glucose tolerance test. Often, the "abnormal results" are variations of normal. The OGTT, in my experience, is not useful in diagnosing clinical disorders of carbohydrate metabolism of childhood. In my own mind, the OGTT is a huge trap that should be avoided."] ◄

11–2 **Transient Congenital Hypoparathyroidism: Possible Association With Anomalies of the Pulmonary Valve.** Eight children were evaluated for suspected DiGeorge's syndrome by Lawrence E. Mallette, James B. Cooper, and John L. Kirkland (Houston). The evidence of DiGeorge's syndrome was unequivocal in 4. Each had nondetectable immunoreactive parathyroid hormone (iPTH) despite profound hypocalcemia; 3 of these 4 patients died before reaching age 2.

The second 4 patients had only some of the features of DiGeorge's syndrome. Each had a congenital cardiac defect involving the pulmonary valve. At 2–3 weeks, each had symptomatic hypocalcemia and hyperphosphatemia. In 3 of the 4 patients, the serum phosphate concentration was less elevated than in the patients with DiGeorge's syndrome; the iPTH initially was in the borderline detectable range in all. Response to intravenous and oral calcium administration was satisfactory, and treatment with vitamin D congeners was not necessary. That the degree of hyperphosphatemia was less in these patients than in patients with severe hypoparathyroidism, that these patients responded readily to oral calcium supplements alone, and that the iPTH was borderline detectable all might have suggested that normal parathyroid function eventually would develop. Delayed appearance of parathyroid function could indicate parathyroid hypoplasia, rather than aplasia, analogous to the thymic hypoplasia sometimes seen with DiGeorge's syndrome. Recovery of parathyroid function leaves these patients with only their cardiac and somatic anomalies to suggest DiGeorge's syndrome.

The strength of the association between pulmonary valve lesions and delayed maturation of parathyroid function is not clear at this time, and further study will be necessary to clarify this point and to search for possible causes.

► [Congenital hypothyroidism may be permanent or transient. The cases reported here were of the transient variety and were seen in association with abnormalities of the pulmonary valve. It is not clear whether these patients should be considered to have a partial form of DiGeorge's syndrome or a separate entity. One could consider the delayed appearance of normal parathyroid function to indicate parathyroid hypoplasia rather than aplasia. Nonetheless, the 4 patients did have parathyroid dysfunction and a cardiac anomaly that, at least superficially, suggests DiGeorge's syndrome. For right now, it may be best to set these cases aside for a year or so, while waiting to see what other people's experiences have been (the patients in this study had absent pulmonary valves, pulmonary stenosis, or tetralogy of Fallot).—J.A.S., III] ◄

(11–2) J. Pediatr. 101:928–931, December 1982.

11–3 **Association of the DiGeorge Anomalad With Partial Monosomy of Chromosome 22.** Recently, de la Chapelle et al. described a family with 3 siblings and a paternal cousin in which the DiGeorge anomalad segregated with an unbalanced chromosomal rearrangement producing partial duplication of chromosome 20(pter→q11). Richard I. Kelley, Elaine H. Zackai, Beverly S. Emanuel, Mildred Kistenmacher, Frank Greenberg, and Hope H. Punnett (Philadelphia) describe 3 unrelated patients (and briefly present a fourth) in whom the DiGeorge anomalad was associated with the same deletion of chromosome 22.

Findings in the 3 patients are compared with those reported by de la Chapelle (table). All patients showed evidence of conotruncal-great vessel malformation, absent or hypoplastic thymus, and hypocalcemia or absent parathyroids. Karyotypes showed deletions of 22pter→q11 and 10q26→qter in the first patient and her father. The second infant had a derivative chromosome 3 with normal parental karyotypes. In the third, a missing chromosome 22 was consistent with malsegregation of a 20;22 translocation. The mother appeared to carry a balanced 20;22 translocation. The patient cited in the addendum showed an identical deletion of chromosome 22 in a mother and her son. Two other sons had died at 1 and 4 months with congenital heart disease and with truncus arteriosus and missing thymus and parathyroids, respectively.

The discovery of the 22pter→q11 deletion associated with the classic DiGeorge anomalad in four separate families and involving translocations with three different autosomes is substantial evidence that

FINDINGS IN PATIENTS WITH DIGEORGE'S ANOMALAD AND MONOSOMY 22pter→q11

	This report			*de la Chapelle et al*[18]			
	Patient 1	*Patient 2*	*Patient 3*	*III-12*	*III-17*	*III-18*	*III-23*
Sex	F	M	M	F	M	F	M
DiGeorge anomalad							
Heart	Truncus VSD	TGA, VSD PA, RAA	TGA, VSD DORV, PS	DAA VSD	Truncus VSD, AR	IAA VSD	TGA VSD
Thymus	↓ T cells	absent	Cervical remnants	Absent	Absent	Absent	Absent
Parathyroids	Hypocalcemia	Absent	Absent	?	Absent	Absent	?
Other defects							
Cleft lip +/or palate	–	+	–	+	–	+	+
Bifid uvula	+	+	–	–	–	–	–
Malformed ears	–	+	+	+	–	+	–
Hypertelorism	–	–	–	–	–	+	–
Dysplastic/cystic kidneys		–	+	–	+	+	+
Jejunal web	+	–	–	–	–	–	–
Malformed lungs		–	+	–	+	–	–
Additional chromosomal defects	$10q^-$	$3q^-$	$20p^+$	$20p^+$	$20p^+$	$20p^+$	$20p^+$

IAA, interrupted aortic arch; PA, pulmonary valve atresia; PS, pulmonic stenosis; RAA, right aortic arch; TGA, transposition of the great arteries; VSD, ventricular septal defect; DAA, double aortic arch; AR, aortic ring; DORV, double-outlet right ventricle.

(Courtesy of Kelly, R. I., et al.: J. Pediatr. 101:197–200, August 1982.)

(11–3) J. Pediatr. 101: 197–200, August, 1982.

the deletion causes the condition. The 3 patients described here are the only ones in whom the authors have found chromosomal abnormalities. However, reexamination of karyotypes or focused karyotyping for the specific defect may lead to discovery of a significant association, such as has occurred in aniridia-Wilms' tumor, retinoblastoma, and possibly with the Prader-Willi syndrome.

► [As a reminder, the DiGeorge anomalad is a developmental field defect of the third and fourth pharyngeal pouches characterized by an absent or hypoplastic thymus, absent or hypoplastic parathyroids, and a great vessel and conotruncal cardiac malformation. In some patients there are additional findings of a dysmorphic face, hypertelorism, cleft lip and palate, bifid uvula and low-set ears. In the 17 years since the recognition of the DiGeorge anomalad as a unique malformation complex, there have been a few reports of chromosomal abnormalities associated with one or more of the cardinal manifestations of this syndrome. The discovery reported above of the same chromosomal abnormality (partial monosomy of chromosome 22) in four separate families is substantial evidence for deletions of this chromosome causing the DiGeorge anomalad. What isn't clear is how frequently this precise relationship exists. In Philadelphia, where this study was done, of the 6 patients who had complete karyotyping with banding who also had DiGeorge's syndrome, 3 were found to have the partial monosomy of chromosome 22.

We probably will be hearing more about this relationship in the future now that we have been made more aware of it. Obviously, the more you look, the more you will find. This was the situation with aniridia-Wilms' tumor, where deletions of chromosome 11 frequently can be found; with retinoblastoma and deletions of chromosome 13; and with Prader-Willi syndrome and defects of chromosome 15.—J.A.S., III] ◄

11–4 **Primary Hyperparathyroidism in Children, Adolescents, and Young Adults.** Maria Allo, Norman W. Thompson, Jay K. Harness, and Ronald H. Nishiyama (Univ. of Michigan, Ann Arbor) report the findings in 53 patients younger than age 30 with proved primary hyperparathyroidism (HPT) seen from 1971 to 1980.

There were 30 male and 23 female patients; nearly one-third had symptoms before age 18 years. Among patients older than age 18, the sex ratio was 2 males to 1 female. Common symptoms included hematuria and renal colic (50%), renal calculi (50%), and hypertension (17%); two thirds of the hypertensive patients had headache as the primary symptom. Nonspecific complaints of weakness, fatigue, and malaise were reported by one third of the patients. There was objective weight loss in about half of the patients with nonspecific symptoms. Bone changes occurred in only 3 patients (6%). Five patients were asymptomatic at the time of diagnosis.

Among the entire group, two thirds of the patients had parathyroid adenomas and the remainder had chief cell hyperplasia. Among patients younger than age 18 years, 47% had adenomas and 53% had hyperplasia. No adenomas were seen in prepubertal girls, and only 2 boys younger than age 16 had adenomas. Among patients older than age 18, 77% had adenomas and 23% had hyperplasia. Twice as many male patients older than age 18 had adenomas as did female patients (the opposite of what one would expect in the total adult population). The incidence of hyperplasia was equal among male and female patients of all ages.

The table lists associated diseases. One child had hereditary neo-

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(11–4) World J. Surg. 6:771–776, November 1982.

DISEASES ASSOCIATED WITH HYPERPARATHYROIDISM IN YOUNG PEOPLE

Disease	No. of patients
MEA I syndrome	6
MEA II syndrome	4
Neurofibromatosis	1
Papillary carcinoma of thyroid	1
Craniopharyngioma	1
Metaphyseal chondromatosis	1
Fibrous dysplasia of the jaw	1
Familial solitary adenoma [12]	2
Kallmann's syndrome	1

(Courtesy of Allo, M., et al.: World J. Surg. 6:771–776, November 1982.)

natal parathyroid hyperplasia. The approach to patients with multiple endocrine adenomatosis type II differs from that to patients with hyperplasia due to other causes. Only the enlarged glands are removed, even in patients who are asymptomatic at the time of thyroidectomy for medullary carcinoma of the thyroid.

Primary HPT is more common in young people than previously suspected. Symptoms of renal stones, hypertension, persistent headaches, unexplained anorexia and weight loss, irritability, fatigue, malaise, or constipation that cannot be ascribed to some other cause should prompt evaluation for primary HPT. If hyperplasia is found, the patient and family should be investigated for associated endocrinopathies.

▶ [Primary hyperparathyroidism has only rarely been reported in children and is unusual in teenagers and young adults. I don't know whether the incidence of this is gradually increasing or not; however, if you look back through the literature and the reviews that have appeared, you see a fairly significant change in the past decade. To collar this for you, the first cases were reported in 1930. By 1970 there were only 43 documented cases in the world's literature. By 1975 this number had increased to 60 cases. By 1982, when the largest single review appeared in the literature (Garrard, R. M., et al.: *Can. J. Surg.* 25:11, 1982), 86 documented cases of hyperparathyroidism in childhood could be tracked down in the world's literature. Garrard et al. found that of these patients, 17 had disease in the neonatal period (all had parathyroid hyperplasia), 1 had familial hyperparathyroidism, 68 had no known genetic condition, 54 had adenomas, 3 had hyperplasia, and in 11 no pathologic findings were reported. This study by Allo et al. from Ann Arbor is remarkable in that it is, as far as I am aware, the largest single experience within one institution in terms of numbers of patients. These cases were all evaluated within the past 13 years and the uniqueness of this series is that it allows a perspective in one institution where the approaches obviously are very much the same. Curiously, the frequency of hereditary neonatal hyperplasia was remarkably low in the Ann Arbor experience. The most striking feature of this report is the extremely high incidence of associated conditions of the type known as the multiple endocrine adenomatosis syndromes. Overall, two thirds of the patients had adenomas and one-third had hyperplasia of the parathyroids. Treatment of adenomas is simply to remove them, whereas treatment of hyperplasia depends on the presence or absence of associated problems. For example, in patients who have idiopathic hyperplasia, it is usually best to remove 3½ of the 4 parathyroid glands. For patients who have hyperplasia in association with multiple endocrinopathies, these authors suggest removing only the enlarged glands. A more extensive surgical removal in the latter group of patients invariably resulted in permanent hypocalcemia, in the authors' experience.

It's easy to make a diagnosis of hyperparathyroidism when the patient presents with renal colic. We are all trained to do a certain battery of tests in patients who have renal stones. The more difficult diagnostic dilemma is that of the child who has much more subtle symptoms of anorexia, irritability, weight loss, fatigue, or constipation. I would suspect that the diagnoses in most of these children are thought of only after a nonspecific panel of chemistry assays shows an elevated calcium level. This is one of the few reasons why I like chemistry profiles.

Although this has little to do with the study under discussion, I think that the readers of the YEAR BOOK should be aware that cimetidine should be used with extraordinary caution in patients who have pseudohypoparathyroidism. These patients seem to be extremely sensitive to hormone receptor antagonists such as cimetidine. A 16-year-old girl with pseudohypoparathyroidism accidentally ingested a relatively small quantity of cimetidine. Within 4 hours she was extraordinarily agitated and somnolent and had slurred speech and dilated pupils (Rushton, A. R., et al.: *Ann. Intern. Med.* 98:677, 1983). I almost want to apologize to the manufacturers of cimetidine. It seems that every comment concerning this drug in the YEAR BOOK tends to be negative. I can't remember when we said something particularly terrific about it. When you are dealing with a drug that has such a complex mechanism of action, it seems obvious that it will come under the gun quite frequently. Many things in life are obvious; remember the last time you walked into a movie theater and they were selling granola bars instead of Juicy Fruits? It was a good bet—wasn't it?—that they'd be showing a movie with subtitles and a lot of rain in it.—J.A.S., III] ◄

11–5 **Solitary Thyroid Nodules in Children and Adolescents** require the physician to rule out the presence of malignancy. Such nodules are rare; in one series of children aged 1–18 years, the incidence was 1.8%. Appropriate evaluation and management have been controversial. Wellington Hung, Gilbert P. August, Judson G. Randolph, Richard M. Schisgall, and Roma Chandra (Washington, D.C.) describe 39 patients aged 3–15 years with solitary nodules; 31 were girls. All were clinically euthyroid. None had a history of receiving goitrogens or of exposure to external irradiation. In 5, one or both lobes of the thyroid gland were enlarged. The 5 patients with cancer as well as 9 patients with benign lesions had firm or hard nodules. Cervical lymphadenopathy was present in 2 with carcinoma and 6 with benign lesions. Patients with chronic lymphocytic thyroiditis all had positive antithyroid antibody determinations. The patient with medullary carcinoma had elevated serum calcitonin levels. Thyroid scintiscan was done using ^{123}I or ^{99m}Tc. Patients with cold nodules had chest x-ray studies. Ultrasonography in 17 patients with cold nodules showed 9 patients with a cyst or cystic component. In 27 patients, the nodule was cold; in 3, warm; and in 9, hot.

All patients with cold nodules had surgical excision with no attempt to decrease the nodule size, whereas patients with warm or hot nodules had thyroid hormone suppression therapy for at least 4 months before biopsy. Three warm nodules either failed to decrease or increased in size and were excised. Five of the 9 hot nodules were excised; the other 4 patients elected to be observed indefinitely.

Histologic diagnosis of the excised nodules is shown in the table. No complications and no deaths occurred. Five patients, all with cold nodules, had carcinomas; 3 of these patients were boys (60%) although only 22.9% of the entire series were boys.

Histologic diagnosis is the only reliable diagnostic tool for distinc-

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(11–5) J. Pediatr. Surg. 17:225–229, June 1982.

HISTOLOGIC DIAGNOSIS IN 35 PATIENTS WITH SOLITARY THYROID NODULE

Diagnosis	Number of Patients	
Follicular adenoma	24	(68.6%)
Carcinomas	5	(14.3%)
Chronic lymphocytic thyroiditis	3	(8.6%)
Intrathyroidal thyroglossal duct cyst	2	(5.7%)
Colloid cyst	1	(2.8%)

(Courtesy of Hung, W., et al.: J. Pediatr. Surg. 17:225–229, June 1982.)

tion of benign from malignant solitary nodules. Laboratory evaluation and scintiscan can distinguish the patients with ectopic thyroid tissue and the hot toxic nodule. After abnormalities in development of the thyroid anlagen, or in migration of the thyroid gland have been ruled out, or after antithyroid therapy in patients with a hot toxic nodule, surgical removal should be done.

▶ [Determination of the etiology of a solitary nodule of the thyroid is obviously difficult. The first step is a careful history to rule out any goitrogen ingestion and to determine if the patient has received irradiation to the head, neck, or chest. The physical examination also can be partially helpful. A soft compressible well-circumscribed nodule is not likely to be malignant; it is more likely to be a colloid or adenomatous cyst. Tenderness suggests an inflammatory process. Thyroid malignancy should be suspected if the nodule is hard, fixed, or is associated with palpable lymph nodes in the area or vocal cord paralysis. You see the authors of this article referring a lot to warm, hot, or cold nodules. A warm nodule is one in which radioisotope concentration on thyroid screening is similar to the concentration in the remainder of the thyroid gland. A hot nodule is one in which the isotope is more concentrated in the nodule than in the rest of the gland, and obviously a cold lesion is one that does not pick up the radioisotope significantly at all. A hot nodule may represent a follicular adenomatous goiter, hyperplasia, chronic lymphocytic thyroiditis, a colloid goiter, or, rarely, a carcinoma. Although technetium scanning provides less radiation exposure to the thyroid, a carcinoma occasionally may appear as a hot nodule with this technique, whereas radioactive iodine scanning produces a cold nodule on scintiscanning of the thyroid. It obviously is necessary to follow up every hot nodule scan performed with technetium with a scan with radioactive iodine. Some hot nodules can be suppressed with thyroid hormone, obviating the need for surgical treatment in many instances. A cold nodule presents the greatest clinical problem in differentiating malignant from benign lesions. Cold nodules may be found in chronic lymphocytic thyroiditis, cysts, follicular adenomas, abscesses, carcinomas, and embryonic defects such as intrathyroidal thyroglossal duct cysts. Clinical criteria suggestive of thyroid cancer include a history of exposure to radiation, rapid growth of the nodule, a hard nodule, fixation of the nodule, presence of adenopathy, cord paralysis, as mentioned above, and an abnormal chest x-ray film. A medullary carcinoma should be suspected in any patient who presents with multiple mucosal neuromas, appearing as whitish nodules on the tongue, lips, or palpebral conjunctiva. Many of these patients will have a marfanoid body build. We should all remember that medullary thyroid carcinomas occur in association with pheochromocytoma and hyperparathyroidism (multiple endocrine neoplasia, type II).

There are other tests you can do in addition to routine thyroid chemistries and thyroid scans in working up a patient with thyroid nodules. You can do a sonogram of the neck that helps to tell cystic from solid lesions. Cystic lesions of the thyroid generally are considered to be benign. You can attempt to suppress the size of the gland with thyroid hormones. Malignancies rarely respond to this form of management. Of course, autonomous nonmalignant nodules would not respond either.

Despite all this discussion, I tend to favor the final recommendations of these au-

thors. They say that in their experience the only reliable diagnostic tool for totally accurate distinction of benign from malignant solitary nodules of the thyroid is histologic examination. Every other test has some limitations to its usefulness. Their final recommendation is for surgical removal of all thyroid nodules after abnormalities in the development of the thyroid or in migration of the thyroid gland have been ruled out. This is one of the times that I believe in the surgical dogma of: "When in doubt, cut it out."—J.A.S., III] ◄

11–6 **Vasculitis, Pulmonary Cavitation, and Anemia During Antithyroid Drug Therapy.** Antithyroid drugs are often the preferred initial treatment of juvenile thyrotoxicosis, but they can produce toxic side effects that may be serious. Fernando G. Cassorla, David N. Finegold, John S. Parks, Alfred Tenore, Hasina Thawerani, and Lester Baker (Children's Hosp. of Philadelphia) describe two thyrotoxic girls who had serious, quite similar illnesses during antithyroid drug therapy.

Girl, 9, was seen for emotional lability, tremor, and weight loss, and hyperthyroidism, with mild exophthalmos, was diagnosed. Methimazole was given in a dosage of 40 mg daily for 18 months without significant improvement. Propylthiouracil then was given in a dosage of 300 and later 450 mg daily, but the goiter remained large and the serum triiodothyronine concentration was 350 ng/dl. After 18 months the dosage was increased to 600 mg daily in preparation for thyroidectomy, and iodine solution was given. A purpuric rash developed on the legs. The hemoglobin concentration fell markedly to 5.3 gm/dl in a short time, with no evident acute blood loss. Propylthiouracil was discontinued. Coombs tests were negative. Hematuria was present and resolved on treatment with 80 mg of prednisone daily. The serum IgM concentration was elevated at 2.1 mg/dl. Antinuclear antibody tests were transiently positive. A skin biopsy showed a lymphocytic infiltrate surrounding dermal vessels, and swollen vascular endothelium. The vessels in the upper corium stained weakly for IgG, IgM, and IgA.

The patient was given 11 mCi of ^{131}I. Findings of pneumonia developed and failed to respond to treatment with several antibiotics. A large cavitation was found after hemoptysis occurred (Fig 11–1). Multiple cultures were neg-

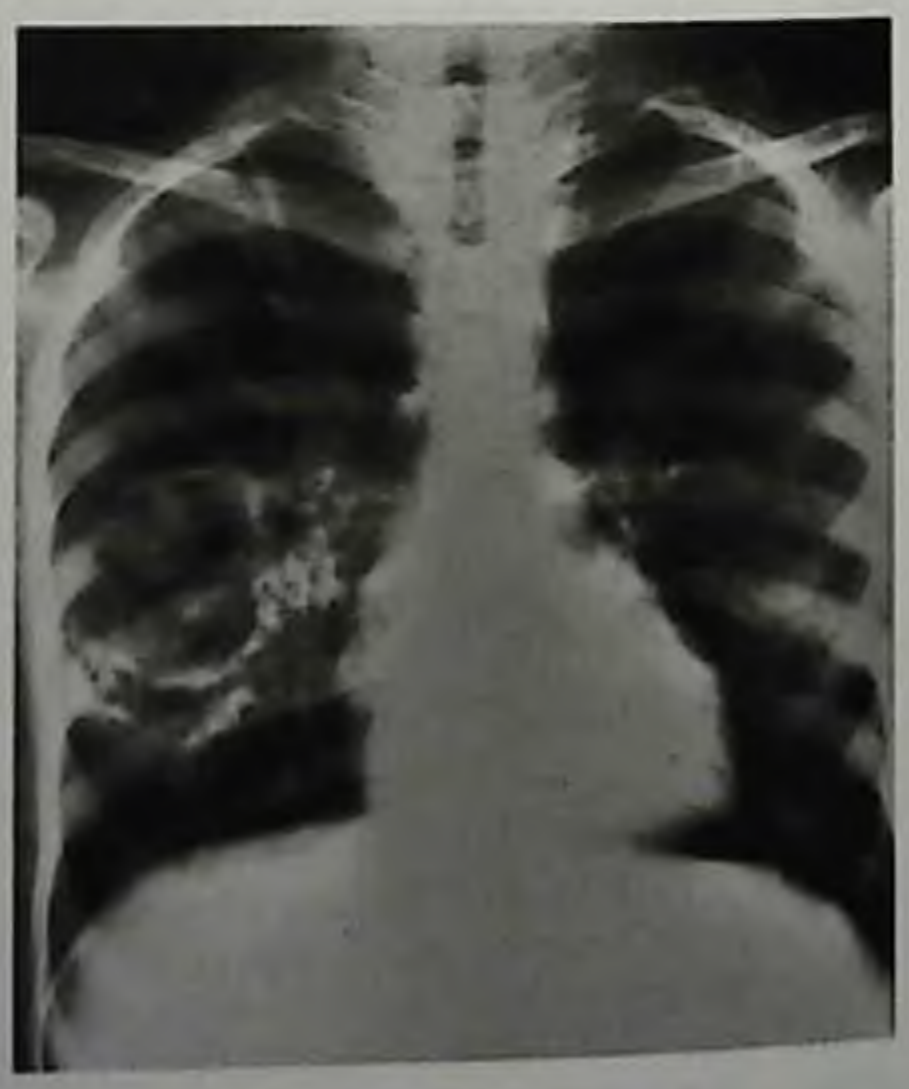

Fig 11–1.—Cavitary lesion in right lower lobe. (Courtesy of Cassorla, F. G., et al.: Am. J. Dis. Child. 137:118–122, February 1983; copyright 1983, American Medical Association.)

(11–6) Am. J. Dis. Child. 137:118–122, February 1983.

ative. The patient improved and was discharged taking 40 mg of prednisone daily and iron replacement. Corticosteroid therapy was continued for 6 months. The patient remained euthyroid with no evidence of persistent anemia, nephritis, or pulmonary parenchymal disease.

The role of propylthiouracil in the severe illness was less clear in the second patient, who had evidence of selective IgA deficiency. Major reactions to antithyroid drugs appear to be infrequent, and they continue to be preferred for patients with juvenile thyrotoxicosis. Regular follow-up of treated patients is necessary, however, because toxic reactions can occur at any time. Both the authors' patients recovered.

► [Although patients taking antithyroid medications have developed purpuric skin rashes and migratory polyarthritis, the report of Cassorla et al. is the first to add to these problems pulmonary cavitation, hemoptyosis, and severe anemia. The thionamides (propylthiouracil and methimazole) are known to be bad actors when it comes to drug reactions. They commonly cause pruritus, skin rashes, urticaria, fever, arthralgia, and mild neutropenia. Infrequently, they cause agranulocytosis, erythema multiforme, polyarthritis, periarteritis, and a systemic lupus erythematosus-like syndrome. The cases reported above may not be due unequivocally to the antithyroid medications. These patients were taking iodine, which also might cause the same problem. One of the patients was also IgA deficient. Patients with IgA deficiency, of course, can have a higher incidence of respiratory tract infections. They also are known to develop all kinds of autoimmune phenomenon, including hemolytic anemias and immune thrombocytopenia. Despite these reservations, the data reported in this article are sufficiently worrisome that we should keep them in mind as being potential problems for patients receiving propylthiouracil or methimazole. If we start seeing additional similiar case reports, they may even influence our decision to use antithyroid medication when other forms of treatment that would not be associated with these problems also exist (^{131}I).—J.A.S., III] ◄

11–7 **Thyroid Function Tests in Neonates Fed Human Milk.** Human milk contains small amounts of thyroid hormone, the physiologic significance of which is uncertain. Henry B. Hahn, Jr., A. Michael Spiekerman, W. Randy Otto, and Doris E. Hossalla (Temple, Texas) compared serum thyroid hormone concentrations in breast-fed and formula-fed infants aged 2 to 3 weeks. Twenty-two breast-fed infants

RESULTS OF THYROID FUNCTION TESTS (MEAN VALUES)

	Breast-fed Infants (n=22)	Formula-fed Infants (n=25)	P	Normal Adults
Thyroxine, μg/dL	13.11	11.84	<.005	5.0-11.5
Triiodothyronine, ng/dL	224.2	179.4	<.0005	100-200
Triiodothyronine-resin uptake, %	37.36	37.72	>.25	35-45
Thyroid-stimulating hormone, μU/mL	5.86	5.28	>.10	2-15
Thyroxine-binding globulin,* mg/L	14.15	13.79	>.5	10-30

*For these values, n = 20 for breast-fed group and n = 21 for formula-fed group.
(Courtesy of Hahn, H. B., et al.: Am. J. Dis. Child. 137:220–223, March 1983; copyright 1983, American Medical Association.)

(11–7) Am. J. Dis. Child. 137:220–222, March 1983.

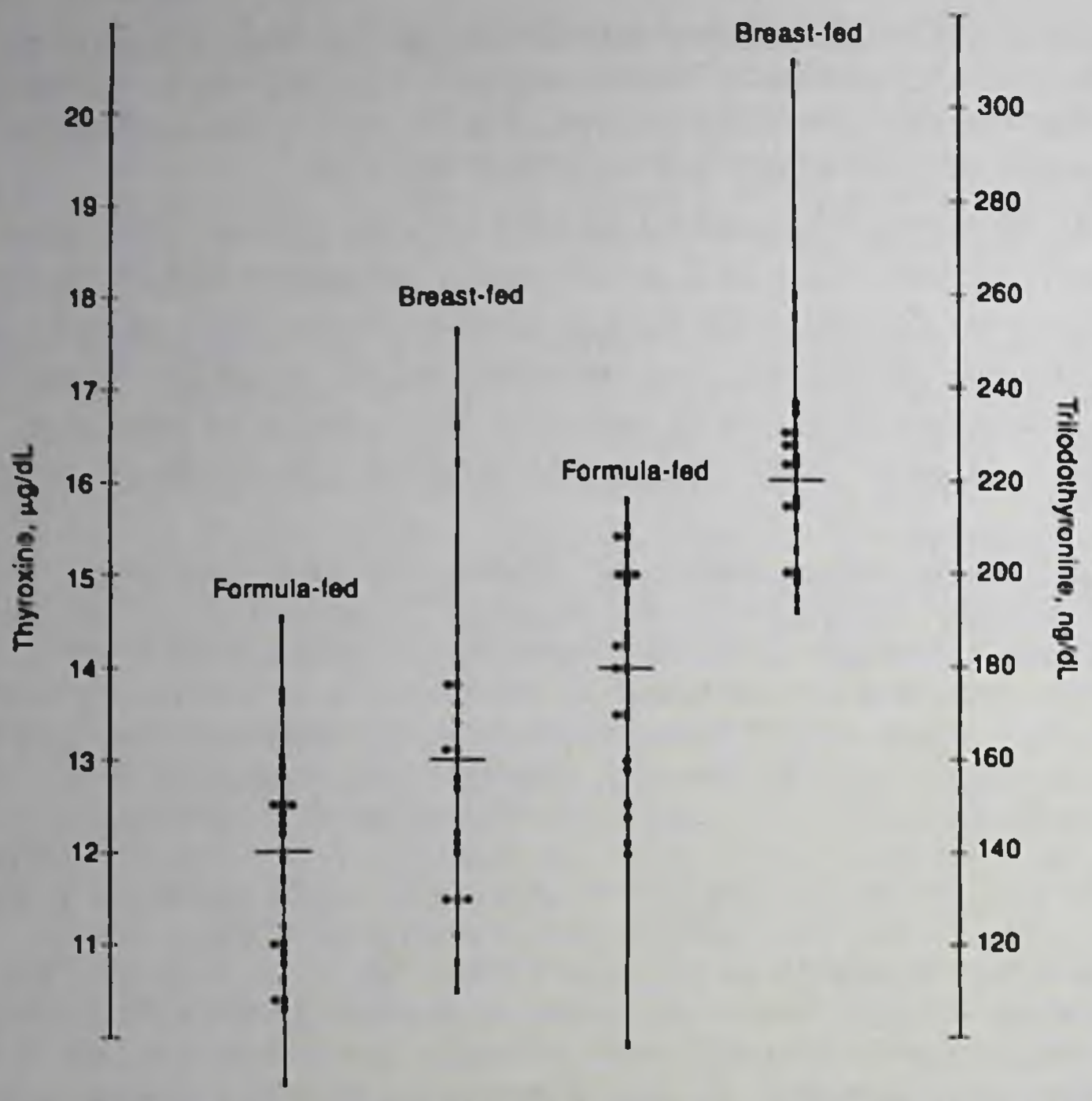

Fig 11–2.—Distribution of serum T_4 and T_3 concentrations in formula-fed and breast-fed neonates. Note skewed distribution. (Courtesy of Hahn, H. B., Jr., et al.: Am. J. Dis. Child. 137:220–222, March 1983; copyright 1983, American Medical Association.)

with a mean age of 17.5 days and 25 formula-fed infants with a mean age of 16.5 days were studied. All were term infants and were healthy. Their mean birth weights did not differ significantly.

The mean thyroid function test results are given in the table, and the distribution of serum thyroxine (T_4) and triiodothyronine (T_3) values is shown in Figure 11–2. Serum T_4 and T_3 concentrations were significantly greater in breast-fed than in formula-fed infants. Within the breast-fed group, concentrations were comparable in infants aged 17 days and younger and in older infants and in male and female infants.

Elevated T_3 concentrations in breast-fed infants was the chief finding in this study. If healthy breast-fed infants have higher serum T_3 concentrations than formula-fed infants, the same should be true of hypothyroid infants. The physiologic effect of T_3 elevation in healthy infants and hypothyroid infants, if any, remains to be elucidated.

▶ [I had thought the business of looking at thyroid hormones in breast milk was a dead issue. It may be a dead issue, but apparently it has not been buried yet. You will recall from previous discussions in the YEAR BOOK that about 3 years ago it was theorized that the small quantities of thyroid hormone present in breast milk might be protective against neurologic damage in infants with congenital hypothyroidism. This theory subsequently came under much attack, and most follow-up studies indicated that the amounts present in breast milk were so trivial, or nonexistent, that there was no way that such passively transmitted hormone could be protective of anything. With a failure in this regard as a background, for some reason Hahn et al. decided to look at what the consequences of breast-feeding would be on thyroid function, not of hypothyroid babies, but of normal babies. They did find slightly elevated levels of T_4

in breast-fed babies compared to formula-fed babies. The same was true, but to a greater extent, for T_3. There was sufficient overlap of T_4 values between the two groups to suggest that the T_4 differences would be expected to have little or no physiologic significance. A more interesting finding was the elevated T_3 concentrations, but, again, the significance of this would be totally speculative. There obviously is no way of knowing why these differences exist between breast-fed and formula-fed babies. There also is no evidence to document that the hormones present in breast milk accounted for these differences.

The only reason why T_3 is of any interest during this past year relates to its suggestive role in sudden infant death syndrome (SIDS). Just 1 year ago at this time, a number of articles appeared discussing these issues. By way of background, 3 years ago it had been reported that a postmortem elevation of plasma T_3 levels could be found in infants dying of SIDS, compared with an autopsy control group and an age-matched control group of healthy infants. Peterson et al. (*J. Pediatr.* 102:206, 1982) reported that the average T_3 concentration of SIDS victims was significantly higher than that of both living and dead controls. They also looked at the neonatal screening values for T_3 and T_4 in SIDS victims. There, they could not show any difference. Lee et al. (ibid., p. 257) speculated that the elevated T_3 levels in both SIDS victims and autopsy controls might be caused by degeneration of T_3 after death. Schwartz et al. (ibid., p. 200), while finding elevated levels of T_3 in SIDS victims, showed that babies who had been healthy before they died also had elevated levels of T_3, but chronically ill infants had depressed levels of T_3 at autopsy. A. W. Root and W. K. Lee finally made some sense out of all this discussion in a commentary in the *Journal of Pediatrics* that followed these articles by a few months (ibid. 103:251, 1983). It was their conclusion that the bulk of data presently available indicate that (1) T_3 concentrations increase after death, most likely as a consequence of continued conversion of T_4 to T_3; (2) postmortem T_3 concentrations simply reflect the level of T_4 prior to death; (3) elevated postmortem T_3 levels are not specific for SIDS and are seen in anyone who has a normal or elevated T_4 level prior to death; and (4) premortem T_3 concentrations in no way predict the victims of SIDS.

This business of T_3 and SIDS is a classic example of stumbling across an observation that results in much chasing of one's tail. As far as the story of breast milk being protective of congenital hypothyroidism is concerned, I hope it is dead, buried, and in a sealed coffin. Unfortunately, I suspect that we will still see a few more unbelievable reports in this regard from people who did not read all the prior studies objectively. Some people just don't read scientific reports objectively, and when they think they do, they are merely rearranging their own prejudices.—J.A.S., III] ◀

11–8 **Preliminary Results on Mental Development of Hypothyroid Infants Detected by Quebec Screening Program.** Untreated patients with congenital hypothyroidism are characterized by neurologic and mental retardation. There is disagreement as to whether treatment begun before age 3 months leads to normal development. J. Glorieux, J. H. Dussault, J. Letarte, H. Guyda, and J. Morissette (Ste Foy, Que.) prospectively studied the mental development of infants discovered by screening to have congenital hypothyroidism and treated with sodium L-thyroxine from the mean age of 27 days.

The Griffiths developmental test (locomotor development, personal-social, hearing-speech, eye-hand coordination, and performance scales) was administered to 45 hypothyroid infants and 37 controls (matched for several variables) at age 12 months, to 77 hypothyroid and 41 control infants at age 18 months, and to 59 hypothyroid and 40 control children at age 36 months. The test given at 36 months included, besides the foregoing scales, a sixth scale measuring practical reasoning.

There were no significant differences in the various test scores be-

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(11–8) J. Pediatr. 102:19–22, January 1983.

tween the two groups at age 12 months. At 18 and 36 months, hypothyroid children had lower scores in hearing-speech, performance, and practical reasoning, which also decreased their global quotient. However, mean scores were still above 100, and only 9 were below 85. Significant correlations were found among serum thyroxine concentration at 3 weeks, bone age at 3 weeks (as an indirect biologic indication of the duration of hypothyroidism), and global quotient at 36 months. All 31 hypothyroid and 11 control children assessed at all three ages showed significant correlation between the scores at ages 18 and 36 months, suggesting that scores obtained at 18 months may have important predictive value.

Mental development at age 6 must be assessed before definitive statements can be made about the long-term mental development of hypothyroid infants in whom treatment is begun early. Infants with extremely low serum thyroxine concentrations and bone ages at diagnosis and below-mean developmental quotients at age 18 months may be at particular risk and may benefit from speech and occupational therapy and psychologic guidance.

▶ [The great unknown with newborn screening programs for detecting congenital hypothyroidism is whether these children will ever achieve totally normal neurologic status. The Quebec Network for Genetic Medicine has had its newborn screening program underway sufficiently long that we are beginning to see some of these answers. Our Canadian neighbors, as you know, have screened every newborn infant in Quebec for congenital hyperthyroidism since April 1974, using filter blood spot thyroxine (T_4) and thyroid-stimulating hormone (TSH) measurements. They are now reporting follow-up of these babies through age 3 years. What we see is that the average baby does have a normal IQ. About 20% have IQs below 85, however. Of some concern is the fact that a percentage of the children with normal IQs seem to have evidence of neurologic dysfunction on testing similar to what might be seen with the minimal brain dysfunction syndrome. The data in the latter regard seem too preliminary to make any convincing statements. In Canada, the average age of the start of treatment was just less than 1 month. It seems reasonable to say that the eventual mental status of congenitally hypothyroid infants depends on a variety of factors, including age at onset of therapy, adequacy of therapy, family IQ, family socioeconomic status, nature and severity of the thyroid defect, and age of the fetus at onset of the defect. The last variable we will never (presumably) have control of, and it is because of this that completely normal neurologic function in all of these children may be a goal that is never achievable.

One bonus of the neonatal screening programs for hypothyroidism is that babies with congenital nephrosis also may be detected. These babies generally tend to have low T_4 but normal TSH values. The T_4-binding globulin level would be expected to be low. This disorder is obviously more rare than congenital hypothyroidism, but it is nice to detect it as well.—J.A.S., III] ◀

11–9 **Short Stature Associated With Normal Growth Hormone and Decreased Somatomedin C Concentrations: Response to Exogenous Growth Hormone.** Children with short stature, decreased somatomedin C concentrations, and normal or elevated GH values who have growth responses to exogenous GH have been proposed to have a biologically inactive GH. G. M. Bright, A. D. Rogol, A. J. Johanson, and R. M. Blizzard (Univ. of Virginia) administered exogenous GH to two such patients, both prepuberal boys with low serum somatomedin C and normal GH concentrations. Both patients, aged 13½ and 7

(11–9) Pediatrics 71:576–580, April 1983.

years, had metabolic responses to human GH (hGH) and accelerated growth on long-term treatment. Linear growth was below normal both before and after GH administration. The patients had initial growth rates of 3.4 and 4.3 cm per year, respectively; both had a two-fold to threefold increase in growth velocity with 6 months of GH therapy. After treatment, the growth velocity reverted to subnormal values in both patients.

The short stature of these patients may be secondary to a biologically inactive GH molecule that is immunologically reactive or to decreased responsiveness of the cells producing somatomedin when exposed to usual concentrations of endogenous GH. Subresponsiveness presumably is overcome by increasing the circulating concentration of GH. The subresponsiveness, if present, might result from a circulating inhibitor of GH, abnormal GH receptors, a postreceptor defect in the somatomedin-producing cells, or an abnormally structured GH molecule. Somatomedin C should be measured as part of the complete evaluation of short stature in children and, if warranted, the response to exogenous GH should be determined.

11–10 **Growth Hormone-Dependent Growth Failure.** Teresa Frazer, James R. Gavin, William H. Daughaday, Richard E. Hillman, and Virginia V. Weldon (Washington Univ.) encountered 5 patients, resembling the 2 children previously described by Kowarski et al., who had high radioimmunoassayable growth hormone (GH) values, low basal somatomedin (Sm) bioactivity, and enhanced Sm generation in response to exogenous GH. A defective GH not causing Sm production was suggested. All the authors' patients were prepuberal when first seen. One had a diagnosis of Kenny syndrome. After evaluation and observation, the children received intramuscular injections of 0.1 unit of GH per kg three times weekly for 6 months. The dose then was raised to 0.2 unit per kg for 6 months more.

All 5 children had vigorous GH responses to arginine-L-dopa and an equally large spontaneous GH peak during sleep. Four children had a GH with reduced radioreceptor activity compared with radioimmunoassayable activity. Serum Sm bioactivity rose to normal after acute GH administration in all children. Growth velocities initially were below the 10th percentile. Growth rates increased with exogenous GH therapy in all patients but 1 and regularly declined when GH was discontinued. The child who failed to respond was the patient whose GH appeared to be capable of binding to the receptor.

The cause of GH-dependent growth failure is unclear, and it is likely that these patients are not homogeneous. They do release GH physiologically, and their cells appear to be responsive to exogenous GH. The findings are compatible with an abnormal endogenously produced GH, but an inhibitor of cellular binding of GH is a possibility. Evaluation of the Sm response to short-term exogenous GH administration may identify growth-retarded children who will benefit from GH treatment.

▶ [Dr. Robert Richman, Associate Professor of Pediatrics and Chief of the Division of Pediatric Endocrinology, State University of New York at Syracuse, comments:

(11–10) J. Pediatr. 101:12–15, July 1982.

"Progress in understanding the growth hormone-somatomedin axis in the past year has exceeded reasonable expectations. In my YEAR BOOK comment only 1 year ago, I had speculated that the hypothalamic growth hormone-releasing hormone (GHRH) would be found in the near future. Since then, a peptide with GHRH activity has been isolated from a pancreatic islet cell carcinoma. It has been purified to homogeneity, its structure determined, and a monoclonal antibody raised to it in vitro. Studies to date indicate that it is most likely identical to the hypothalamic GHRH. Clinical studies with synthetic GHRH already have begun in children. It would seem safe to predict that in the not-too-distant future we will be able to use GHRH not only for diagnostic purposes, but also to treat GHRH-deficient children. If an analogue was found that could be administered orally, this would obviate the trauma associated with receiving growth hormone injections three times a week.

"The controversy surrounding which children with short stature would benefit from therapy with human growth hormone has intensified. The article by Frazer et al., as in the one discussed in the 1983 YEAR BOOK, raises the provocative question as to whether there are some short children with normal growth hormone secretion who would benefit from growth hormone therapy. The children described by Fraser and colleagues had short stature, decreased height velocity, delayed skeletal maturation, and normal growth hormone secretion, but decreased somatomedin C levels. When they were given growth hormone acutely, somatomedin levels increased as they do in growth hormone-deficient children. Four of the 5 grew normally when treated for 1 year. The authors suggest several possibilities for the growth hormone-dependent growth failure in their patients. Further studies are needed to categorize the abnormalities of these patients.

"Even more intriguing are the findings of G. V. Vliet et al. (*Pediatr. Res.* 17:174A, 1983). They reported that some children with short stature who had normal growth hormone secretion and somatomedin C concentration grew normally when treated with exogenous growth hormone. These authors, contrary to Fraser et al., did not find that the somatomedin response to acute administration of growth hormone correlated with the long-term growth response to growth hormone therapy.

"Clearly, further research is necessary to define which children are reasonable candidates for therapy with human growth hormone. With the expected abundant supply of growth hormone synthesized by the technique of recombinant DNA, we should be able to treat all children who would benefit with an increase in height velocity when given the hormone. However, we must first systematically identify who these children are. We must know whether the increase in height velocity stimulated by growth hormone is sustained throughout childhood as long as the hormone is given. We also must determine if the final adult height of such treated children is increased or whether they reach their ultimate stature at an earlier age. Certainly, there are psychological benefits to the latter, but we must be able to compare these to the risks of therapy. The answers to these questions will require a large well-controlled study over the next 15 years. Until then, it must be decided how to use the available growth hormone in the most efficacious way. As parents become more aware that their children might benefit from growth hormone therapy, they may apply great pressure to pediatricians to treat their children. What is clear at the moment is that we should not use growth hormone indiscriminantly. As with any potent pharmacologic agent, the physician must be experienced with its use, benefits, and potential complications. We already have seen in our practice 1 child with a craniopharyngioma who was treated by his physician for 1 year with growth hormone purchased from a commercial source. Unfortunately, the height velocity of the boy did not accelerate until we reduced his dosage of hydrocortisone. I would recommend that, at present, human growth hormone be used, in consultation with a pediatric endocrinologist, to treat only those children with unequivocal growth hormone deficiency. Any other use should be considered purely investigational."] ◀

11–11 **Prospective, Randomized Study of Testosterone Treatment of Constitutional Delay of Growth and Development in Male Adolescents.** Constitutional growth delay is the most common form of short stature seen at pediatric endocrine clinics. Occasionally sig-

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(11–11) Pediatrics 69:681–687, June 1982.

nificant growth retardation in male adolescents, especially with delayed sexual maturation, leads to a sense of incompetence, impaired self-esteem, declining academic performance, and social isolation. Ron G. Rosenfeld, Gregory B. Northcraft, and Raymond L. Hintz (Stanford Univ.) undertook a prospective study of androgen therapy in 16 boys, aged 14 to 17 years, who were below the 5th height percentile and had delayed puberty, with no evidence of endocrine or other systemic disease. Treatment was with four intramuscular injections of 200 mg of testosterone enanthate at 3-week intervals.

Predicted adult heights were comparable in the 8 treated and 8 control patients at the outset. All treated subjects had excellent growth rates at follow-up after 1 year, ranging from 7.2 to 11.6 cm per year. Mean height age increased from 12.05 to 13.45 years. The cumulative growth rate was significantly greater in the treatment group, with a mean annual growth of 9.2 cm per year, compared with 6.05 cm per year for controls. Baseline testosterone concentrations were not correlated with subsequent growth in the treatment group. Weight increase was also greater in treated subjects. All patients in the testosterone group had clearly entered puberty at follow-up. Mean bone ages after 1 year did not differ significantly in the testosterone and control groups. Both groups had improved self-image at follow-up. Social activities increased in treated subjects but declined in controls.

Short-term testosterone treatment is generally effective in promoting linear growth and the appearance of secondary sex characteristics in male adolescents with constitutional growth and maturation delay. No acceleration of skeletal age or compromise in adult height has been evident. Sympathetic reassurance is also important in the management of these patients. Most patients still are managed adequately by reassurance alone.

▶ [Dr. Alfred M. Bongiovanni, Department for Sick and Injured, Pennsylvania Hospital, and Professor of Pediatrics, University of Pennsylvania, comments:

"This is a recurrent theme with innumerable variations in pediatric endocrinology dating from the time that androgens became available for therapy. My most cogent comment is already contained in the last sentence of the above abstract. Most patients are managed adequately by reassurance alone. The data presented clearly indicate that short-term treatment with testosterone enanthate at the dosage used does not unduly advance epiphyseal maturation. Therefore, larger doses given for a longer time or more potent agents are best avoided. The authors thoughtfully included a "control" group that, despite evidence of disturbed self-image at the start of the study, nonetheless demonstrated improvement in self-image during the course of the 1-year enrollment. Therefore, reassurance alone is frequently effective. In the original article, the authors also indicate that such therapy should be combined with psychological support and should be used judiciously in select patients. I have only one disagreement, from my own experience. The control group in this study demonstrates significant disadvantages in social activity. Careful history-taking in my own clinic has revealed that some 20%–25% are, if anything, socially aggressive, do not shy away from any curricular or extracurricular activities, and, indeed, are so often "Napoleonic" that their peers often regard them as a nuisance. I have found this particular manifestation to be an advantage in the long run."] ◀

12. Nutrition and Metabolism

12–1 **Amount of Milk Consumed by 1- to 3-Month-Old Breast- or Bottle-Fed Infants.** Y. Hofvander, U. Hagman, C. Hillervik, and S. Sjölin (Univ. Hosp., Uppsala, Sweden) studied the consumption of breast milk by the weighing method in 75 infants aged 1, 2, and 3 months (±1 week); 25 infants were in each age group. The same number of infants in the same age groups, bottle-fed ad libitum, also were studied; milk consumption and the consumption pattern were compared among the groups.

The mean and range of consumed amounts of both types of milk were similar to those found in other studies. On an average, bottle-fed infants of all three age groups consumed a slightly greater volume of milk than did breast-fed ones. The means for breast milk were 656, 773, and 776 gm and for breast milk substitutes 713, 811, and 853 gm in the 1-, 2-, and 3-month-old infants, respectively, but with wide variations (Table 1). In all age groups and for both breast milk and breast milk substitutes, boys on an average consumed more than girls (Table 2).

When expressed as kcal/kg, milk consumption appeared to be virtually no different between the two feeding groups (Table 3). The bottle-fed infants had fewer meals and a more even consumption from meal to meal; breast-fed babies tended to eat more in the morning and less in the evening.

It is concluded that infants largely regulate themselves according to the intake they require. It is necessary to judge the requirements of each child individually and to base evaluation mainly on the gen-

TABLE 1.—Consumption in gm/24 Hours (Mean and Range) of Breast Milk Substitutes (BMS) and Breast Milk (BM) by 150 Infants Aged 1–3 Months Fed ad Libitum

Age (months)	BMS (g)	BM (g)
1	713 (500–1 000)	656 (360–860)
2	811 (670–1180)	773 (575–985)
3	853 (655–1 065)	776 (600–930)

(Courtesy of Hofvander, Y., et al.: Acta Paediatr. Scand. 71:953–958, 1982.)

(12–1) Acta Pediatr. Scand. 71:953–958, 1982.

TABLE 2.—MEAN 24-HOUR CONSUMPTION FOR BOYS AND GIRLS

Age (months)	Boys g	*n*	Girls g	*n*	Difference (boys > girls = +)	*p*
Breastmilk						
1	663	(12)	649	(13)	+14	NS
2	791	(14)	750	(11)	+41	NS
3	811	(12)	743	(13)	+68	<0.05
Breastmilk substitute						
1	753	(10)	687	(15)	+66	NS
2	863	(13)	753	(12)	+110	<0.01
3	862	(13)	843	(12)	+19	NS

(Courtesy of Hofvander, Y., et al.: Acta Paediatr. Scand. 71:953–958, 1982.)

TABLE 3.—CONSUMPTION (MEAN AND RANGE) OF BREAST MILK SUBSTITUTES (BMS) AND BREAST MILK (BM) BY 150 INFANTS AGED 1–3 MONTHS FED AD LIBITUM

Age (months)	BMS (kcal/kg)	BM (kcal/kg)
1	120 (78–201)	112 (74–146)
2	107 (75–168)	108 (74–145)
3	101 (76–130)	96 (70–120)

(Courtesy of Hofvander, Y., et al.: Acta Paediatr. Scand. 71:953–958, 1982.)

eral behavior and weight increase of the child. Mean energy consumption was lower than the Recommended Dietary Allowances and the Food and Agriculture Organization/World Health Organization requirements (115 and 120 kcal/kg, respectively, for this age group). This is in agreement with findings in other similar studies and would support the need for reevaluation of the recommendations.

► [It is becoming increasingly evident that previous recommendations regarding the caloric requirements of infants—particularly breast-fed infants—during the first 6 months of life require reevaluation. Infants appear to grow quite well with much less than we believed necessary. Perhaps the most convincing data, to date, come from N. F. Butte and associates, who described the relationship between breast milk intake and growth performance in 45 full-term infants who were exclusively breast-fed during the first 4 months of life (*Am. J. Clin. Nutr.* 37:697, 1983). These infants were growing well; their mean percentile weight-for-age was 65% at birth and 64% at age 4 months. Their mean caloric intake averaged 110 kcal/kg/day at age 1 month, 83 kcal/kg/day at age 2 months, 74 kcal/kg/day at age 3 months and 71 kcal/kg/day at age 4 months. The protein nitrogen intake ranged from 1.24 gm/kg/day at age 1 month to 0.98 gm/kg/day at age 4 months. It looks like these infants hadn't read the recommendations. All of this serves to reaffirm the old guidelines regarding infant feeding—if the breast-fed infant is growing well, don't add supplements of any kind regardless of what you may calculate the baby's caloric need to be.—F.A.O.] ◄

12-2 **Differences in Infant Care and Health Independent of Socioeconomic Status.** Recent findings indicate that breast-feeding is superior to artificial formula feeding for normal infants of healthy mothers, but controversy persists regarding the adequacy of breast milk for sustaining optimal weight gain in the first 6 months of life, and also whether solid food supplements increase the risk of obesity. K. Bloom, R. B. Goldbloom, and F. E. Stevens undertook a prospective longitudinal study of solid food intake, weight gain, and illness in 539 infants in a Canadian urban population who were followed from birth to age 6 months. All weighed at least 2,500 gm at birth and had Apgar scores of 5 or above. Initially, 46% of the mothers chose to breast-feed their infants. At 6 weeks, 3 months, and 6 months, 29%, 14%, and 15%, respectively, reported having discontinued breast-feeding.

The proportions of infants given solid foods at various intervals after birth are compared in Figure 12–1. A high socioeconomic status was associated with the decision to breast-feed initially. The use of solid foods was related more closely to feeding practice than to feeding choice, solid foods being introduced significantly earlier to formula-fed infants. The incidence of illness is shown in Table 1, and that of digestive upset in Table 2. Breast-fed infants had less reported illness and less digestive upset in the first half year of life than did formula-fed infants. Weight gains are given in Table 3.

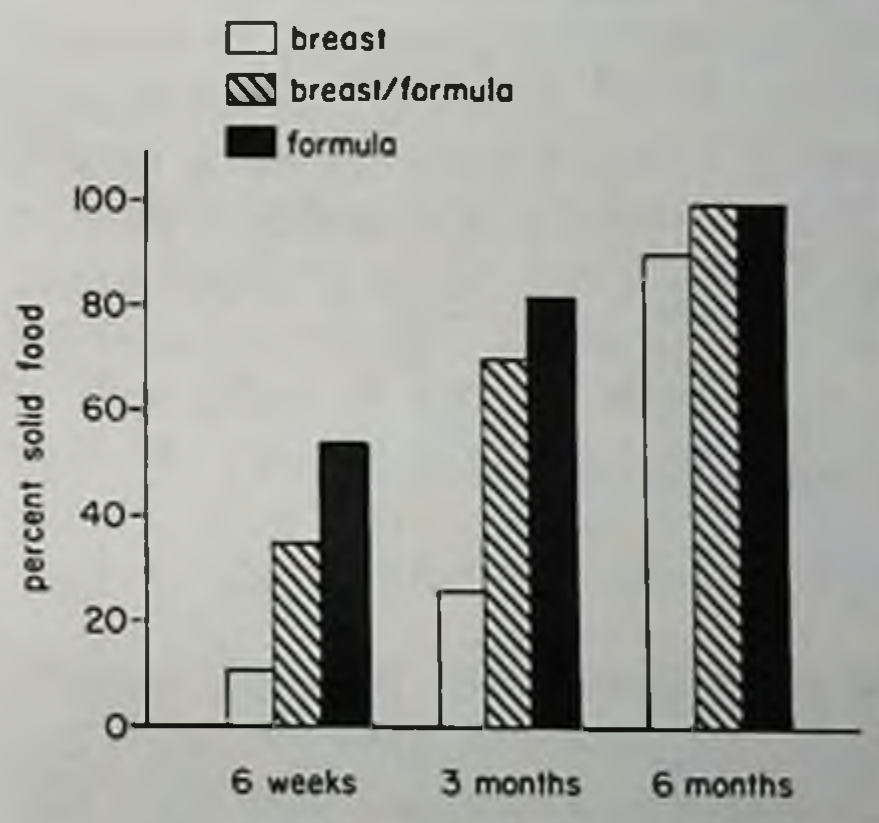


Fig 12–1.—Percent of infants given solid food at 6 weeks, 3 months, and 6 months. (Courtesy of Bloom, K., et al.: Acta Paediatr. Scand. [Suppl.] 300:15–26, 1982.)

TABLE 1.—INCIDENCE OF ILLNESS

Age	% breast	% breast/ formula	% formula
6 weeks	22.4	30.0	35.0
3 months	39.1	39.0	48.0
6 months	31.3	40.0	47.5

Breast-fed vs. formula-fed at 6 weeks, $\chi^2 = 6.3$, $P < .02$; at 6 months, $\chi^2 = 4.9$, $P < .05$.

(Courtesy of Bloom, K., et al.: Acta Paediatr. Scand. [Suppl.] 300:15–26, 1982.)

(12–2) Acta Paediatr. Scand. [Suppl.] 300:15–26, 1982.

TABLE 2.—INCIDENCE OF DIGESTIVE UPSET*

	% breast	*% formula*		
6 weeks	2.5	12.3	$\chi^2=10.6$	$p<0.01$
3 months	1.8	8.3	$\chi^2=5.00$	$p<0.05$
6 months	1.4	9.0	$\chi^2=4.10$	$p<0.05$
	% breast/ formula	*% formula*		
6 weeks	14.2	12.3	NS	
3 months	6.6	8.3	NS	
6 months	5.7	9.0	NS	
	% breast	*% breast/ formula*		
6 weeks	2.5	14.2	$\chi^2=10.70$	$p<0.01$
3 months	1.8	6.6	NS	
6 months	1.4	5.7	NS	

*As a percentage of total sample of each age.
(Courtesy of Bloom, K., et al.: Acta Paediatr. Scand. [Suppl.] 300:15–26, 1982.)

TABLE 3.—WEIGHT GAIN AS A PERCENTAGE OF BIRTH WEIGHT

	Male		Female	
	Breast	Formula	Breast	Formula
4 weeks	28.2	26.4	30.4	25.2
6 weeks	36.1	43.4	34.5	34.5
8 weeks	61.6	58.6	52.8	55.0
12 weeks	83.0	81.4	76.7	72.0
26 weeks	135.0	134.0	109.0	124.0

(Courtesy of Bloom, K., et al.: Acta Paediatr. Scand. [Suppl.] 300:15–26, 1982.)

This longitudinal study indicates that breast-fed infants receive solid foods less often than do formula-fed infants and also are fed commercially prepared solid foods less frequently. They are less often ill. Weight gain is comparable in the two groups over the first 6 months of life. The fact that the weight gain of exclusively breast-fed and formula-fed infants is virtually the same supports the view that, in the first half year of life, infants can thrive on a diet of breast milk alone.

► [This study serves to confirm previous observations regarding weight gain in the breast-fed infant (see 1981 YEAR BOOK, pp. 312–314, and the preceding article by Hofvander et al.) and, more importantly, provides additional evidence that the breast-fed infant is healthier than the non-breast-fed infant, as documented in the United States by A. S. Cunningham (*J. Pediatr.* 95:685, 1979, in 1981 YEAR BOOK, pp. 314–316).

Scientific support for this "well-being" continues to be documented. M. Cooperstock and associates (*J. Clin. Microbiol.* 17:830, 1983) reported that infants fed formula were four times more likely to carry *Clostridium difficile* in the stool than those who were exclusively breast-fed—62% versus 16%. Breast-fed infants who also re-

ceived formula or solids had an intermediate rate of colonization. R. I. Glass and coworkers (*N. Engl. J. Med.* 308:1389, 1983) concluded that breast milk contained antibodies against cholera that did not prevent colonization with *Vibrio cholerae* 01 but did protect against disease in those who were colonized. Add these findings to the list that already includes breast milk antibodies against other diarrheal agents such as enterotoxigenic *Escherichia coli* and rotavirus.

If diarrhea protection doesn't excite you—how about otitis media? See the following article, please.—F.A.O.] ◀

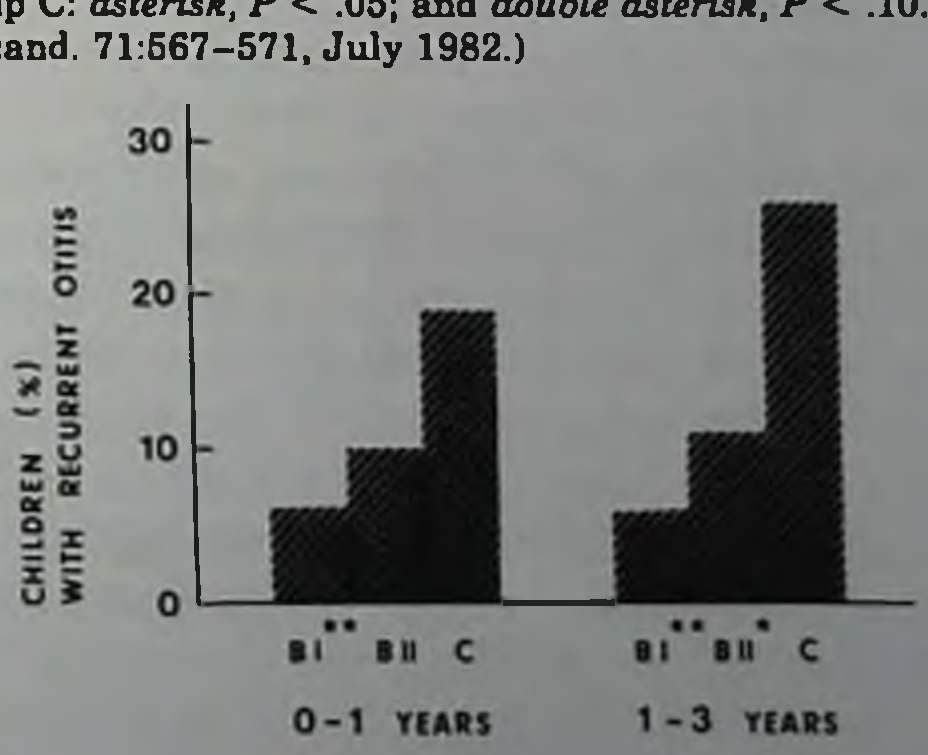
12–3 **Prolonged Breast-Feeding as Prophylaxis for Recurrent Otitis Media.** Ulla M. Saarinen (Univ. of Helsinki) studied the incidence of otitis media in 237 healthy children with reference to duration of breast-feeding. Follow-up was from birth to age 3 years. Mothers were encouraged to breast-feed for as long as possible. Infants were weaned to a commercial or home-prepared cow's milk-based formula. Solid foods were started at age 3.5 months. Data on day nursery subjects were excluded to avoid bias.

Recurrent otitis media was associated strongly with early bottle-feeding, in contrast to prolonged breast-feeding, which had a protective effect up to age 3 years (Fig 12–2). From birth to age 6 months, no middle ear infection was detected in the breast-fed group, whereas 10% of the cow's milk group already had suffered from otitis. The longer exclusive breast-feeding was continued, the fewer were the subsequent episodes of otitis.

The incidence of otitis media was not constantly elevated among infants of the cow's milk group; instead, certain infants had recurrent episodes. Early-onset otitis seemed to predispose to recurrences. There were no milk-related differences in infants who had mild respiratory infections without antibiotic treatment. Respiratory infections needing antimicrobial therapy were more frequent in bottle-fed infants before age 1 year.

The effect of day nursery care was extremely strong from age 6 to age 12 months but was, at most, slightly noticeable thereafter. The role of atopic disease as a factor predisposing to recurrent otitis was observable, but it was not very strong.

Fig 12–2.—Recurrent otitis media (defined as 2 or more episodes from birth to age 1 year and 4 or more episodes from age 1 to 3) in the different study groups. *BI*, long breast-feeding; *BII*, intermediate breast-feeding; *C*, cow's milk group, short or no breast-feeding. Significance of differences in comparison with group C: *asterisk*, $P < .05$; and *double asterisk*, $P < .10$. (Courtesy of Saarinen, U. M.: Acta Paediatr. Scand. 71:567–571, July 1982.)



(12–3) Acta Paediatr. Scand. 71:567–571, July 1982.

It is uncertain whether the prophylactic effect of prolonged breast-feeding on recurrent otitis is due to protection by human milk from infection or allergy or to avoidance of harmful effects caused by cow's milk.

▶ [We turned to Dr. Jerome O. Klein, Professor of Pediatrics, Boston University, who is "Doctor I.D." to all of New England, for his perspective on this finding. Doctor Klein writes:

"The results of this study by Saarinen add further evidence indicating that the experience with middle ear infections of breast-fed children is different from that of bottle-fed children. The longer the duration of breast-feeding, the greater the apparent benefit. The protective effect continues for some time, up to years, after cessation of breast-feeding. Studies in Canadian Eskimo children (Schaefer, O.: *Can. J. Public* Health 62:478–489, 1971; and Timmermans, F. J., and Gerson, S.: *Can. Med. Assoc. J.* 122:545–547, 1980), Indian children (Chandra, R. K.: *Acta Paediatr. Scand.* 68:691–694, 1979), and children in New York State (Cunningham, A. S.: *J. Pediatr.* 90:726–729, 1977) also suggest that children who are breast-fed have fewer episodes of acute otitis media. A study of Boston Children (Teele, D. W., et al.: *Pediatr. Res.* 14:494, 1980) indicated that breast-feeding did not protect children from acute infection, but did shorten significantly the duration of middle ear effusion.

"It is unlikely that the Saarinen study will end debate about the value of breast-feeding for the prevention of otitis media or for a decrease in time spent with effusion. There are some defects in design in this study and with the others, including retrospective analysis, criteria for diagnosis, absence of multivariable analysis, and insufficient sample size to provide appropriate analysis of confounding variables. Nevertheless, the cumulative evidence is persuasive that breast-fed infants have fewer problems with otitis media than do bottle-fed infants.

"Is breast-feeding beneficial or bottle-feeding harmful? A number of hypotheses have been suggested.

"1. Immunologic factors that prevent bacterial and viral infections are provided in breast milk.

"2. Facial muscles that affect eustachian tube function develop differently in breast-fed children when compared with bottle-fed children.

"3. Aspiration of fluids into the middle ear occurs during bottle-feeding because high negative intraoral pressure is necessary, whereas breast-feeding involves nipple massage and reflex "let-down" of milk.

"4. The breast-fed infant is held in a vertical or semivertical reclining position, whereas the bottle-fed infant may be placed in a horizontal position that may result in reflux of milk into the middle ear.

"5. Allergy to one or more components in cow's milk or formula milk may result in alteration of the mucosa of the eustachian tube and middle ear.

"The middle ear is a cul-de-sac of the respiratory tract. The mucosa of the middle ear contains ciliated cells, mucus-producing cells, and cells with immunologic functions that are similar to those in the mucosa in other sections of the respiratory tree. Further investigations directed to questions about otitis media, such as the effects of breast-feeding, will likely enhance our understanding not only of otitis, but also of infection and immune response throughout the respiratory tract."] ◀

12–4 **Growth and Biochemical Response of Preterm Infants Fed Human Milk or Modified Infant Formula.** Steven J. Gross (Duke Univ.) studied the rates of growth and the biochemical status of healthy preterm infants fed preterm human milk (milk expressed from mothers of preterm infants during the postpartum week corresponding to their postnatal age), mature human milk (milk produced during the mature stage of lactation by mothers of term infants), or a whey-based premature infant formula (Enfamil). The compositions of the three milks are shown in Table 1.

(12–4) N. Engl. J. Med. 308:237–241, Feb. 3, 1983.

TABLE 1.—Composition of Three Types of Milk

Component	Mature Human Milk *	Preterm Human Milk † Postpartum Week										Whey-Based Formula ‡
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9&10*	*11&12*	
Protein (g/dl)	1.01±0.03	2.26	1.93	1.62	1.46	1.36	1.32	1.25	1.18	1.16	1.14	1.93
Fat (g/dl)	3.97±0.37	3.18	3.51	3.53	3.84	3.77	3.78	3.63	3.40	3.54	3.41	3.33
Carbohydrate (g/dl)	7.06±0.20	6.67	7.15	7.27	7.26	7.26	7.05	7.10	7.00	7.05	7.21	7.36
Sodium (mg/dl)	15.3±2.1	39.3	31.5	27.6	22.8	19.6	19.6	19.0	17.4	13.1	13.9	24.5
Chloride (mg/dl)	43.6±2.6	78.3	66.4	57.9	51.3	40.5	41.9	41.2	44.0	39.7	43.5	53.0
Potassium (mg/dl)	39.8±5.7	68.3	59.8	50.3	50.3	46.8	45.5	38.9	41.1	41.7	43.9	79.0
Calcium (mg/dl)	26.8±2.1	29.5	30.1	25.3	29.1	29.9	31.1	29.9	32.6	29.2	30.8	81.0
Phosphorus (mg/dl)	12.1±0.8	14.0	15.6	14.5	14.6	13.2	14.4	12.5	12.8	14.2	14.0	39.5
Energy (kcal/dl)	66.8±1.0	63.7	67.0	66.4	68.4	67.3	66.4	65.0	62.3	63.6	63.0	67.0

*Values expressed as means ± SD in ten pooled samples.
†Values for weeks 1 through 5 represent means of two pooled samples.
‡Values represent means of two batches.
(Courtesy of Gross, S. J.: N. Engl. J. Med. 308:237–241, Feb. 3, 1983.)

Sixty healthy infants born at gestational ages of 27–33 weeks and weighing 1,600 gm or less were randomly assigned to one of the three feeding groups. All were fed by gastric lavage according to a strict protocol. Those weighing less than 1,100 gm were fed hourly; those weighing 1,101–1,300 gm, every 2 hours; and those weighing more

than 1,300 gm, every 3 hours. Feedings were begun on days 1–6 of life (mean, day 3) at a volume of 24 ml/kg per day. They were increased by a similar amount daily so that all infants were receiving 180 ml/kg/ per day by the eighth day of feeding. This intake was maintained thereafter by daily adjustments based on weight increases until the infants reached 1,800 gm.

Infants receiving formula or preterm human milk grew more rapidly than those receiving mature human milk (Table 2). By the sixth week of feeding, weights of 1,800 gm had been attained by 90% of infants fed formula, 85% of those fed preterm human milk, and 60% of those fed mature human milk. Similarly, average increments in

TABLE 2.—GROWTH DATA ON THREE GROUPS OF INFANTS

CHARACTERISTIC	INFANT FORMULA (N = 20)	PRETERM HUMAN MILK (N = 20)	MATURE HUMAN MILK (N = 20)
	means ±S.E.M.		
Time to regain birth weight (days)	10.3±0.8 *	11.4±0.8 *	18.8±1.7
Weight gain from regained birth weight to 1800 g (g/day)	27.0±0.8 *	23.7±1.1 *†	15.8±0.8
Crown-to-heel length (cm/wk)	0.72±0.04 ‡	0.75±0.03 *	0.54±0.04
Head circumference (cm/wk)	0.88±0.05 *	0.84±0.03 *	0.70±0.02

*$P < .001$ compared with mature human milk.
†$P < .05$ for preterm human milk compared with infant formula.
‡$P < .005$ compared with mature human milk.
(Courtesy of Gross, S. J.: N. Engl. J. Med. 308:237–241, Feb. 3, 1983.)

TABLE 3.—SERUM TOTAL PROTEIN AND ALBUMIN CONCENTRATIONS ACCORDING TO WEEK OF FEEDING*

WEEK	INFANT FORMULA	PRETERM HUMAN MILK	MATURE HUMAN MILK
	g/dl	*g/dl*	*g/dl*
Total protein			
0	5.7±0.1 (20)	5.8±0.2 (20)	5.9±0.1 (20)
1	6.1±0.2 (20)	6.3±0.2 (20)	5.9±0.2 (20)
2	5.8±0.1 (20)	6.2±0.1 (20)	5.8±0.2 (20)
4	5.6±0.1 (17)	5.9±0.1 (20)	5.5±0.2 (20)
6	5.6±0.2 (6)	5.5±0.3 (8)	5.2±0.2 (16)
8	5.2±0.4 (2)	5.5±0.6 (3)	5.0±0.3 (8)
Albumin			
0	3.2±0.1 (20)	3.0±0.1 (20)	3.2±0.1 (20)
1	3.2±0.1 (20)	3.4±0.1 (20)	3.2±0.1 (20)
2	3.0±0.1 (20)	3.3±0.1 (20)	2.9±0.1 (20)
4	3.2±0.1 (17)	3.1±0.1 (20)	2.9±0.1 (20)
6	3.0±0.1 (6)	3.1±0.1 (8)	2.8±0.1 (16)
8	3.0±0.0 (2)	2.8±0.3 (3)	2.8±0.1 (8)

*Results are means ± SEM; numbers in parentheses indicate number of observations.
(Courtesy of Gross, S. J.: N. Engl. J. Med. 308:237–241, Feb. 3, 1983.)

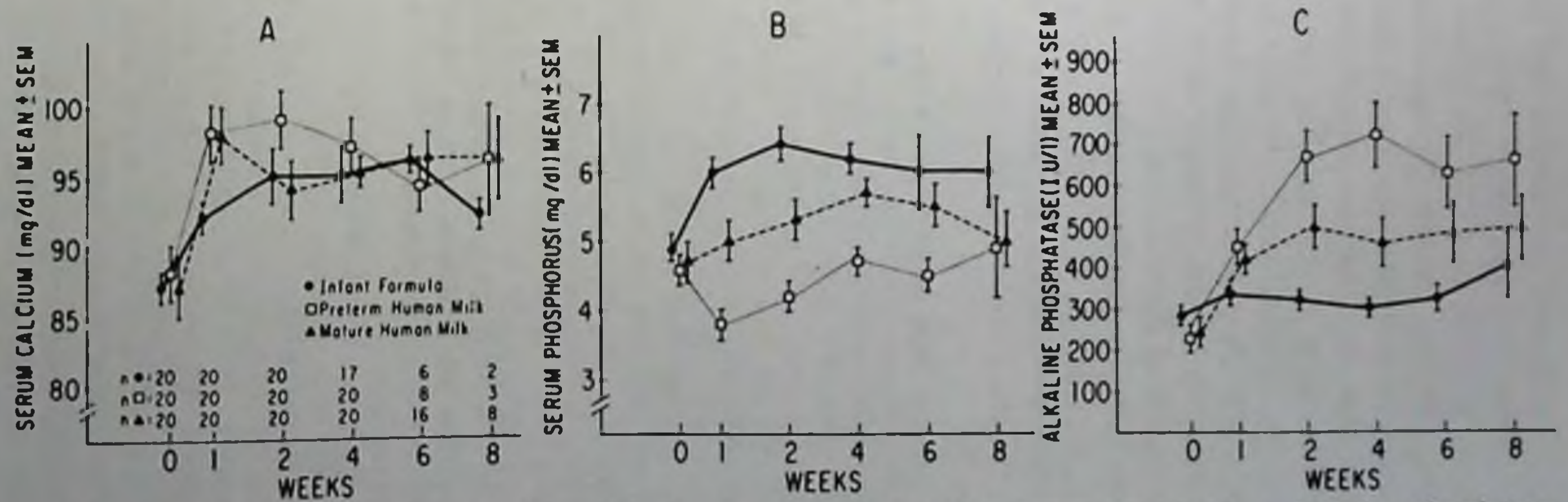


Fig 12–3.—Serum concentrations of calcium (**A**), phosphorus (**B**), and alkaline phosphatase (**C**), according to week of feeding in three feeding groups. Serum phosphorus concentrations were significantly higher in group that received formula than in groups that received preterm human milk ($P < .001$) or mature human milk ($P < .025$). Further, serum phosphorus concentrations were significantly higher in group that received mature human milk than in group that received preterm human milk ($P < .005$). Serum concentrations of alkaline phosphatase were significantly lower in group that received formula than in groups that received preterm human milk ($P < .002$) or mature human milk ($P < .025$). To convert calcium values to millimoles per liter, multiply by 0.25; to convert phosphorus values to millimoles per liter, multiply by 0.32. (Courtesy of Gross, S. J.: N. Engl. J. Med. 308:237–241, Feb. 3, 1983.)

crown-to-heel length and in head circumference were greater for the groups given formula or preterm human milk.

Hyponatremia developed in 50% of infants fed mature human milk, 15% of those fed preterm human milk, and 20% of those fed formula. Serum chloride results were similar. Serum potassium concentrations were normal in all infants. There were no significant differences among feeding groups in mean blood pH or blood urea nitrogen or bicarbonate concentrations. Mean concentrations of serum total pro-

tein and albumin tended to be lowest in infants fed mature human milk, but there were no significant differences among groups (Table 3). There were no significant differences in mean serum calcium concentrations among the three groups. Serum phosphorus values, however, were greater for infants in the formula group than for those in the two human milk groups. Serum alkaline phosphatase values varied inversely with those of serum phosphorus (Fig 12–3).

For healthy preterm infants, feeding with preterm human milk or whey-based formula offers a significant advantage over feeding with mature human milk, resulting in a prompt regaining of birth weight and supporting subsequent rates of growth comparable with those observed during the last trimester of intrauterine life. Although clinical rickets did not develop in any infant, the more normal serum phosphorus and alkaline phosphatase values in infants fed the formula support the need for calcium and phosphorus supplementation in preterm infants fed human milk.

► [The proof is in the pudding. It has been gratifying to follow this story over the past 5 years. First we were told that human milk would be inadequate to support the growth of low birth weight infants. This conclusion was based on armchair calculations that used the known composition of human milk produced by mothers at term. Nature doesn't work that way, and Atkinson and co-workers (*J. Pediatr.* 93:67, 1978) first called attention to the fact that the milk produced by mothers giving birth to preterm infants was significantly different from that of mothers giving birth to term infants. It had more protein (to trace the whole story see 1981 YEAR BOOK, pp. 311–312; 1982 YEAR BOOK, pp. 306–310; and 1983 YEAR BOOK, pp. 330–335). Short-term balance studies suggested that preterm milk could support the growth of preterm infants, and now this study by Gross convincingly proves the point.

Using different feeding protocols, Järvenpää and associates (*Acta Paediatr. Scand.* 72:239, 1983) demonstrated that preterm infants fed human milk could attain weight gain that was similar to what normally would occur in utero if the infants had remained there. Spencer and co-workers (*Br. Med. J.* 285:924, 1982) found that the energy intake of low birth weight infants fed expressed breast milk averaged 138 kcal/kg/day between the second and fourth weeks of life and these infants had a mean weekly increase in weight of 119 gm per week.

At the 1983 annual meeting of the Society for Pediatric Research-American Pediatric Society, Gross presented more data on these low birth weight infants fed their own mother's milk that demonstrated that these babies remained vitamin E and iron sufficient during the first 6 weeks of life without any supplementation (*Pediatr. Res.* 17:188A, 1983). At the same meeting, R. K. Whyte and associates (ibid., pp. 205A) described the composition of weight gain in these low birth weight infants fed either expressed human milk or formula. The weight gain as protein averaged about 10% in both groups, whereas weight gain as fat was somewhat higher, 34%, in the group fed human milk than in the group fed formula, where it averaged about 28%.—F.A.O.] ◄

► ↓As can be seen from the following article, mothers giving birth to preterm infants are both willing and capable of breast-feeding their infants.—F.A.O. ◄

12–5 **High Potential for Breast-Feeding Among Mothers Giving Birth to Preterm Infants.** More rapid growth has been found in preterm infants fed milk from mothers delivering preterm than in those fed milk from mothers giving birth at term. Alf Meberg, Sissel Willgraff, and Hans A. Sande (Oslo) compared the durations of lactation in mothers delivering preterm and healthy term infants between 1978 and 1980. There were 155 mothers in each group. Over two thirds of both groups responded to the questionnaire survey. The find-

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(12–5) Acta Paediatr. 71:661–662, July 1982.

BIRTH WEIGHT, GESTATIONAL AGE, AND DURATION OF HOSPITALIZATION IN PRETERM AND TERM INFANTS, MOTHER'S ABILITY TO BREAST-FEED HER BABY AT DISCHARGE, AND DURATION OF BREAST-FEEDING IN THE TWO GROUPS (MEANS ± SD)

	Pre-term (n=100)	Term (n=108)
Birth weight (g)	1 912±500	3 499±423*
Gestational age (weeks)	33.6±2.4	40.1±1.2*
Infants hospitalized (days)	34.9±23.2	5.8±0.7*
At maternal discharge from nursery		
Totally breast feeding	55	96*
Partly breast feeding	41	8*
No breast milk	4	4
Duration of breast feeding (months)	5.6±3.9	7.0±4.2*

*$P < .05$, statistical difference between the two groups.
(Courtesy of Meberg, A., et al.: Acta Paediatr. Scand. 71:661–662, July 1982.)

ings are given in the table. Mean duration of breast-feeding was longer in the term group than among preterm mothers. In the preterm group the duration was unrelated to birth weight or to gestational age. A high proportion of preterm mothers succeeded in breast-feeding, although the potential for breast-feeding was greater in the full-term group.

The high potential for breast-feeding in women delivering preterm infants is biologic evidence for human milk as a physiologic basis for the nutrition of preterm infants. Separation of a preterm infant in a neonatal care unit does not necessarily impair the mother's ability to breast-feed. The attitudes of staff and the practical routines in nurseries and neonatal care units should support these women in sustaining lactation. This may enhance normal bonding between parturients and their preterm infants.

12–6 **Protein Tolerance of Very Low Birth Weight Infants Fed Human Milk Protein-Enriched Mother's Milk.** The immaturity of amino acid degradation and excretory functions make the difference between minimal and maximal nutritional supply in very low birth weight (VLBW) infants. Although protein and sodium requirements of VLBW infants are not met by feeding of human milk at the level of 130 kcal/kg/day, the immunologic advantages of human milk and avoidance of sensitization against foreign proteins partly compensate for its nutritional shortcomings. S. Hagelberg, B. S. Lindblad, A. Lundsjö, B. Carlsson, R. Fondén, H. Fujita, G. Lassfolk, and B. Lindqvist examined the tolerance of VLBW infants for a high supply of human milk protein added to fresh milk of the infant's mother. Human milk from a milkbank was used in the study with cream sep-

(12–6) Acta Pediatr. Scand. 71:597–601, July 1982.

arated by a separator and lactose and salts separated by ultrafiltration. Each 100 ml of mother's fresh milk had 1.3 gm of protein product and sodium chloride added. When the infants were a mean age of 15 days, feeding was started via a nasogastric tube. Weight, length, and circumference of head were plotted weekly. Plasma sodium, potassium, and urea levels were determined every second day for a week, and weekly thereafter. Tyrosine and valine levels were determined by fluorometry.

Infants' growth followed the intrauterine growth curve. Serum levels of sodium, potassium, urea, and urinary excretion of sodium and potassium were normal. Total protein, albumin, and immunoglobulin levels showed normal values for preterm infants. Blood levels of critical amino acids were at no time higher than levels usually occurring in plasma after a meal. In one infant, whose tyrosine level exceeded 300 μmole/L, administration of vitamin C immediately lowered the level. Valine levels did not indicate protein overload.

The almost double increase of human milk protein was well-tolerated by the four VLBW infants in this study. Human milk fat and sodium monophosphate should also be added; experimental study of such additions is currently under way.

► [This is a neat trick, but may be an example of gilding the lily. K. A. R. Ronnholm and co-workers (*J. Pediatr.* 101:243, 1982) described a similar study. In a group of 18 infants with birth weights of less than 1,500 gm, half were fed human milk alone and the other half received human milk plus protein supplements isolated from mature human milk. By 6 weeks of age, the supplemented group were receiving 3.6 gm of protein per kg per day as compared with 2.0 gm/kg per day for the control group; at 12 weeks of age the groups were receiving 3.4 and 1.9 gm/kg per day, respectively. The infants in the unsupplemented group developed hypoproteinemia at 8 to 12 weeks of age, whereas those receiving the protein supplementation did not. The rate of growth in the two groups was similar.

Speaking of feeding supplementations, the addition of taurine and cholesterol to the formulas of low birth weight infants did not appear to produce any detectable change in growth or metabolism (Järvenpää, A. L., et al.: *Pediatrics* 71:171, 1983).

The Swedes and the Finns deserve much credit for their imagination and the scientific rigor with which they have pursued infant feeding trials—unlike investigators in the United States, where, after all is said and done, a hell of a lot more is said than done.—F.A.O.] ◄

12–7 **Evaluation of Breast Pumps Currently Available on the American Market.** Carmen Acosta Johnson (Univ. of Houston at Clear Lake, Houston) studied 8 breast pumps commonly seen in clinical practice (Table 1) and ranked them for desirability in eight categories: pressure range, pressure control, size and shape of nipple cup, volume accommodation, visual feedback, ease of cleaning, ease of handling, and cost.

A pump with an intermittent suck is less likely to draw blood into the milk than one with a continuous suck. If the pump design allows stimulation of the let-down reflex, the pressure required to extract milk can be much lower. The larger and deeper the flare of the nipple cup, the greater the stimulation of the alveolar region of the breast, which may contribute to activation of the let-down reflex during pumping. The longer and wider the shank of the cup, the better the

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(12–7) Clin. Pediatr. (Phila.) 22:40–45, January 1983.

TABLE 1.—MANUFACTURERS OF PUMPS EVALUATED*

Name of Pump	Manufacturer's Address	Approximate Cost
Bintner	No longer in production	—
Davol	Davol, Inc. Providence, RI	$5.00
Egnell	Egnell, Inc. 412 Park Avenue Cary, IL 60013	$920.00
Evenflo	Evenflo Products Co. 771 N. Freedom Street Ravenna, OH 44266	$3.50
Gomco	Gomco Surgical 828 East Ferry Street Buffalo, NY 14211	$3.50
Kaneson	Okayama National Hospital Children's Medical Center Minimagata 1/13/1 Okayama, Japan 700	$22.00
Loyd-B	Lopuco Ltd. 1615 Old Annapolis Road Annapolis, MD 21777	$35.00
Ora'lac	Nursemate P.O. Box 242 Wenatchee, WA 98801	$25.00

*Several pumps available, or soon to be available, in the United States were not evaluated.

(Courtesy of Johnson C. A.: Clin. Pediatr. (Phila.) 22:40–45, January 1983.)

distention of the nipple, allowing the ducts to unfurl and become competent for the flow of milk.

In the Davol Pump, a spurt of milk easily will enter the bulb, requiring sterilization between uses. The dexterity required for the Lloyd-B pump means that the left breast is more often efficiently evacuated than the right. Table 2 shows the range of negative sucking pressure, source of pressure, and control features for each pump.

Table 3 shows the range in size and shape of nipple cups among the pumps studied and the volume accommodation. The small size of the Gomco cup inhibited nipple distention, requiring a higher pressure to draw milk. The funnel shape of the Davol and Evenflo and the syringe tube of the Kaneson neither inhibited nipple distention nor provided stimulation of the alveolar region.

Table 4 shows the desirability ranking for the observed features and the sum of the ranks for each pump. Three pumps scored relatively high (Egnell, Kaneson, and Lloyd-B), 3 scored low (Gomco, Davol, and Bintner), and 2 appeared to be frequently ineffective (Evenflo and Ora'lac). The Egnell scored highest overall; it appeared

TABLE 2.—Negative Sucking Pressure Ranges, Sources of Pressure, and Control Features

Pump	Negative Pressure*		Source of Pressure	Control
	Highest	Lowest		
Egnell	381	178	Electric	Automatic negative-positive-negative pressure cycle; easy pressure adjustment
Kaneson	381	178	Hand	Requires hand exertion for pressure build-up
Gomco	381	127	Electric	Pressure builds up automatically unless controlled by both hands; heat builds up with prolonged use; noisy
Loyd-B	381	127	Hand	Requires hand exertion for pressure building; hand release
Davol	229	76.2	Hand	A tight seal results in an uncontrollable high, continuous pressure; requires hand release
Bintner	330	76.2	Hand	Same as for Davol
Evenflo	127	81.6	Hand	Air leaks prevent pressure build-up and maintenance
Ora'lac	98	0	Mother's mouth	Mother's strength of suck limits pressure build-up; teeth control release

*Measured in negative mm Hg/sq in. Mean sucking pressures of infants range from −50 to −155, maximum −220. Egnell believed that −200 mm Hg was approximately correct to cause outward flow of milk from the filled gland. Higher pressures would be needed if the breast was not at peak internal pressure.

(Courtesy of Johnson, C. A.: Clin. Pediatr. (Phila.) 22:40–45, January 1983.)

most desirable for stimulation of the let-down reflex, safety, cleanliness, and ease of handling. Where cost or portability are important, the Kaneson and Lloyd-B offer good features. In problem cases, introduction of any pump should be supervised.

► [This type of article could have appeared in *Consumer's Report*, but then doctors

TABLE 3.—SIZE AND SHAPE OF NIPPLE CUPS AND VOLUME ACCOMODATION

	Flare Diameter (mm)	Depth (mm)	Shank Length (mm)	Inner Opening Diameter (mm)	Volume Accommodated (ml) Most	Least
Egnell	82	40	38	24	200	10
Kaneson	68	30	140	26	175	10
Bintner	68	36	40	30	150	10
Evenflo	65	25	47	27	150	10
Davol	62	20	55	60	75	10
Loyd-B	60	26	52	23	30	10
Ora'lac	60	26	54	20–23 (irregular)	20	10
Gomco	47	13	37	20	20	10

(Courtesy of Johnson, C. A.: Clin. Pediatr. (Phila.) 22:40–45, January 1983.)

would have missed it. The conclusions reached by Johnson in this study are similar to those of Dolly Green and associates (*Early Hum. Dev.* 6:153, 1982). Green et al. evaluated the Egnell electric pump, the Lloyd-B pump, the Evenflo hand pump system, and manual expression. The electric pump was the clear-cut winner. In most communities it can be rented and the cost can be shared by several women. For those of you who often are asked for advice regarding breast pumps, a few copies of this article by Johnson would be worth having in the office.

The method of collection also will influence the composition of the milk. C. Garza and co-workers (ibid., p. 295) observed that milk collected by suction contained a higher fat concentration than milk that was expressed by hand. This probably reflects

TABLE 4.--RANKING OF BREAST PUMPS*

Pump	Desirability Ranking†								
	Pressure	Pressure Control	Nipple Cup Size and Shape	Volume Accommo-dation	Ease of Handling	Ease of Cleaning	Visual Feedback	Cost	Sum of the Ranks
Egnell	8	8	8	6.5	8	6	8	2	54.5
Kaneson	7	6.5	7	3	5.5	8	7	6	50.0
Evenflo	4.5	4.5	6	6.5	5.5	2.5	2.5	7	39.0
Loyd-B	6	6.5	3	6.5	1	6	5	4	38.0
Ora'lac	4.5	4.5	2	6.5	2	2.5	2.5	5	29.5
Davol	2	1.5	4	1.5	5.5	2.5	1	8	26.0
Gomco	1	3	1	4	3	6	5	3	26.0
Bintner	3	1.5	5	1.5	5.5	2.5	5	1	25.0

*Most desirable = 8, least desirable = 1.
†Tied ranks were assigned the mean value of all ties.
(Courtesy of Johnson, C. A.: Clin. Pediatr. (Phila.) 22:40–45, January 1983.)

better emptying of the breast, with collection of the "hind" milk with its greater fat content.—F.A.O.] ◀

12–8 **Results of Feeding Special Formula to Very Low Birth Weight Infants.** Small premature infants should be fed to sustain a mean growth rate equivalent to the gestationally corrected in utero growth rate. John S. Curran, Lewis A. Barness, David R. Brown, Ian R. Holzman, Manohar L. Rathi, John Silverio, and Rudolph Tomarelli, following the recommendations of the Committee on Nutrition of the American Academy of Pediatrics for very low birth weight infants, fed a special formula to 58 infants in three newborn nurseries; all weighed less than 1,600 gm at birth. The formula is described in Table 1, and its fatty acid composition is given in Table 2. Infants

TABLE 1.—FORMULA FOR INFANTS OF VERY LOW BIRTH WEIGHT (24 KCAL/OZ OR 81 KCAL/DL)*

Nutrients		Electrolytes (mg/dl)	
Protein (g/dl)	2.0	Calcium	75.0
Lactalbumin (%)	60	Phosphorus	40.0
Casein	40	Sodium	32.0
Fat (g/dl)	4.4	Potassium	75.0
MCT (% added)	10	Chloride	53.0
Carbohydrate (g/dl)	8.6	Magnesium	7.0
Lactose (%)	50	Iron	0.3
Dextrose polymer (%)	50	Zinc	0.5
Ash (mg/dl)	400	Copper	0.07
Osmolality (mOsmol/L)	290	Iodine	8.3
		Manganese	20.0

*MCT = medium chain triglycerides.
(Courtesy of Curran, J. S., et al.: J. Pediatr. Gastroenterol. Nutr. 1:327–332, 1982.)

TABLE 2.—FATTY ACID COMPOSITION (%) OF FORMULA FOR INFANTS OF VERY LOW BIRTH WEIGHT*

Saturated	
C8 Caprylic	8.9
C10 Capric	4.6
C12 Lauric	12.7
C14 Myristic	5.4
C16 Palmitic	10.1
C18 Stearic	5.1
Unsaturated	
C18:1 Oleic	34.2
C18:2 Linoleic	14.9
C18:3 Linolenic	2.4

*Fatty acids found at a concentration > 1%.
(Courtesy of Curran, J. S., et al.: J. Pediatr. Gastroenterol. Nutr. 1:327–332, 1982.)

(12–8) J. Pediatr. Gastroenterol. Nutr. 1:327–332, 1982.

TABLE 3.—Weight Gain and Formula Consumption

	Weight gain (g/day) From birth	Weight gain (g/day) In study	Formula* (kcal/day)	Weight gain* (g/100 kcal)
Study A	18.1 ±0.5	27.1 ±0.9	197.8	13.7
Study B	23.8 ±1.1	31.5 ±1.0	219.7	14.3
Study C	16.5 ±0.9	25.2 ±0.9	179.5	14.0

*During study period ± SEM.
(Courtesy of Curran, J. S.: J. Pediatr. Gastroenterol. Nutr. 1:327–332, 1982.)

without signs of illness were included in the trial on a consecutive basis after surviving for a week or longer.

The three groups of infants were clinically comparable. Daily weight gains from the start of feeding the study formula ranged from 25 to 31.5 gm (Table 3). Weight gains in terms of gm/100 kcal ingested ranged from 13.7 to 14.3. Late metabolic acidosis was not noted. Abnormalities of the serum sodium and chloride concentrations did not occur, even in 3 infants with edema. The serum calcium and phosphorus concentrations were within acceptable ranges for infants of very low birth weight. The blood urea nitrogen value fell from 5.1 to 2 mg/dl. The total serum protein level ranged from 4.5 to 5.1 gm/dl. No infant experienced reactive hypoglycemia. The hematocrit fell progressively during the study.

This formula, designed specifically for infants of very low birth weight, was well accepted and effective.

▶ [I believe that it was the Duchess of Windsor who once said, "Nobody can be either too rich or too thin." In a similar vein, we can never have too many good feeding options for the low birth weight infant. His own mother's milk will not always be available.

This special formula for very low birth weight infants is now commercially available. The manufacturer recommends that it be fed only to infants of less than 1,800 gm because it may contain too much sodium for the more mature infant who is capable of conserving salt. The precise vitamin and mineral requirements for these little infants remain to be determined.

A word of caution regarding these formulas specifically designed for feeding the very low birth weight infant—the added calcium and phosphorus may precipitate out and remain in the bottle and never reach the infant. J. Bhatia and S. J. Fomon identified this problem (*Pediatrics* 72:37, 1983). They restricted their analysis to calcium and phosphorus, but recognize that other formula components also may be left in the sediment. The authors conclude with the following thoughtful advice: "Nutritional management of small premature infants is a new field. It has placed new demands on formula manufacturers and it can be anticipated that there will be new problems to be solved. Testing of infant formulas is clearly a responsibility of the manufacturers, but it is also a responsibility of pediatricians. It is not enough to know what is in the bottle; we must know what is delivered to the infant."

Remember—shake well before using.—F.A.O.] ◀

12–9 **Dietary Protein-Induced Colitis in Breast-Fed Infants.** The de-

(12–9) J. Pediatr. 101:906–910, December 1982

velopment of inflammatory proctocolitis in 6 infants during the first month of life while being breast-fed exclusively is reported by Alan M. Lake, Peter F. Whitington, and Stanley R. Hamilton. All infants had been born at term and had normal growth and development. At the time of evaluation they were passing 4–8 grossly bloody diarrheal stools a day; none of the infants appeared ill or dehydrated. Stool samples were negative for parasitic, viral, bacterial, or toxic causes. Presence of fecal leukocytes was indicative of rectal inflammation, and sigmoidoscopy revealed edema and focal ulcerations. Rectal biopsies demonstrated a wide range of acute and chronic inflammatory changes; fungi, parasites, or viral inclusions were not evident.

Bleeding stopped in all infants within 36 hours of discontinuance of breast-feeding and institution of either hydrolyzed casein formula or soy-based formula. In 5 of the infants, breast-feeding was resumed after 3 days and bleeding recurred within 36 hours. Elimination of cow's milk protein from the mothers' diet prevented further bleeding in 2 infants; hydrolyzed casein formula or soybean-based formula gave the same result in the others. Whole milk was tolerated by 4 infants tested after 1 year.

The clinical course and response of the 6 infants to elimination and reinstitution of breast milk feedings indicate a dietary origin of the inflammations. Maternal ingestion of cow's milk was the presumptive concern. The described disorder appears to be common enough that it should be recognized as a distinct clinical syndrome in infants with inflammatory colitis and negative microbial studies. Failure to appreciate the similarity of the proctoscopic lesions to those of idiopathic inflammatory bowel disease may lead to inappropriate therapeutic measures.

▶ [Nothing is perfect—to err is human. Maternal ingestion of "something" was presumably responsible for the breast milk-induced colitis in most instances, and whole cow's milk was incriminated in 2 cases (for more on this problem, see this edition of the YEAR BOOK, Chapter 3, "Allergy and Dermatology," article 3–1, for the study by Jakobsson and Lindberg).

Human milk was again identified as the culprit in a case of chloride deficiency syndrome (Hill, I. D., et al.: *Arch. Dis. Child.* 58:224, 1983). The chloride deficiency syndrome in infants is characterized by anorexia, failure to thrive, and hypokalemic metabolic alkalosis. It is seen most often in association with excessive vomiting secondary to surgical conditions such as pyloric stenosis. This condition also has been observed with the use of thiazide diuretics, Bartter's syndrome, pseudohypoaldosteronism with renal salt wasting, cystic fibrosis, deficient dietary chloride intake from improperly manufactured formula, and after exchange transfusion with blood containing acid-citrate-dextrose as a preservative. The second infant in whom the syndrome developed as a result of exclusive breast-feeding was being fed by a mother who had virtually no chloride in her milk. The mother was apparently healthy. The baby presented at age 7 weeks with a serum chloride value of 63 mEq/L.

Like I said before, nothing is perfect. Generally speaking, it is dangerous to generalize.—F.A.O.] ◀

12–10 **Plasma Vitamin K_1 in Mothers and Their Newborn Babies.** Plasma vitamin K_1 was assayed in 30 healthy adults, 15 healthy mothers at term, and their newborn infants by M. J. Shearer, S. Ra-

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(12–10) Lancet 2:460–463, Aug. 28, 1982

him, P. Barkhan, and L. Stimmler (Guy's Hosp., London). The mean plasma concentration in the fasting adults was 0.26 ng/ml (range, 0.10–0.66). The mean plasma concentration of 0.20 ng/ml for 8 of 9 mothers with measurable K_1 peak was not detected in the cord plasma of their babies. When 1 mg of vitamin K_1 was given intravenously to 6 mothers shortly before delivery, the plasma levels of vitamin K_1 were substantially raised and were, at the time of birth, up to 500 times the mean value in untreated mothers. Corresponding samples of cord plasma of 4 babies of treated mothers had vitamin K_1 levels of 0.10–0.14 ng/ml—at least a fivefold increase over endogenous levels, but still very low—providing direct evidence of the poor maternal-to-fetal transfer of vitamin K_1.

Early and severe hypoprothrombinemia with hemorrhage seems to be relatively uncommon in Western countries; the incidence is higher in the Far East and perhaps in Third World countries. British reports suggest that the condition occurs later. This late hemorrhagic syndrome is almost entirely confined to breast-fed infants and is probably due to much lower levels of vitamin K in human milk compared with cow's milk and commercial infant formula. The supply of vitamin K_1 to breast-fed infants can be increased readily by giving mothers supplemental vitamin K_1; an oral dose, taken perhaps twice weekly, could be a safe and effective treatment for the prevention of hypoprothrombinemia in breast-fed infants.

▶ [Hemorrhagic disease of the newborn is staging a comeback here in the United States as well as in Great Britain (O'Connor, M. E., et al.: *Am. J. Dis. Child.* 137:601, 1983; and McNinch, A. W., et al.: *Lancet* 1:1089, 1983). The bleeding is making its appearance, not in the first week of life, but usually at age 4–6 weeks. The bleeding is often intracranial. These infants had been breast-fed exclusively and did not receive vitamin K in the newborn period. In the United States, this omission usually occurs because the infant has been delivered at home. In the United Kingdom, the prophylactic use of vitamin K is not routine in all maternity units.

Recent studies suggest that most healthy term infants are not born vitamin K deficient but, instead, their low levels of factors II, VII, IX, and X reflect hepatic immaturity. By the third day of life, as hepatic capacity for protein synthesis improves, vitamin K does become limiting in the ability of the infant to produce the coagulation factors. True vitamin K deficiency may be present. Vitamin K deficiency can, and should, be prevented by following the American Academy of Pediatrics' recommendation of giving 0.5–1.0 mg of phytonadione to all newborn infants. If the mother refuses to have the baby receive the injection, then give the vitamin by mouth. Late hemorrhagic disease, bleeding at age 3–6 weeks, has not been observed in any healthy breast-fed infant, as yet, who received vitamin K at birth. Many breast milk samples have very little vitamin K in them. This reflects the fact that many maternal diets contain inadequate quantities of vitamin K, because when vitamin K is given to a nursing mother it will appear in her milk. Encourage breast-feeding mothers to eat some fresh green, leafy vegetables every day.

Make certain also that pregnant women taking anticonvulsants receive supplemental vitamin K, 20 mg per day, for the 2 weeks prior to delivery to prevent the severe, and frequently fatal, hemorrhage that may occur in their infants as a result of vitamin K deficiency (Deblay, M. F., et al.: ibid. 1:1247, 1982).—F.A.O.] ◀

12–11 **Biochemical Indices of Nutritional Status in Maternal, Cord, and Early Neonatal Blood.** Jitka S. Vobecky, Josef Vobecky, Dennis Shapcott, P.-P. Demers, Denys Cloutier, Roger Blanchard, and Christian Fisch (Univ. of Sherbrooke, Sherbrooke, Que.) undertook a

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(12–11) Am. J. Clin. Nutr. 36:630–642, October 1982.

longitudinal study of the effect of nutrition on health and development in the first 3 years of life. The nutritional status of 556 infants who were well at birth was evaluated using selected biochemical measurements in material venous blood, mixed arteriovenous cord blood, and infant's capillary blood obtained at age 5 days.

The serum levels of selected biochemical measurements are given in Table 1. A significant number of women were deficient in hemoglobin, total protein, vitamin C, iron, folic acid, and calcium (Table 2). Significant correlations between maternal and cord blood were more frequent than in other comparisons. Correlations between measures in maternal venous, cord, and infant capillary blood samples are given in Table 3. Effects of parity and maternal age were more evident for vitamin C in cord blood than in maternal venous blood (Table

TABLE 1.—MEAN SERUM LEVEL OF BIOCHEMICAL MEASUREMENTS IN MATERNAL VENOUS AND CORD BLOOD AT DELIVERY AND INFANT CAPILLARY BLOOD AT 5 DAYS

Nutrient	Maternal blood			Cord blood			Capillary blood		
	n	x̄	SD	n	x̄	SD	n	x̄	SD
HB (g/dl)	529	13.2	4.2	437	16.4	2.2			
Hematocrit (%)	529	37.5	4.7	249	45.3	4.7			
Protein (g/dl)	551	6.5	1.1	504	6.1	0.6	481	6.6	0.7
Cholesterol (mg/dl)	551	251.9	54.7	506	83.7	23.4	499	119.9	26.0
Triglyceride (mg/dl)	543	323.1	131.5	479	69.8	47.2	143	155.3	98.6
Vitamin A (μg/dl)	549	108.4	42.6	504	33.3	18.4	468	42.2	26.5
Vitamin E (mg/dl)	548	1.01	0.18	493	0.23	0.06	461	0.43	0.11
Vitamin C (mg/dl)	513	0.45	0.19	453	0.77	0.29			
Folic acid (ng/ml)	507	16.3	9.8	237	23.3	7.3	24	19.7	7.1
Calcium (mg/dl)	517	8.9	1.0	485	9.9	1.1	450	9.2	1.1
Iron (μg/dl)	507	102.8	33.4	276	110.4	29.5			
Magnesium (mg/dl)	550	1.65	0.31	505	1.68	0.31	453	1.93	0.34

(Courtesy of Vobecky, J. S., et al.: Am. J. Clin. Nutr. 36:630–642, October 1982.)

TABLE 2.—FREQUENCY OF DEFICIENT AND MARGINAL VALUES IN MATERNAL VENOUS BLOOD AT DELIVERY

Nutrient	n	Nutritional status: Deficient			Marginal			Both	
		Limit	n	%	Limit	n	%	n	%
Hb* (g/dl)	529	<9.5	18	3.4	9.5–10.9	33	6.2	51	9.6
Hematocrit* (%)	529	<30.0	32	6.1	30.0–32.0	12	2.3	44	8.3
Protein* (g/dl)	551	<5.5	22	4.0	5.5–5.9	62	11.3	84	15.3
Vitamin C* (mg/dl)	513	<0.20	36	7.0	0.20–0.29	65	12.7	101	19.7
Vitamin A* (μg/dl)	549	<10.0			10.0–19.0				
Serum iron* (μg/dl)	507	<40.0	15	3.0				15	3.0
Folic acid† (ng/ml)	507	<2.0	18	3.6	2.0–5.9	89	17.6	107	21.1
Vitamin E‡ (mg/dl)	548	<0.2			0.2–0.6	2	0.4	2	0.4
Calcium† (mg/dl)	517	<7.5	27	5.2				27	5.2

*Ten State Nutrition Survey in the United States—1968–1970, Department of Health, Education, and Welfare, publication number (HSM) 72-8129-72-8134, 1974.

†Nutrition Canada National Survey. Nutrition national priority. Health and Welfare Canada. Ottawa: Information Canada, 1973.

‡Laboratory Indices of Nutritional Status in Pregnancy. Committee on Nutrition of the Mother and the Preschool Child. Washington, D.C.: Food and Nutrition Board, National Research Council, National Academy of Sciences, 1978.

(Courtesy of Vobecky, J. S., et al.: Am. J. Clin. Nutr. 36:630–642, October 1982.)

TABLE 3.—Correlations Between Biochemical Measurements in Maternal Venous Blood, Cord Blood, and Infant Capillary Blood

	Maternal vs cord	Cord vs infant	Maternal vs infant
Hb	0.08		
Hematocrit	0.14		
Protein	0.15*	0.08	0.15*
Cholesterol	0.30†	0.24†	0.13*
Triglyceride	0.23†	0.35†	0.18*
Vitamin E	0.26†	0.21†	0.02
Vitamin A	0.34†	0.27†	0.12*
Vitamin C	0.63†		
Folic acid	0.64†	0.55†	0.77*
Iron	−0.03		
Calcium	0.45†	0.23†	0.21†
Magnesium	0.64†	0.43†	0.33†

*$P < .05$.
†$P < .01$.
(Courtesy of Vobecky, J. S., et al.: Am. J. Clin. Nutr. 36:630–642, October 1982.)

TABLE 4.—Mean Serum Levels of Vitamin C in Maternal Venous and Cord Blood According to Maternal Age and Parity

Maternal age	Parity ≤ 2			Parity ≥ 3			All			F	p
	n	x̄	SD	n	x̄	SD	n	x̄	SD		
Maternal venous blood											
<20	22	0.53	0.25				22	0.53	0.25		
20–24	134	0.46	0.20	5	0.42	0.20	139	0.46	0.20	0.25	NS
25–29	166	0.44	0.16	40	0.47	0.14	206	0.44	0.16	2.00	NS
30+	47	0.50	0.22	41	0.43	0.21	88	0.47	0.22	1.06	NS
Total	369	0.46	0.19	86	0.45	0.18	455	0.46	0.19	0.22	NS
ANOVA: F		2.13			0.69			1.71			
p		NS			NS			NS			
Cord blood											
<20	16	1.01	0.47				16	1.01	0.47		
20–24	120	0.82	0.27	4	0.90	0.36	124	0.82	0.27	0.37	NS
25–29	148	0.78	0.32	33	0.71	0.29	181	0.77	0.31	1.29	NS
30+	41	0.73	0.29	34	0.75	0.27	75	0.74	0.29	0.09	NS
Total	325	0.80	0.31	71	0.74	0.28	396	0.79	0.31	2.31	NS
ANOVA: F		3.78			0.83			4.57			
p		0.05			NS			0.01			

(Courtesy of Vobecky, J. S., et al.: Am. J. Clin. Nutr. 36:630–642, October 1982.)

4). Iron levels in maternal blood and cord blood declined in association with parity (Table 5).

These findings indicate the risk of nutritional deficiency in neonates even with uneventful pregnancy and in an economically favored population. Longitudinal biochemical analyses are useful in assessing the risk of such deficiencies. Nutritional surveillance during pregnancy must remain an important part of preventive health care.

TABLE 5.—MEAN SERUM LEVELS OF IRON IN MATERNAL VENOUS AND CORD BLOOD ACCORDING TO MATERNAL AGE AND PARITY

Maternal age	Parity ≥ 2			Parity ≤ 1			All			F	p
	n	x̄	SD	n	x̄	SD	n	x̄	SD		
Maternal venous blood											
<20	22	106.6	33.9				22	106.6	33.9		
20–24	129	105.9	32.3	5	99.2	23.0	134	105.7	32.0	0.21	NS
25–29	161	104.5	32.9	38	93.3	29.2	199*	102.4	32.6	3.78	>0.05
30+	46	100.3	34.9	46	100.6	36.3	92	99.9	35.6	0.02	NS
Total	358	104.6	33.0	89	96.8	32.6	447†	103.1	33.1	4.01	0.05
ANOVA: F		0.35			0.59			0.67			
p		NS			NS			NS			
Cord blood											
<20	9	118.4	20.8				9	118.4	20.8		
20–24	72	108.2	25.7	5	99.8	17.5	77	107.7	25.6	0.52	NS
25–29	92	111.3	28.8	20	104.6	24.4	112‡	110.0	33.3	1.07	NS
30+	15	124.7	30.9	27	112.9	24.9	42§	117.1	26.8	1.82	NS
Total	188	111.5	31.0	52	108.5	24.5	240	110.8	29.6	0.43	NS
ANOVA: F		2.98			1.04			1.16			
p		0.05			NS			NS			

*$t_{197} = 1.93$; $P < .05$.
†$t_{110} = 2.5$; $P < .01$.
‡$t_{445} = 2.00$; $P < .05$.
§$t_{40} = 1.96$; $P < .05$.
(Courtesy of Vobecky, J.S., et al.: Am. J. Clin. Nutr. 36:630–642, October 1982.)

12–12 **Histologic Osteomalacia due to Dietary Calcium Deficiency in Children.** Although an adequate calcium intake is necessary for optimal growth and mineralization of the skeleton, the effects of calcium deficiency on bone metabolism are unclear. Pierre J. Marie, John M. Pettifor, F. Patrick Ross, and Francis H. Glorieux undertook a histomorphometric study of trabecular bone formation and resorption in undecalcified sections of iliac crest from 3 children with evidence of rickets associated with dietary calcium deficiency. The children were blacks aged 4 to 13 years from an area with a high prevalence of hypocalcemia. A dietary survey of affected children from the area showed a dietary calcium intake of only 125 mg daily and a normal phosphorus intake.

Active rickets was evident initially in all patients. There was no overt evidence of undernutrition other than growth retardation. Serum calcium concentrations were low, and urinary calcium excretion was reduced. Serum alkaline phosphatase values were elevated in all patients. Serum concentrations of 25-hydroxyvitamin D were normal. Mild osteopenia was seen before treatment, with severe osteomalacia. Calcium supplementation led to a great increase in calcified bone volume and a marked reduction toward normal in the amount of osteoid. The calcification front rose to normal. The osteoblastic surface and indicators of bone resorption remained elevated in 2 of the 3 patients.

Osteomalacia may be associated with pure calcium deficiency in children. Adequate amounts of calcium may rapidly improve bone

(12–12) N. Engl. J. Med. 307:584–588, Sept. 2, 1982.

mineralization in such rachitic children. Although osteomalacia was the chief abnormality in these three calcium-deficient children, some histologic abnormalities were suggestive of secondary hyperparathyroidism.

12–13 **Growth and Bone Mineralization of Normal Breast-Fed Infants and Effects of Lactation of Maternal Bone Mineral Status.** Gary M. Chan, Charles C. Roberts, David Folland, and Richard Jackson (Univ. of Utah) investigated whether a human milk diet provides for adequate growth and bone mineralization in the first year of life, compared with formula feeding, and examined the effects of 6 months of lactation on maternal calcium and bone mineral status. Ninety-one healthy term infants were included in the study. Fifty-one were breast-fed and 40 were fed Similac. Twenty-nine breast-fed infants received a supplement of 400 IU of vitamin D daily. All lactating mothers supplemented their daily diets with 400 IU of vitamin D and 250 mg of calcium. Limited solids were permitted the infants, but not encouraged, after age 4 months.

No significant differences in calcium (Ca), ionized calcium (iCa), or phosphorus (P) concentrations were found, but the breast-fed infants had higher serum 25-hydroxyvitamin D (25-OH D) concentrations at 2 months than at 2 weeks (Table 1). Bone mineral content (BMC) was similar in the dietary groups. Infants receiving Similac had a lower

TABLE 1.—BIOCHEMICAL VALUES FOR INFANTS*

	Postpartum age			
	2 wk	2 m	4 m	6 m
Human milk alone				
Total Ca (mg/dl)	10.1 ± 0.5	10.2 ± 0.2	10.4 ± 0.2	10.1 ± 0.3
iCa (mg/dl)	3.8 ± 0.1	3.7 ± 0.1	3.9 ± 0.1	3.8 ± 0.1
P (mg/dl)	4.2 ± 0.4	5.2 ± 0.3	5.0 ± 0.3	6.1 ± 0.1
AP (IU/l)	110 ± 15	128 ± 6	91 ± 7	113 ± 8
25-OH D (ng/ml)	20 ± 3	17 ± 2	17 ± 3†	19 ± 2
n	20	22	23	19
Human milk + D				
Total Ca	9.9 ± 0.4	10.4 ± 0.3	9.8 ± 0.3	10.3 ± 0.3
iCa	3.8 ± 0.1	3.8 ± 0.2	3.9 ± 0.1	3.8 ± 0.1
P	5.1 ± 0.3	5.8 ± 0.4	5.0 ± 0.3	6.3 ± 0.3
AP	115 ± 9	145 ± 6	103 ± 10	121 ± 8‡
25-OH D	14 ± 1	19 ± 2§	22 ± 3	23 ± 3
n	29	23	24	20
Similac				
Total Ca	10.4 ± 0.2	9.7 ± 0.2	10.2 ± 0.2	9.2 ± 0.4
iCa	3.7 ± 0.1	3.8 ± 0.2	4.0 ± 0.1	3.9 ± 0.1
P	4.9 ± 0.4	5.0 ± 0.3	4.7 ± 0.3	7.0 ± 0.3
AP	85 ± 7‖	121 ± 9	106 ± 6	99 ± 8
25-OH D	20 ± 2	27 ± 4	25 ± 2	18 ± 2
n	40	39	40	30

*Mean ± SEM.
†($P < .05$) significantly lower than human milk + D and Similac groups.
‡($P < .05$) significantly higher than Similac group.
§($P < .05$) significantly higher than 2-wk value.
‖($P < .05$) significantly lower than human milk and human milk + D groups.
(Courtesy of Chan, G. M., et al.: Am. J. Clin. Nutr. 36:438–443, September 1982.)

(12–13) Am. J. Clin. Nutr. 36:438–443, September 1982.

TABLE 2.—SERUM VALUES* AND BONE MINERAL STATUS OF NURSING MOTHERS

	Postpartum age			
	2 wk	2 m	4 m	6 m
Total Ca (mg/dl)	10.0 ± 0.4	10.1 ± 0.3	9.8 ± 0.3	10.0 ± 0.3
iCa (mg/dl)	3.9 ± 0.1	3.7 ± 0.2	4.0 ± 0.1	4.1 ± 0.1
P (mg/dl)	4.7 ± 0.3	4.8 ± 0.3	4.2 ± 0.2	4.7 ± 0.3
AP (IU/l)	46 ± 4	40 ± 4	39 ± 3	41 ± 3
25-OH D (ng/ml)	24 ± 4	19 ± 1	20 ± 2	19 ± 2
BMC (gm/cm)	0.957 ± 0.027	0.962 ± 0.024	0.959 ± 0.026	0.971 ± 0.025
n	49	45	47	39

*Mean ± SEM.
(Courtesy of Chan, G. M., et al.: Am. J. Clin. Nutr. 36:438–443, September 1982.)

mean alkaline phosphatase (AP) value at age 2 weeks. No significant maternal biochemical changes were observed during 6 months of lactation (Table 2). Social indices were comparable for the various dietary groups.

Breast-fed and formula-fed infants in this study grew similarly over the first year. Bone mineralization was similar in the two groups of infants. It is concluded that human milk provides for adequate growth and bone mineralization in the first year. Where environmental and social conditions are favorable, daily vitamin D supplementation may be unnecessary for breast-fed infants. Mothers in this study who were lactating and received vitamin D and calcium supplements had normal calcium and bone mineral status.

▶ [Dr. Reginald C. Tsang, Professor of Pediatrics, Obstetrics, and Gynecology, University of Cincinnati Medical Center, provided us with a commentary. Reggie, who is "all-world" with me, wrote the following:

"The study from Utah is well designed and thought out and attempts to answer the question of whether infants who are breast-feeding require supplemental vitamin D for proper bone mineralization and vitamin D metabolism. A comprehensive examination of mother and infant relationships is also an important feature of the study. One of the major problems of the study, however, is that it is not a "blinded" trial. In a nonblinded trial where the control group is not given a therapeutic agent, there is always the possibility that subjects will change their habits or performance overtly or covertly in a desire to minimize any "problems" that they perceive could happen to them. For example, parents of infants who are in the "no vitamin D supplemented group" would be aware that the study involves the determination of vitamin D concentration in blood and that sunshine would play a role in vitamin D synthesis. These parents may decide, consciously or unconsciously, that their infants should be given greater exposure to sunshine because of concern that their infants may not be receiving "adequate" vitamin D. Alternatively, the parents may decide to give vitamin D supplementation without the investigators' knowledge, especially since the parents realize other infants are receiving vitamin D supplementation.

"In contrast, a study by Greer et al., in Cincinnati, utilized a careful prospective double-blinded trial of breast-fed infants with or without vitamin D supplementation (*J. Pediatr.* 98:696–701, 1981). Significant differences in bone mineral content and serum 25-hydroxyvitamin D concentrations were detected between the two groups. Bone mineral content progressively decreased with age in unsupplemented infants and was significantly lower than values in supplemented infants. Serum 25-hydroxyvitamin D concentrations fell in infants without vitamin D supplementation and were significantly lower than levels in supplemented infants. Moreover, some of the unsupplemented infant serum 25-hydroxyvitamin D concentrations fell into undetectable ranges that are commonly associated with rickets.

"On close inspection of the paper by Chan et al., it is apparent that a number of their subjects also had low serum 25-hydroxyvitamin D concentrations at 4 months.

The mean ± standard error serum 25-hydroxyvitamin D concentration at 4 months in infants not given vitamin D supplementation was 17 ± 3 ng/dl. Adjusting for the number of subjects, the standard deviation of the mean would be 14.4 ng/dl. Thus, a large proportion of subjects would have serum 25-hydroxyvitamin D concentrations below 10 ng/dl, the normal lower limit in the authors' laboratory. Furthermore, the mean minus 1 standard deviation level would be at 3 ng/ml, which is in the undetectable range. Finally, serum 25-hydroxyvitamin D concentrations at this time also were significantly lower than those of infants who were fed human milk plus vitamin D, or infants fed Similac. Thus, it appears that vitamin D metabolism might be affected adversely in the breast-fed infants studied in Utah, despite the saguine conclusions of the authors.

"These facts, plus the large number of anecdotal reports of rickets occurring in breast-fed infants (Tsang, R. C., and Erenberg, A.: *Pediatric Update*, Elsevier, New York, 1980, pp. 193–242), remind us of the dangers of being too casual in regard to vitamin D supplementation of breast-fed infants. The authors comment on the finding of high contents of "vitamin D sulfate" in breast milk. However, using much more sophisticated, modern methods of analysis, it is abundantly clear that there is *no* vitamin D sulfate in human milk and that even if vitamin D sulfate were present in human milk, its bioactivity is negligible (Tsang, R. C.: *Lancet*, in press.) Thus, while the study of Chan et al. is provocative, their data are not supported by other studies and should not be extrapolated readily to recommendations that vitamin D supplementation is not necessary in breast-fed infants. Unless one is assured of adequate sunshine exposure, we feel it is more likely that human milk does not provide sufficent vitamin D for prevention of rickets."] ◀

13. The Musculoskeletal System

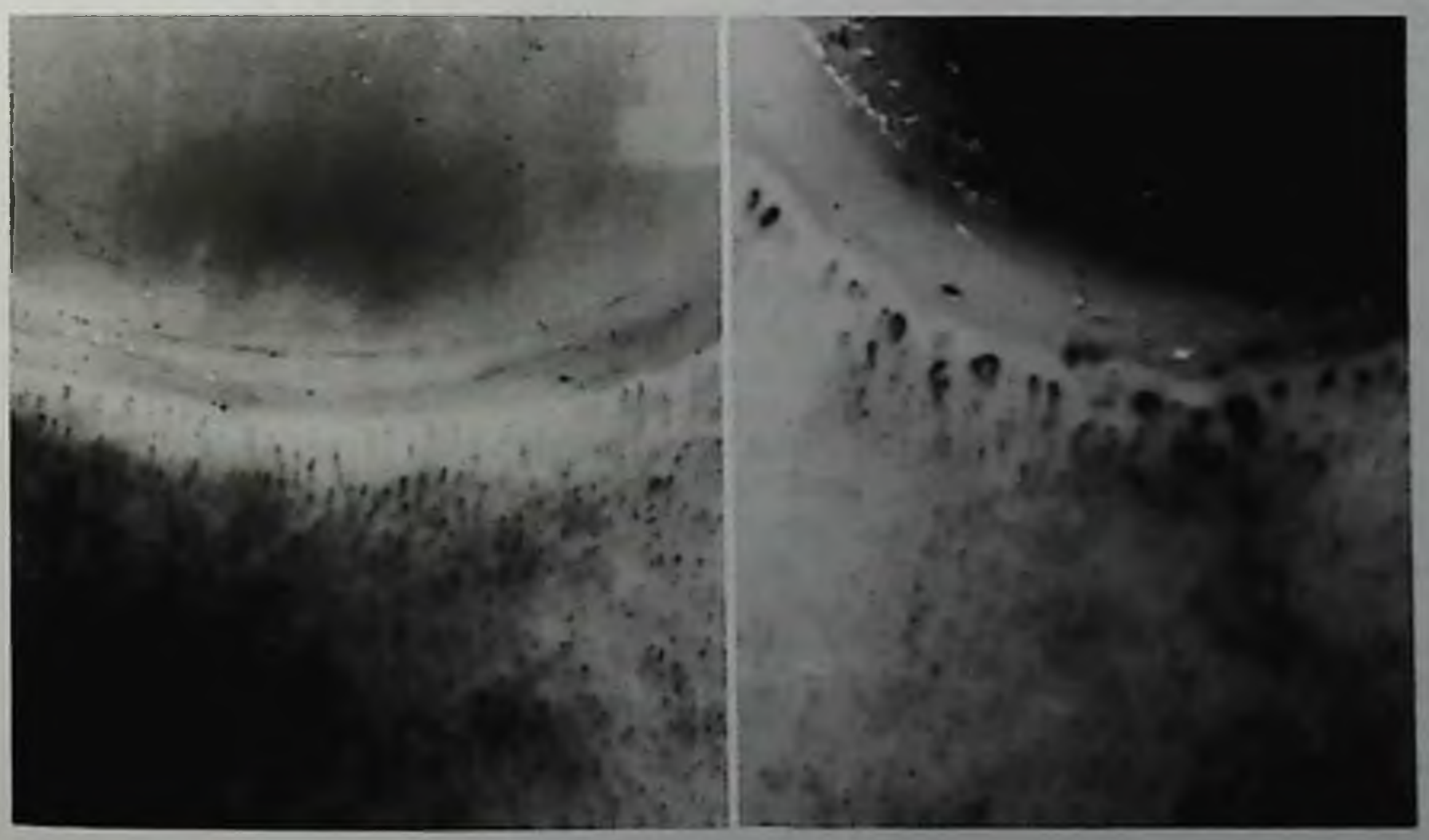
13–1 **Nail Fold Capillary Abnormalities in Childhood Rheumatic Diseases.** Distortion of the nail fold capillary pattern has been described in some adult rheumatic disease populations, including patients with scleroderma, mixed connective tissue disease, and idiopathic Raynaud's phenomenon. George Spencer-Green, Margaret Schlesinger, Kevin E. Bove, Joseph E. Levinson, Jane G. Schaller, Virgil Hanson, and William E. Crowe examined the nail fold capillary patterns of 84 patients with a variety of childhood rheumatic diseases and 34 normal controls. Childhood dermatomyositis was present in 32 patients, juvenile rheumatoid arthritis in 22, scleroderma in 19, systemic lupus erythematosus in 7, and mixed connective tissue disease in 4. Nine patients had systemic and 10 had localized scleroderma.

The normal and abnormal appearances on nail fold capillaroscopy are shown in Figures 13–1 and 13–2. Abnormalities were found in 29 subjects, all with scleroderma or dermatomyositis. Nine of the 19 patients with scleroderma and 20 of the 32 with dermatomyositis had nail fold capillary abnormalities. The abnormalities were similar in these groups, although highly arborized capillary loop clusters were

Fig 13–1 (left).—Normal nail fold pattern with homogeneous distribution and uniform appearance of loops.

Fig 13–2 (right).—Abnormal nail fold pattern with distinct population of dilated capillary loops (systemic sclerosis).

(Courtesy of Spencer-Green, G., et al.: J. Pediatr. 102:341–346, March 1983.)



(13–1) J. Pediatr. 102:341–346, March 1983.

more frequent in patients with dermatomyositis. All affected scleroderma patients had systemic disease. Seven of the patients with dermatomyositis had a highly arborized, tortuous capillary pattern besides dilatation or dropout of nail fold capillary loops.

Nail fold capillaroscopy is a relatively simple, noninvasive procedure that can help characterize some types of rheumatic disorder and may be useful as an index of vascular involvement in dermatomyositis. The study also may help distinguish localized from systemic scleroderma in children. Prospective studies are needed to determine at what stage of disease the nail fold capillary abnormalities develop and whether they change during exacerbations or remissions of disease.

▶ [Dr. Walter Tunnessen, Professor of Pediatrics, State University of New York at Syracuse, comments:

"The average general pediatrician will have little exposure to children with connective tissue diseases, with the possible exception of juvenile rheumatoid arthritis (JRA), during his practicing years. This article by Spencer-Green et al. may not generate more than passing interest to most readers, particularly because the nail fold capillary abnormalities are described only in systemic scleroderma and dermatomyositis, and not in JRA, systemic lupus erythematosus (SLE), or mixed connective tissue disease. In addition, the authors used a stereomicroscope with 25× or 40× magnification to examine the capillary patterns, hardly your standard office equipment. But wait, there's hope for us all! Minkin and Rabhan (*J. Am. Acad. Dermatol.* 7:190–193, August 1982) describe their experience using the standard ophthalmoscope (set at +40) and found this ubiquitous instrument was similarly effective in picking up nail fold abnormalities. In fact, 20 of 27 (74%) of their patients with systemic sclerosis demonstrated the dilated capillary loops noted in the report of Spencer-Green et al., while the other 7 showed nonspecific changes. None was normal. Similar capillary dilatations were noted in 82% of 11 patients with dermatomyositis. The remaining 18% had nonspecific changes. A tortuous, disorganized pattern was found in 8 of 15 patients with SLE. Five other SLE patients had a nonspecific pattern, 1 had the dilated pattern, and 1 was normal. The age range of these patients was not given.

You might ask, 'Why bother?' The clinical features of systemic sclerosis and dermatomyositis are usually clear enough that this added evidence of vasculopathy is gilding the lily. In most cases this is true. But, detection of nail fold capillary abnormalities may be helpful in two situations: (1) the patient with the Raynaud phenomenon, and (2) the separation of localized scleroderma or morphea from systemic sclerosis.

The Raynaud phenomenon is relatively common in children, particularly teenagers. We are often faced with the uncertainty of trying to decide if the pallor followed by cyanosis is primary (Raynaud's disease) or secondary (Raynaud's phenomenon) to an underlying disorder. Systemic sclerosis may present with the Raynaud phenomenon long before the appearance of tight skin or systemic symptoms. A careful examination of the nail fold capillaries may forecast who goes on to develop the relentless downhill course of systemic sclerosis. Maricq et al. (*Arthritis Rheum.* 23:716, 1980) followed 18 patients with Raynaud's disease for 9 months to 5 years. Nine had nail fold capillary dilations, 4 of whom eventually developed clinical systemic sclerosis. None of the other 9 without dilation developed this disease. The possible predictive value of this simple examination is obvious.

Localized scleroderma or morphea is many times more common than systemic sclerosis, in my experience. Unfortunately, patients often are told they have the systemic form of scleroderma when they have the usually benign local disease. Occasionally, systemic sclerosis may begin as apparent localized disease. Nail fold capillaries are abnormal in systemic sclerosis but normal in morphea.

I'm sure we'll hear more about this technique in the future. Keep your ophthalmoscopes ready!

One last comment: Acrocyanosis, a persistent dusky discoloration of the hands

and feet, is much more common than the Raynaud phenomenon, especially in teenage girls. The pallor and discomfort of the latter disorder are not present, and the color change is usually symmetric rather than spotty. Be careful to separate these two phenomena."] ◄

13–2 **Diffuse Fasciitis With Eosinophilia in Childhood.** Diffuse fasciitis with eosinophilia is a newly recognized connective tissue disease appearing initially to be scleroderma or dermatomyositis. It has clinical and histologic features that allow it to be separated from both disorders and has a more favorable prognosis.

There have been about 100 cases of this syndrome reported, showing a 2:1 male predominance, restriction to white patients, and aggregation of clinical onset between ages 17 and 65 years. Edward M. Sills (Johns Hopkins Univ.) reports the cases of 2 girls, aged 7 and 14½ years, respectively, with this disorder.

The disease involves the extremities and, at times, the trunk diffusely. The face is always spared; the hands and feet are very infrequently involved. The skin is firm and swollen, often puckered or ridged, and tightly bound to underlying structures; contractures result in several weeks. The thickened subcutaneous tissue and limited joint motion usually follow a brief prodrome of fever, myalgia, and easy fatigability. Increased erythrocyte sedimentation rate, hypergammaglobulinemia (IgG), and hypereosinophilia (circulating count of >300/cu mm) are characteristic. The disorder often has been confused with scleroderma, morphea, and dermatomyositis (Tables 1 and 2).

For diagnosis, full-thickness biopsies extending from skin through subcutaneous tissue, fascia, and muscle are taken together as one block. These tissues should not be separated from each other. The diagnostic lesion is in the fascia, which is thickened with edema, fibrosis, and mononuclear cells. The dermis occasionally shows mild perivascular inflammation.

The clinical response to steroids is prompt and favorable. The dis-

TABLE 1.—CLINICAL COMPARISONS OF RELATED DISORDERS*

	Diffuse Fasciitis With Eosinophilia	Scleroderma	Morphea	Dermatomyositis
Responsiveness to systemic corticosteroids	++	0	0	++
Joint contracture/stiffness	++	++	+-	+
Thickened, indurated skin	+	++	++	+
Antecedent unusual physical exertion	+	0	0	0
Raynaud's phenomenon	0	++	+	0
Systemic involvement	0	++	0	-+
Esophageal dysfunction	0	++	0	+
Intestinal dysfunction	0	++	0	+
Pulmonary dysfunction	0	++	0	+
Telangiectasis	0	++	+	0
Muscle pain	+	+	+	++
Muscle weakness	0	+	+	++
Periorbital rash	0	0	0	-+
Rash over extensor surfaces of joints	0	0	0	++

*Symbols: 0, absent or rare; +, occasional; ++, frequent.
(Courtesy of Sills, E. M.: John Hopkins Med. J. 151:203–207, November 1982.)

(13–2) Johns Hopkins Med. J. 151:203–207, November 1982.

TABLE 2.—CLINICAL LABORATORY COMPARISONS OF RELATED DISORDERS*

	Diffuse Faciitis With Eosinophilia	Scleroderma	Morphea	Dermatomyositis
Peripheral eosinophilia	+ +	0	0	0
Increased erythrocyte sedimentation rate	+ +	+	0	+
Hypergammaglobulinemia	+ +	+	0	+
Late appearance of autoimmune thrombocytopenia/aplastic anemia	+ +	0	0	0
Elevated serum levels of muscle enzymes	+	+	0	+ +
Antinuclear antibody (fluorescent)	+	+	+	+
Inflammatory electromyography	0	0	0	+ +

*Symbols: 0, absent; +, occasional; + +, frequent.
(Courtesy of Sills, E. M.: Johns Hopkins Med. J. 151:203–207, November 1982.)

order has a 10%–20% spontaneous remission rate. Biopsies performed years after clinical remission and cessation of therapy show that inflammation and thickening of the deep fascia has persisted despite the absence of clinical or laboratory abnormalities. There also has been, in some patients, IgG antibody-mediated thrombocytopenic purpura and aplastic anemia.

Review of reported cases reveals that, when the time of onset was noted, the great majority of cases started in the fall or winter months. This has provoked speculation that a seasonal antigen might be evoking an unusual response in a susceptible host.

▶ [Doctor Sills nicely brings us up to date with the current status of a disorder that was first described only 10 years ago. As he points out, eosinophilic fasciitis is an uncommon problem that must be distinguished from scleroderma, morphea, and dermatomyositis. There is one other disorder that also should be distinguished from eosinophilic fasciitis, and that is eosinophilic cellulitis. This is a completely different problem, first described in 1971 by G. C. Wells (*Trans. St. John's Hosp. Dermatol. Soc.* 57:46, 1971). Eosinophilic cellulitis is characterized by reddened elevated areas of the skin that rapidly increase in size over several days. With eosinophilic fasciitis, facial involvement can occur. With eosinophilic cellulitis, there is marked edema and moderate erythema, and most often the skin is thought to have bacterial cellulitis. There is no response to antibiotics, however. The lesions of eosinophilic cellulitis resolve over several weeks without scarring or other permanent changes. The natural history is one of recurrent episodes over several months or even a few years, but with eventual resolution and uniformly good results in the long run. This is not necessarily true of eosinophilic fasciitis, as described in this article by Sills. The laboratory hallmark of both eosinophilic cellulitis and eosinophilic fasciitis is marked peripheral blood eosinophilia. The skin lesions of eosinophilic fasciitis also begin rapidly, but evolve into scleroderma-like skin changes. Eosinophilic fasciitis tends to follow a more chronic course and the individual lesions, if they resolve at all, take months or years to do this. With eosinophilic fasciitis, if healing does occur, it can be complete, but there are residual atrophic skin changes. Histologically, eosinophilic fasciitis is characterized by inflammation and thickening of the collagen bundles of the deep fascia with some extension into the muscle and subcutaneous tissue. With eosinophilic cellulitis, on the other hand, there is massive infiltration of eosinophils into the soft tissue. Only in the very early stages of eosinophilic fasciitis are there any eosinophils in the actual skin lesions. If you wish to read more about eosinophilic cellulitis, please see the excellent discussion of this disorder by R. T. Saulsbury et al. (*J. Pediatr.* 102:266, 1983).—J.A.S., III] ◀

13–3 **Infantile Myositis.** Charlotte E. Thompson (St. Mary's Hosp. and Med. Center, San Francisco) describes 3 children with infantile myos-

(13–3) Dev. Med. Child. Neurol. 24:307–313, June 1982.

REPORTED CASES OF INFANTILE POLYMYOSITIS

Patient	*Onset (mths)*	*sex*	*Biopsy*	*EMG*	*CPK*	*Rx*	*Outcome*
Thompson (1968)	3	M	1. Diffuse inflammation 2. Increased CT†	Myopathic	40×	Prednisone	Improved
Cape *et al.* (1970)	10	F	1. Extensive inflammation	Myopathic	6×	—	Spontaneous improvement
Walton and Adams (1958)	12	M	Focal degeneration Perivascular inflammation Increased CT	—	—	ACTH	Improved
Nattrass (1954)	12	F	Fat and fibrous tissue	—	—	—	Improved
Haas (1966)*	6	M	1. Fibrous tissue 2. Round-cell infiltration	Myopathic	3·5×	Prednisone	Improved but in wheelchair
Carpenter *et al.* (1979)	12	M	Increased CT, fat intense inflammatory reaction	?Denervation	10×	Prednisone	Improved
	6*	M	Necrotic fibers Inflammation Atrophic fibers Regeneration	Equivocal	25×		

*Personal communications.
†Connective tissue.
(Courtesy of Thompson, C. E.: Dev. Med. Child Neurol. 24:307–313, June 1982.)

itis who responded well to steroid treatment. The original diagnosis in these cases had been congenital muscular dystrophy. Because infantile polymyositis is rarely diagnosed, potentially treatable disease in children may be missed.

It appears that the general criteria to establish a diagnosis of pure polymyositis would be proximal, progressive muscle weakness or diffuse weakness at birth, specific changes on muscle biopsy specimens,

serum enzyme elevation, and, most importantly, a therapeutic response to steroids.

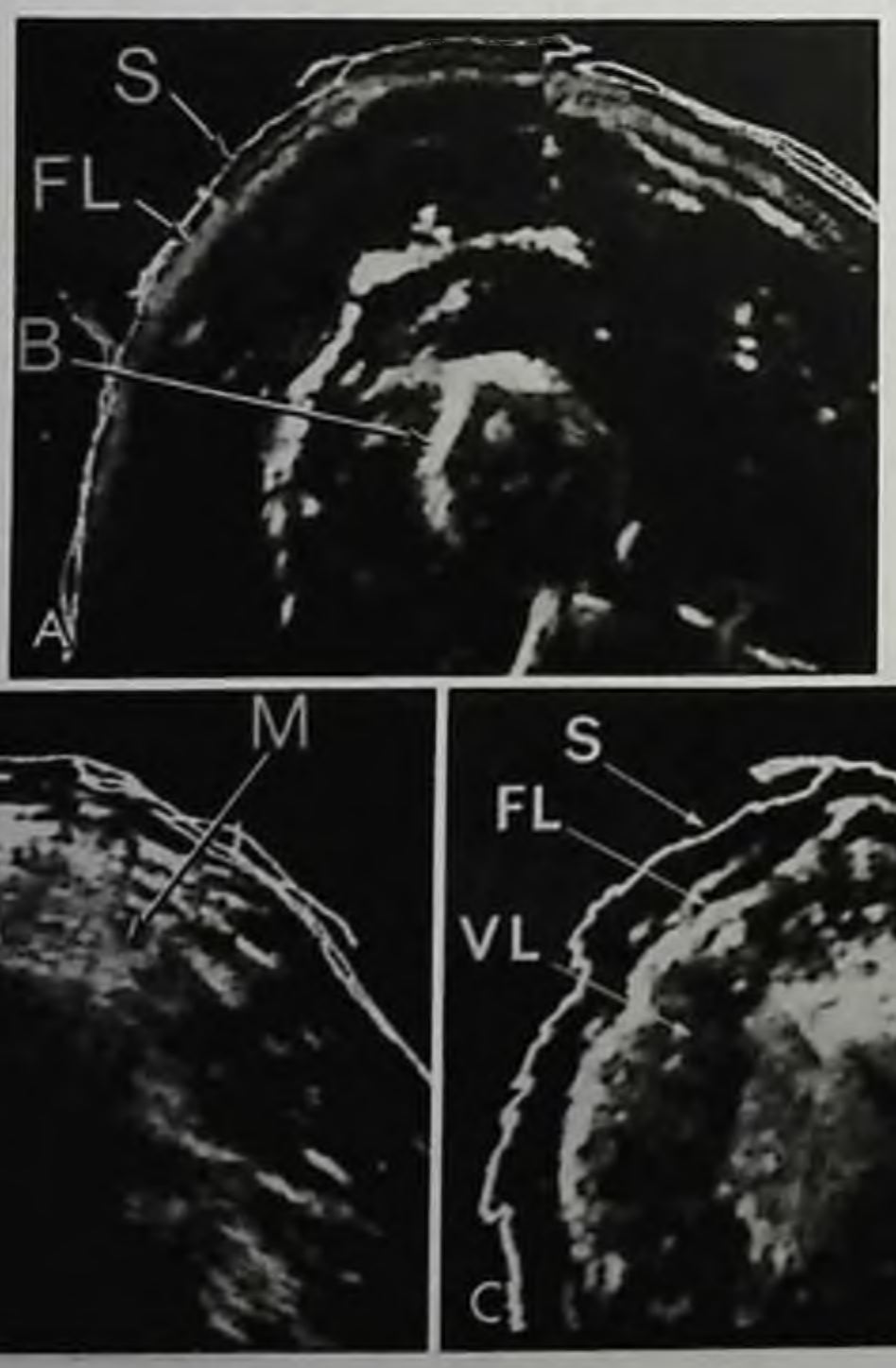
There have been only 5 previous case reports of myositis in infants younger than age 1 year (table). Unlike 2 of the cases presented in this report, the infants previously described showed no hypotonia at birth.

The term "polymyositis" is generally used to include both dermatomyositis and polymyositis, but that seems to be too all-inclusive for childhood cases. Infantile myositis would be defined as polymyositis affecting infants younger than age 1 year.

Experience with the cases in this report suggests that hypotonic infants with highly elevated creatine phosphokinase concentrations and nonspecific changes on biopsy specimens should be given at least a short trial on steroids.

13–4 **Ultrasound Imaging in the Diagnosis of Muscle Disease.** J. Z. Heckmatt, S. Leeman, and V. Dubowitz (Hammersmith Hosp., London) performed a comparative study of the static B-scan ultrasound appearance of the quadriceps muscle of the thigh in 60 new patients with neuromuscular disorders and in 60 control children. A 6-mm di-

Fig 13–3.—Transverse scans of the thigh in 3 boys, all aged 8 years. **A**, normal thigh showing relatively echo-free muscle, vastus lateralis and intermedius *(VL* and *VI)*, between the echogenic fascia lata *(FL)* and the strong bone echo *(B)*. **B**, thigh of boy with Duchenne's dystrophy showing increase in muscle echo *(M)* and complete loss of bone echo. **C**, thigh with central core disease showing marked increase in muscle echo, mainly from vastus intermedius, and loss of bone echo. *S*, skin. (Courtesy of Heckmatt, J. Z., et al.: J. Pediatr. 101:656–660, November 1982.)



(13–4) J. Pediatr. 101:656–660, November 1982.

ameter, 5-MHz transducer was used that focused the sound at a depth of 2 cm.

In control subjects there was good visualization of bone and fascia, which stood out clearly against the background of echo-free muscle tissue (Fig 13–3, A). Muscular dystrophies were associated with an increase in the intensity of echo reflected from the muscle substance, with corresponding loss of bone echo (Fig 13–3, B). Spinal muscular atrophies and neuropathies likewise showed an increase in muscle echo, along with muscle atrophy and increase in depth of subcutaneous tissue. Various congenital myopathies also showed changes (Fig 13–3, C). Infants with hypotonia from nonneuromuscular causes had normal scans.

Except in progressive muscular dystrophy, severity of change on the scan did not relate to functional disability; some children had good function, yet strikingly abnormal scans. However, the degree of change on the scan correlated with the degree of disruption of muscle architecture on biopsy.

Ultrasound imaging has proved to be a useful noninvasive screening tool in investigation of children with neuromuscular disease. The main limitation to the use of ultrasound in "floppy" infants is that those with severe spinal muscular atrophy, particularly with a short history, may have a normal scan. It also may be difficult to pick up change in the early stages of Duchenne's, Becker's, and limb-girdle dystrophy. In some instances, ultrasound scanning allowed distinction between myopathy and neuropathy. It seems that ultrasound reflects altered fascicular structure rather than variation in size of individual muscle fibers.

▶ [Dr. Carl Crosley, Associate Professor of Pediatrics and Head, Section of Pediatric Neurology, State University of New York at Syracuse, comments on the preceding two studies:

"Charlotte Thompson has given us an interesting perspective on that large group of children collectively labeled 'floppy babies.' The 3 cases of infantile myositis she describes are established by not unreasonable modifications of fairly standard criteria. Her strong recommendations for steroid therapy may well lead to additional curable cases of infantile hypotonia. However, a clear clinical response to treatment is an additional absolute necessity prior to continuing any such therapy long term. The biochemical bases for most neuromuscular diseases are unknown. It is not surprising, therefore, that without a specific diagnostic procedure or simple blood test, confusion between specific entities can occur. The individual criteria used by Doctor Thompson may be found individually and collectively in the more common muscular dystrophies (e.g., Duchenne's muscular dystrophy, facioscapulohumeral dystrophy), in which steroids have been generally ineffective. Doctor Thompson says she has given us the sixth, seventh, and eighth reported cases of infantile myositis and, as such, has provided us with reasonable criteria to distinguish them from another rare entity, congenital muscular dystrophy, yet, despite our yearning to see one of these treatable children, we should recognize that even large medical centers can expect to see thousands of children hypotonic from other causes before one of these children arrives.

"The use of ultrasound of the thigh, as described by Heckmatt et al., has a potentially broader base of application. In their hands, the presence of a disease affecting the motor unit apparently is detected easily. They report no false positive and few false negative results using this technique. In addition, the false negative results occurred in circumstances in which the presence of disease was clinically obvious. The ability of this test to distinguish between neuropathic and myopathic conditions is a further bonus. Perhaps this examination will have widespread potential use as a

screening tool for the large number of floppy infants in whom concerns about neuromuscular disease persist. As the authors correctly point out, logistic simplicity and cost are, at present, advantages that ultrasound has over computed tomography scanning. Of course, we would hope that all others seeking to use ultrasound of the extremities in evaluating floppy babies would use the care in methodology and controls demonstrated by these authors."] ◄

13–5 **Significance of Antinuclear Antibodies in Juvenile Rheumatoid Arthritis Associated With Chronic Bilateral Iridocyclitis.** Chronic iridocyclitis occurs in almost 10% of patients with juvenile rheumatoid arthritis (JRA); more than 80% have pauciarticular onset of disease, often associated with antinuclear antibodies (ANA). The possibility that uveal inflammation is secondary to deposition of immune complexes (IC) was supported by experimental induction of iridocyclitis in animals, using intravenous injection of heterologous serum. Else-Marie Egeskjold, A. Johansen, H. Permin, H. M. Høyeraal, and T. Sørensen examined serum samples from 8 children with JRA and chronic bilateral iridocyclitis, 5 children with JRA and chronic bilateral iridocyclitis, 5 children with JRA but without iridocyclitis, and 3 healthy children. Analytic rate zonal ultracentrifugation was performed with sedimentation coefficients from each cut calculated by computer. Immunofluorescent examination of the anti-IgG antibodies of the IgA, IgM, and IgG classes and immunofluorescent examination of the ANA of the IgA, IgM, and IgG classes together with complement C3 fixing ANA were also performed.

Rate zonal ultracentrifugation generally separates serum samples into two peaks, the first containing lighter proteins, the second containing macroglobulins. The first peak in all patients and controls was within normal limits. Five of 8 patients showed the second peak displaced significantly to the right ($P = .05$). Only patients with iridocyclitis showed IgM ANA and IgM anti-IgG; both types of patients showed IgG ANA and IgG anti-IgG, although they were more common in patients with iridocyclitis. Low titers of IgM ANA were found in patients with IC > 22S, whereas patients with no detectable IC showed high titers of IgM ANA and positive reactions for IgM anti-IgG. The C3 fixing ANA was found only in patients with iridocyclitis and IC > 22S. The severity of iridocyclitis was clinically impossible to distinguish.

Results support the suggestion that ANA may be involved in the pathogenesis of chronic iridocyclitis and may explain why chronic iridocyclitis rarely develops in ANA-negative patients with JRA.

► [Iridocyclitis very rarely occurs in patients with the systemic form of juvenile rheumatoid arthritis. Now we see that antinuclear antibodies (ANA) may be involved in the etiology of chronic iridocyclitis, and this observation may explain why ANA-negative patients with juvenile rheumatoid arthritis only infrequently develop iridocyclitis.

It is a shame we don't know as much about juvenile rheumatoid arthritis as we do about Lyme arthritis. In short order, this was an affliction that came on the scene and was well described, and now we know the etiology of it after the isolation of a *Treponema*-like spirochete from *Ixodes dammini*, a genus of ticks serving as the vector of Lyme disease (Burgdorfer, W., et al.: *Science* 216:317, 1982; and Bosler, E. M.: ibid. 220:321, 1983). As far as juvenile rheumatoid arthritis is concerned, although we don't know much about its etiology, we ever so gradually are learning more and more about how to take care of this problem. Preparations of gold given by mouth may

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(13–5) Acta Pediatr. Scand. 71:615–620, July 1982.

soon be commonplace in its management. E. H. Giannini et al. (*J. Pediatr.* 102:138, 1983) reported their experience with an orally administered gold preparation, auranofin. Injectable preparations of gold generally are used as a last resort when all else has failed. The chief advantage of orally administered gold in the pediatric population may be the use of the oral rather than the parenteral route with a drug that has a very low incidence of adverse side effects. In fact, the possibility exists that orally administered gold may replace nonsteroidal anti-inflammatory agents in some patients. Additionally, auranofin can be given just once a day. You also may have read a great deal about the use of plasmapheresis as part of the management for rheumatoid arthritis. One recent study, hopefully once and for all, lays to rest the issues involved with this approach. I. L. Dwosh et al. (*N. Engl. J. Med.* 308:1124, 1983) concluded that plasmapheresis does not have a clinical benefit in chronic rheumatoid arthritis, even though it improves some of the laboratory parameters associated with this disease. Most of the studies of plasmapheresis in rheumatoid arthritis have been reported in adults. There is probably little reason to think that children would respond any better or worse, however. If you keep an eye out for definitive favorable reports with plasmapheresis in the pediatric literature, you are going to be half blind for a long time.

(If you are interested in reading what I think is the best review of the shortcomings of dimethyl sulfoxide (DMSO) in the management of rheumatoid diseases, see Jimenes, R. A. H.: *J. Lab. Clin. Med.* 100:489, 1982. It is much better than discussions of DMSO that have appeared on "60 Minutes" or in the Congressional Hearing Report, the popular book, and innumerable other newspaper and magazine articles.)—J.A.S., III] ◄

13–6 **Technetium Phosphate Bone Scan in Diagnosis of Osteomyelitis in Childhood.** D. W. Howie, J. P. Savage, T. G. Wilson, and Dennis Paterson (North Adelaide, Australia) reviewed technetium phosphate bone scans from 280 consecutive children referred with a clinical diagnosis of possible osteomyelitis. The average age was 6 years. Osteomyelitis was confirmed in 58 patients, and 5 others had confirmed recurrent osteomyelitis. In 45 patients the diagnosis was based on clinical criteria only. Of the remainder, 93 had nonosseous sepsis and 79 had no sepsis. Scans were made with ^{99m}Tc-labeled pyrophosphate initially, and later with ^{99m}Tc-methylene diphosphonate.

Scans correctly identified sites of osteomyelitis in 55 of 62 instances in patients with confirmed disease. The scan results were correctly negative in all but 5 patients who had no infection. The sensitivity of scanning was 89%, its specificity was 94%, and its overall accuracy was 92%. Three scans showed cold spots that represented sites of osteomyelitis. Six of the 7 false negative studies showed increased uptake in the area of involvement that was misinterpreted. Scanning was much more sensitive than radiography was early in the course of osteomyelitis. Scans showed positive findings in all patients with recurrent osteomyelitis. Scan results were positive in 27 of the 45 patients who had a clinical diagnosis of osteomyelitis. Scans correctly distinguished all 33 patients with cellulitis, all 7 with soft tissue abscesses, and all 7 with other forms of sepsis, e.g., septicemia. Scan results were reported as positive for osteomyelitis in 8 of 39 patients with septic arthritis. Half of the positive readings were made in the femoral neck where osteomyelitis frequently coexists with septic arthritis.

Phosphate bone scanning is highly sensitive and specific in diagnosing osteomyelitis in children. Scans usually distinguish focal bone

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(13–6) J. Bone Joint Surg. [Am.] 65-A:431–437, April 1983.

disease from other sites of sepsis or nonseptic disorders. Scan results in neonates must be interpreted cautiously, as must those obtained very early in the course of disease.

▶ [Since the introduction of technetium-labeled phosphate compounds in the early 1970s, the technetium phosphate bone scan has been the most widely used diagnostic tool in the assessment of osteomyelitis. Over a decade later, however, there is still considerable disagreement in the literature regarding the accuracy of this technique. Sensitivity of this test for the diagnosis of osteomyelitis has been reported to range from less than 60% to more than 90%. What this study does is to attempt to resolve this confusion by using very strict criteria for interpretation of the scans. The scan correctly identified osteomyelitis at 55 of 62 sites and was correctly negative in 74 of 79 patients without osteomyelitis. This is not a bad record overall. But this false negative and false positive rate still means that clinicians will have to use their own judgments no matter what the scan shows. As mentioned in previous YEAR BOOKS, osteomyelitis in the neonatal period often is associated with a negative bone scan. I don't think the bone scans should be faulted for having problems in the neonatal period. Neonatal osteomyelitis seems to be a different disease from osteomyelitis in older children. It generally has a more mild nature, frequently with absence of systemic disturbances. This results in late detection and multicentric disease in the newborn. A recent review of osteomyelitis in the neonate (Mok, P. M., et al.: *Radiology* 145:677, 1982) also shed some new light on the latter problem. They found that newborns had osteomyelitis that was classifiable into two types. One was multicentric, which almost invariably was found in infants who had umbilical arterial or umbilical venous catheterization. The other type was unifocal, and it was rare that infants with this type of disease had umbilical catheterization. The authors of this study also noted that only one third of infected sites in neonates could be detected by nuclear scanning.

The problem with technetium labeling is that its accumulation in bone reflects a reparative bony process. Some investigators are now beginning to suggest that white blood cell scanning might be better. This is the infusion of leukocytes that have been labeled with indium-111-oxine. These cells would go to any area of inflammation in the body. Another advance in the detection of early osteomyelitis has been the improved sophistication of computed tomography. Computed tomography scanners have sufficient contrast in spatial resolution now to detect early bone demineralization. In a discussion of all these various potential techniques recently (Raptopoulous, V., et al.: *AJR* 131:1077, 1982), white blood cell scans and computed tomography appeared to be more sensitive than technetium scans, which in themselves are more sensitive than conventional radiography.—J.A.S., III] ◀

13–7 **Association of Septic Thrombophlebitis With Subperiosteal Abscesses in Children.** Jesse B. Jupiter, Michael G. Ehrlich, Robert A. Novelline, Harold C. Leeds, and Daniel Keim (Harvard Med. School) describe an association of septic thrombophlebitis with acute osteomyelitis in 4 children. Each patient presented with physical findings consistent with thrombophlebitis.

Venography, done in 2 patients, showed significant acute thrombophlebitis; another patient had an infected venous cutdown. A subperiosteal abscess was the predominant bony involvement found in all 3 patients who underwent surgical drainage.

The initial radiographs were normal in each case. Technetium-99m-sulfur colloid and ^{99m}Tc-diphosphonate bone scans showed diffuse increase in activity in the extremity, consistent with hyperemia. Gallium-67-citrate scans showed focal increased uptake in 1 patient. Computerized tomography, done in 2 patients, failed to show any bony abnormality, although subperiosteal abscesses were drained

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(13–7) J. Pediatr. 101:690–695, November 1982.

within 48 hours of each study. Cultures grew *Pseudomonas aeruginosa* (1 patient) and *Staphylococcus aureus* (3 patients).

Reverse collateral venous flow through the bone, associated with a rise in intramedullary pressure, may be responsible for the findings. The association of acute thrombophlebitis and of osteomyelitis may occur with greater frequency than previous studies would indicate. Greater use of venography when clinically indicated might reveal more cases. Earlier needle aspiration of the bone and subperiosteal space may sometimes give information when other diagnostic tests are unclear.

▶ [The association of septic thrombophlebitis with acute osteomyelitis in children has not been documented clearly in the medical literature, despite extensive studies of childhood osteomyelitis. This report should be read in detail because there was great difficulty in making the diagnosis of osteomyelitis in these patients. The bone scans showed nonspecific activity rather than focal areas of increased uptake. For this reason, the patients were thought simply to have phlebitis without osteomyelitis. Computed tomography, despite what I said in the previous commentary, in these cases failed to reveal any bony abnormality. It was only at surgical drainage that a massive amount of subperiosteal abscess was seen. Ultimately, the routine x-ray films became abnormal and were diagnostic of osteomyelitis.

This report is truly scary. When we see a child with cellulitis or phlebitis and a nonspecific bone scan, we tend to ease up in our concern about osteomyelitis. If nothing else, this report should tell us to keep a heightened awareness of the potential for concomitant osteomyelitis no matter what the studies show.—J.A.S., III] ◀

13–8 **Lumbar Disk Excision in Children and Adolescents.** James K. DeOrio and Anthony J. Bianco, Jr. (Mayo Clinic and Found.) studied the long-term results of excision of a lumbar disk and the value of spine fusion at initial operation in 50 patients, aged 16 years or younger, who had a herniated lumbar disk.

Many patients were both heavier and taller than average. The presence of physical signs such as scoliosis, lumbar muscle spasm, and decreased range of motion of the spine was similar to that in adults. The straight-leg-raising sign was positive in 86% of patients; knee or ankle jerk was decreased in 42% of patients, sensation was decreased in 10%, and muscle strength was decreased in 32%.

Of the patients, 94% had had excellent or good relief of symptoms after the initial operation. Subsequently, 28 of 37 patients who initially only had disk excision required additional treatment for low-back pain or sciatica; 12 needed second operations, which included 9 diskectomies (6 with a concomitant spinal fusion), 2 spinal fusions alone, and 1 refusion. Of the 37 patients who initially had had disk excision alone, 3 had a recurrent disk protrusion and 5 had a disk protrusion at another level. Of 16 patients who had had multiple subtotal hemilaminectomies at the initial operation, either for involvement of multiple disks or for exploration, 7 needed reoperation.

In 12 patients who had had both a disk excision and a lumbar spinal fusion as the initial operation, there were no recurrent disk protrusions and only 1 patient had a protrusion at another level.

Follow-up ranged from 5 to 30 years (average, 19 years); 90% of the patients stated that the back condition had little or no effect on their

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(13–8) J. Bone Joint Surg. [Am.] 64-A:991–996, September 1982.

current way of life, despite the presence of continuing back complaints in some. The results of the initial diskectomy at follow-up were rated as excellent or good in 73.5% and poor in 26.5% of the patients.

Six patients with defects of the neural arch did not have a spinal fusion, but none needed a repeat diskectomy or had a poor rating at follow-up. Moreover, the incidence of other structural anomalies was not proportionately higher in patients with a recurrence than in the total group. Thus, fusion does not seem to be warranted for structural anomalies per se unless preoperative instability is detected. Long-term follow-up is essential in these young patients, as shown by the fact that half of the reoperations in this study were not needed until 3½ years after the original diskectomy.

▶ [Dr. John Lubicky, Assistant Professor of Orthopedic Surgery and Pediatrics, State University of New York at Syracuse, comments:

"This article by DeOrio and Bianco is a good review of the subject of disk herniations (HNP) in children. Their results show that, overall, 73.5% had good or excellent results at follow-up, although some required additional treatment after their inital operation.

"A key point in this article is that HNP requiring surgery in children is an unusual problem—0.5% of the total number of operations for all age groups in their series. The second important point is that 92% of the patients had sciatica. Only 2% of the patients had back pain alone. The significance of this finding is, of course, that there is nerve root compression and irritation. The question of whether or not spinal fusion should be performed at the initial operation remains a controversial point in orthopedic circles. Anecdotally, however, there are many reports that seem to indicate that this is advantageous.

"The article, however, discusses what to orthopedic surgeons are more or less classic cases of HNP. For every one of these, we see many more children with vague back complaints without sciatica and with little or no physical findings. They often complain of pain so severe that they cannot attend school. Their parents are often at wits' end to find out what is wrong with them and often see a number of physicians of varying specialties.

"The differential diagnosis of back pain in children should be known to pediatricians because there are many more things that cause back pain besides HNP. The list of specifics is long, but one should know that neoplasms, infections, and deformities can lead to severe back pain. By way of example, idiopathic scoliosis should not be a painful disease aside from occasional backache. However, children who have very painful scoliosis, "especially with an unusual curve pattern," with painful limited back motion should be assumed to have some type of intraspinal pathology until proved otherwise.

"As far as preliminary workup of a child with unremitting back pain is concerned, routine spine films, complete blood count and differential, sedimentation rate, and bone scan constitute a fairly thorough initial evaluation. Further investigation might include myelography, computed tomography scans, etc. As a final point, one should not forget psychological overlay in some of these patients. Secondary gain from illness may be a real problem and may potentiate a minor physical problem and prevent the child from getting well. Unfortunately for both pediatricians and pediatric orthopedic surgeons, the number of children presenting with backache appears to be increasing, and careful evaluation is needed to determine which of them needs extensive workups."] ◀

13–9 **Comparative Study of the Efficiency of Different Types of School Screening for Scoliosis.** It is important to detect progressive scoliosis as early as possible because of the severe secondary

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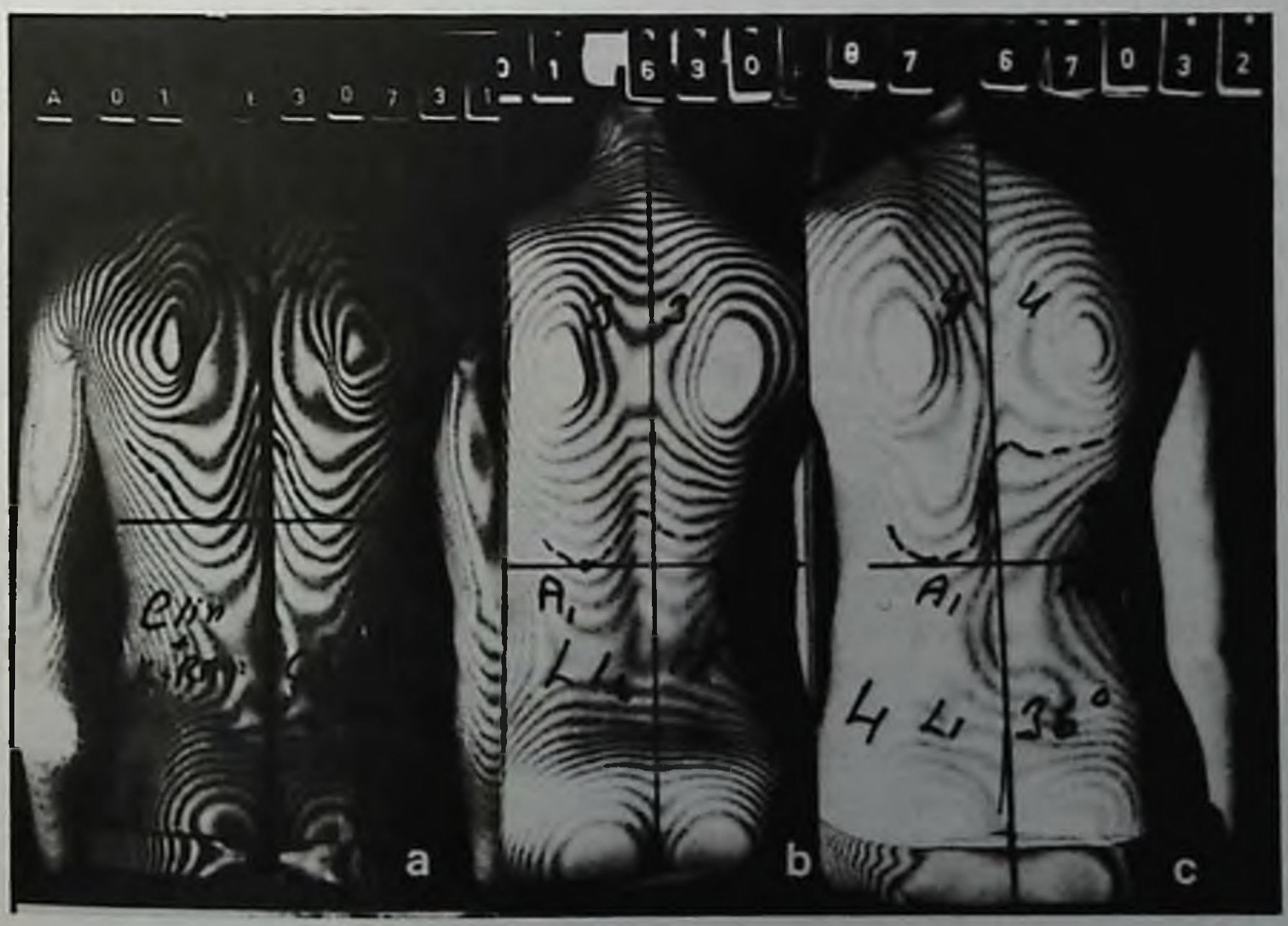
(13–9) Acta Orthop. Scand. 53:769–774, October 1982.

problems that can occur and because operation can be avoided in many cases by early bracing. Stig Willner (Univ. of Lund) evaluated the efficiency of both conventional clinical screening for scoliosis and a combined moiré-visual screening program in schoolchildren in Malmö, Sweden. Totals of 15,082 boys and 14,949 girls aged 7 to 15 years were screened. The moiré topographic method is illustrated in Figure 13–4. Visual observations of the back were made with the subject standing erect and bending forward, and subjects with any visible asymmetry were moiré-photographed.

A total of 108 children with scoliosis were treated between 1971 and 1980, representing 0.66% of girls and 0.06% of boys. The mean degree of scoliosis curves at diagnosis decreased as the intensity of screening increased, from 34 degrees in 1971 to 29 degrees in 1980. The best results were obtained by the combined visual-moiré method. The mean degree of scoliosis at diagnosis was greater in patients who were later operated on. More cases were diagnosed during the prepuberal growth period with more efficient screening. The clinical-moiré approach also resulted in a decrease in the number of roentgenograms of the spine made for smaller curves.

A combined clinical-moiré screening technique has given the best results in surveying schoolchildren for scoliosis. Scoliosis is being diagnosed at an earlier age with this approach, and fewer operations are necessary. The cost of effective screening at school can be met merely by avoiding a few operations. The moiré method of three-di-

Fig 13–4.—Moiré photography: a, straight spine with symmetric trunk; b, left convex 17-degree lumbar curve with deviation of two moiré fringes; c, left convex 36-degree thoracolumbar curve with deviation of five moiré fringes. (Courtesy of Willner, S.: Acta Orthop. Scand. 53:769–774, October 1982.)



mensional documentation of the status of the back permits better comparison between serial observations than do clinical methods alone.

► [Almost every study that has compared routine clinical school screening programs for scoliosis (visual observations of the back standing erect and bending forward) with the moiré photography technique has shown that screening for scoliosis simply by inspecting the back and using a forward bending test is inadequate. The moiré technique has been discussed in earlier YEAR BOOKS. As you can see from Figure 13–4, it is an extremely sensitive test to pick up asymmetry of the back. Moiré photography and the necessary handling of the projector and camera are actually quick and simple. The screening is also safe and quite inexpensive and causes no discomfort for the patient. These are obviously essential criteria in the selection of any screening procedure. In areas that have used moiré photography, it has been reported that you can screen approximately one patient per minute. The photography can be done by a school nurse or paramedical staff, with more highly qualified personnel later examining the photographs themselves. The weakness of the moiré topographic technique is the large number of false positive results that can be seen with this approach. The false positive rate is much higher than with routine clinical inspection of the back. However, the purpose of screening tests, I believe, is to have high sensitivity even if the specificity is off a bit. The reliability of a negative moiré picture is high, however, as almost 100% of patients with symmetric moiré pictures do not suffer from scoliosis.

If this study doesn't convince you, try to seek out someone who is using the Moiré technique and see how it works for yourself. I think you will be impressed. It may not be applicable for your office setting, but it could be something that you will recommend to your school board.—J.A.S., III] ◄

13–10 **Etiology and Interrelationship of Some Common Skeletal Deformities.** The Edinburgh Register of the Newborn 1964–1968 and the Edinburgh Scoliosis Clinic 1964–1971 were used to establish the population frequency in that city of idiopathic forms of talipes equinovarus and calcaneovalgus, metatarsus varus, congenital dislocation of the hip, and infantile scoliosis. The survey by Ruth Wynne-Davies, Anne Littlejohn, and Jess Gormley (Edinburgh) was delayed so that the children could be examined when between ages 7 and 11 years, thus excluding defects secondary to additional neurologic disorders.

One hundred sixty-five patients with a total of 174 deformities were found; they were compared with a control group of 692 normal infants born over the same period. There were 33 patients with talipes equinovarus, 22 with talipes calcaneovalgus and 10 with metatarsus varus, 83 with neonatal congenital dislocation of the hip, and 26 with infantile idiopathic scoliosis. When all types of deformity are considered, 16 of 189 (8.5%) siblings of index patients also had a deformity. Twin pregnancy could contribute to deformity through intrauterine compression, as 4.2% of the index group had a twin, whereas the figure in the control group was only 1.2%. Neonatal congenital dislocation of the hip was the only condition occurring more often in patients born in the winter. The mother had had an antepartum hemorrhage in 7 of the 33 patients with talipes equinovarus (21.2%), compared with an incidence of 8.7% of the controls. Chronic illness or drugs taken by the mother during pregnancy did not seem to increase the appearance of deformities in the offspring appreciably.

The survey confirms others in suggesting a multifactorial genetic

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(13–10) J. Med. Genet. 19:321–328, October 1982.

background for these deformities, although it appears likely that the entire group is etiologically related. Environmental factors must "trigger" the deformities and, while the genetic background may be similar for the entire group, each case has differing environmental factors determining which individual deformity finally develops. For instance, an unexpected excess of mothers was noted who had an upper respiratory infection during pregnancy, most after the first trimester. Does the fetus perhaps also have an infection and fail to move and kick for a crucial period as it should? It is concluded that all described deformities are likely to have a common multifactorial genetic background associated with differing intrauterine or postnatal environmental factors.

▶ [It is customary to consider skeletal deformities as separate entities, and their central similarity often is overlooked. What Wynne-Davies et al. are hypothesizing is that the idiopathic deformities of talipes equinovarus and calcaneovalgus, metatarsus varus, neonatal congenital dislocation of the hip, and infantile scoliosis are all etiologically related, because 1 subject may have more than one of these defects and each of them may appear within the same family. If this hypothesis is correct, inheritance is likely to be multifactorial, with environmental factors that trigger the deformity. Compression in utero because of hydramnios or oligohydramnios could not be shown to be a causative factor in this study.

Amitai et al. reported from Jerusalem the observation of an association between dislocation of the hip and short maternal stature based on a study of 33 cases and 54 controls. When I first saw this report it seemed to make sense, because maternal factors play an important role in affecting the available space for the fetus in utero and because of the known consequences of cramping on certain of the congenital malformations. Obviously, not everyone believed this report, because one center, at least, reviewed their own experience and failed to substantiate this finding. Dunn et al. (*Arch. Dis. Child.* 57:961, 1982) looked at maternal height in 330 cases of congenital dislocation of the hip and found absolutely no unexpected shortness in these mothers in England. There must be some way to resolve this conflict. It is possible that double, triple, or quadruple diapering is done in Israel and not in England? I swear that I lost some part of a millimeter on those rare occasions when I bent over to change the diapers of our 4 children when they were infants. Can you imagine how many diapers Fiorello LaGuardia must have changed if this theory is correct? He didn't mind being short. When asked what it felt like to be small he quipped, "Like a dime among pennies."—J.A.S., III] ◀

13–11 **Injuries Among Wrestlers in School and College Tournaments.** Wrestling now is the fifth most popular sport among high school boys in the United States, with nearly 250,000 participants. Richard H. Strauss and Richard R. Lanese (Ohio State Univ., Columbus) reviewed the injuries occurring at four wrestling tournaments totalling 1,049 participants at the grade school, high school, and college age levels. There was a total of 102 injuries. Two clearly were serious, a wrist fracture and an elbow dislocation. Knee and ankle sprains of mild to moderate severity were the most common diagnoses (20%). There were no pinna injuries, presumably because ear protectors were used. Injuries were least frequent in boys aged 9–14 years, partly because their matches were the shortest. Twelve percent of high school and college wrestlers were injured. The risk did not relate to weight class or successive matches. Nearly 40% of injuries represented aggravation of old injuries.

(13–11) JAMA 248:2016–2019, Oct. 22/29, 1982.

Rehabilitation after injury is important in preventing further wrestling injuries. Most wrestling injuries are not severe, but the overall injury rate of 12% in high school and college wrestlers in this survey would appear to warrant attendance by medically trained personnel at tournaments.

▶ [Dr. Bruce E. Baker, Associate Professor, University Sports Medicine Service, Department of Orthopedics, State University of New York at Syracuse, comments:

"Statistically, wrestling is the fifth most popular sport for high school boys, with 245,000 participants. Doctors Richard H. Strauss and Richard H. Lanese studied four wrestling tournaments that totaled 1,049 participants. The purpose of their study was to compare the incidence and types of injuries sustained by wrestlers at different ages and skill levels. Their data was collected from observation at tournaments at which boys between the ages of 9 and 18, as well as college-level wrestlers, competed.

"They found that the injury rate per 100 participants, or per 100 matches, was lowest in the boys' tournament. When the injury rate was adjusted for time differential by calculating the injury rate per 1,000 minutes of match time, the boys seemed to be injured at about the same rate as the collegiate wrestlers, whereas the high school wrestlers had a higher rate of injury.

"It was noted that the contribution of aggravated old injuries to total injuries was 39% overall, and there was no difference in injury rate according to weight class. The second period of the three-period matches was found to produce the highest rate of injury in all tournaments. The most frequent diagnoses, in descending order of frequency, were knee sprain, ankle sprain, and musculotendinous strain at 10% each, brachial plexus injury at 7%, concussion at 6%, and laceration of the face and scalp at 6%. Even though the takedown to on-mat wrestling ratio was 1 to 1, it was felt that takedown was a high-risk activity because of the relatively short time of the total match in which takedowns are an active part of the match. They also concluded that aggravation of preexisting injury was a significant cause of injury during competition and that adequate rehabilitation after previous injury is a significant preventive measure.

"In my experience, injuries associated with wrestling, particularly at the intercollegiate level, occur nearly as frequently as in highly aggressive contact sports such as football. Head and neck injuries are not uncommon, and several life-threatening cervical spine injuries have occurred in this locality, one resulting in quadriplegia. The importance of adequate preparation, coaching, and rehabilitation of previous injuries cannot be overemphasized. Additionally, available medical coverage during practice situations is mandatory, as well as on-site physician coverage of competitive matches. The physician who does choose to participate at wresting matches as the attending physician should be prepared to deal with the compromised airway and other life-threatening situations."] ◀

13–12 **Falls in Children.** Accidents are the major cause of mortality in children in developed countries, and falls account for about 5% of fatal accidents in those aged 1–14 years. C. P. Shah, C. A. Smith, L. Finkelstein, and M. Friendly (Univ. of Toronto) reviewed the injuries sustained by children in falls in 1977 at the only pediatric hospital serving metropolitan Toronto. Falls accounted for one third of all injuries seen in the emergency department (Table 1). About 10% of children injured in falls were admitted. About half the falls were from a height, and one third of these were accidents on stairs or steps. Accidents in children aged 4 years and younger accounted for over two thirds of such falls. The age and seasonal distribution of injuries is shown in Table 2, and the types of injury are listed in Table 3. Superficial injuries were most common, followed by fractures and lacera-

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(13–12) Can. Fam. Physician 28:1576–1580, September 1982.

TABLE 1.—INCIDENCE OF ADMISSIONS AND DEATHS FROM INJURIES SEEN AT EMERGENCY DEPARTMENT OF HOSPITAL FOR SICK CHILDREN, 1976 AND 1977

	1976		1977	
	N	%*	N	%*
All injuries	17,366	100.0	17,373	100.0
Admissions	1,616	9.3	1,648	9.4
Deaths	17		40	
Injuries due to falls	5,860	34.0	5,871	34.0
Admissions	599	3.4	603	3.5
Deaths	1		4	

*Of all injuries.

(Courtesy of Shah, C. P., et al.: Can. Fam. Physician 28:1576–1580, September 1982.)

TABLE 2.—SEX, AGE, AND SEASONAL DISTRIBUTION (PERCENTAGES) OF CHILDREN INJURED IN FALLS, SEEN IN EMERGENCY DEPARTMENT, 1977

	Sex		Age Group (yr)			Season					
Type of Fall	Male	Female	0-4	5-9	10 & over	Jan-Mar	Apr-June	July-Sept	Oct-Dec	Total	%
1. From Heights										2,894	49.3
From furniture or household equipment	53.9	46.1	85.7	11.1	2.2	24.8	24.2	24.3	26.7	909	31.4
On or from stairs or steps	54.4	45.6	68.2	19.2	12.6	21.9	28.8	26.4	22.9	872	30.1
From playground equipment	53.4	46.6	16.5	56.2	27.3	12.5	37.1	34.5	15.9	377	13.0
On or from building or other structure	66.7	33.3	48.9	33.9	17.2	10.6	45.2	31.8	12.4	128	4.4
Others	67.7	32.3	53.6	28.6	17.8	16.0	31.8	34.2	18.0	608	21.1
2. From Same Level										2,902	49.4
Sports	62.5	37.5	1.9	22.9	75.2	28.2	28.5	18.3	25.0	745	25.7
Skateboarding	67.9	32.1	0.7	11.5	87.8	7.6	47.0	36.0	9.4	184	6.3
Ice-skating	47.8	52.2	1.9	36.1	61.7	44.0	6.0	1.7	48.3	116	4.0
Other sports	64.1	35.9	2.6	24.0	73.4	32.5	26.7	15.4	25.4	445	15.4
Others at same level	55.8	44.2	42.6	33.3	24.1	21.2	31.0	27.0	20.8	1,412	48.6
Totals 1 & 2	**57.5**	**42.5**	**50.9**	**25.7**	**23.4**	**21.4**	**30.2**	**26.6**	**21.8**	**5,796**	**98.7**
3. Unclassified Falls										75	1.3

(Courtesy of Shah, C. P., et al.: Can. Fam. Physician 28:1576–1580, September 1982.)

TABLE 3.—TYPES OF INJURY DUE TO FALLS SEEN IN EMERGENCY DEPARTMENT, 1977

Type of Injury	Falls from Heights %	Falls from Same Level %	N
Superficial	62.8	37.2	1,252
Fracture	51.1	48.9	1,063
Laceration-wound	50.9	49.1	1,038
Hematoma-abrasion	45.9	54.1	710
Multiple injury	70.4	29.6	660
Dislocation and/or sprain	31.1	68.9	429
Concussion	62.0	38.0	100

(Courtesy of Shah, C. P., et al.: Can. Fam. Physician 28:1576–1580, September 1982.)

tions. Dislocations, sprains and hematomas were more frequent with falls from the same level.

Falls cause considerable morbidity in children. It is important for parents to know the potential abilities of their children. Physicians should advise parents of the injury potential associated with various stages of motor development. Falls by children may be viewed as part of the price exacted by growing up, and most falls are innocuous, but accident proneness is a consideration. Repeated childhood accidents may be seen as a sign of underlying family stress. Further work is needed to identify children at risk of injury from falls and to ascertain the benefit that may be derived from involving public health personnel in the prevention of future falls.

▶ [Injury has replaced communicable diseases as the major cause of childhood morbidity and mortality. This study from Canada compares favorably with the results of the report of the Statewide Childhood Injury Prevention Program in Massachusetts (Gallagher, S. S., et al.: *N. Engl. J. Med.* 307:1015, 1982). This program was set up in Massachusetts to determine the overall extent of the problem of accidental injuries in children. Whereas motor vehicle accidents were the most common cause of childhood injuries resulting in death (28% of the total), childhood falls were the most common cause of emergency room visits related to childhood injuries. For example, in the group younger than age 5 years, falls constituted half of the injuries with which children presented themselves. Clearly, this is no minor problem. If you want to learn more about what to do about it, please read the aforementioned *New England Journal of Medicine* article in detail. You will see in there the comment that the average pediatrician devotes less than 10 seconds of time per patient in practice with respect to anticipatory guidance on the prevention of injuries.

The reason why children fall often is because they are so active. Readers of the YEAR BOOK already know this commentator's feelings about excessive activity, especially when it comes to exercises such as jogging. Running does have some positive aspects, however. It is a mildly effective birth control measure because it may cause oligomenorrhea or amenorrhea (Shangold, M. M., et al.: *Am. J. Obstet. Gynecol.* 143:862, 1982). It is also great at lowering your blood sugar—sometimes to unacceptable ranges (Felig, P., et al.: *N. Engl. J. Med.* 306:895, 1982). If you think some of the comments on these pages have been unduly harsh on joggers, you haven't read the report entitled "Running: An Analog of Anorexia," which appeared last year in the *New England Journal of Medicine* (308:251, 1983). This study attempted to characterize the personality characteristics of what they called "obligatory runners." I don't want to misinterpret what they said, so I'm going to quote it verbatim from their abstract. It reads, "Obligatory runners resemble anorexic women in terms of family background; socioeconomic class; and such personality characteristics of inhibition of anger, extraordinarily high self-expectations, tolerance of physical discomfort, denial of potentially serious debility, and a tendency toward depression. Anorexic women and members of their family are often compulsively athletic, and obligatory runners may demonstrate a bizarre preoccupation with food and an unusual emphasis on lean body mass. We speculate that both phenomenon could represent a partially successful—albeit dangerous—attempt to establish an identity." And I thought I was hard on runners! If you get the impression that the conclusions of that report are about as mean as a grizzly bear with a thorn in his side, you are wrong. They are as mean as a grizzly bear with five thorns in his side.—J.A.S., III] ◀

13–13 **Congenital Ingrown Toenails: Clinical Significance.** Paul J. Honig, Alan Spitzer, Robert Bernstein, and James J. Leyden (Philadelphia) evaluated the great toenails of 302 "normal" newborn infants to identify a specific conformation that might predispose to chronic paronychia. Nails were graded as follows: normal (Fig 13–5, A), with the nail plate growing out over the end of the toe without

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(13–13) Clin. Pediatr. (Phila.) 21:424–426, July 1982.

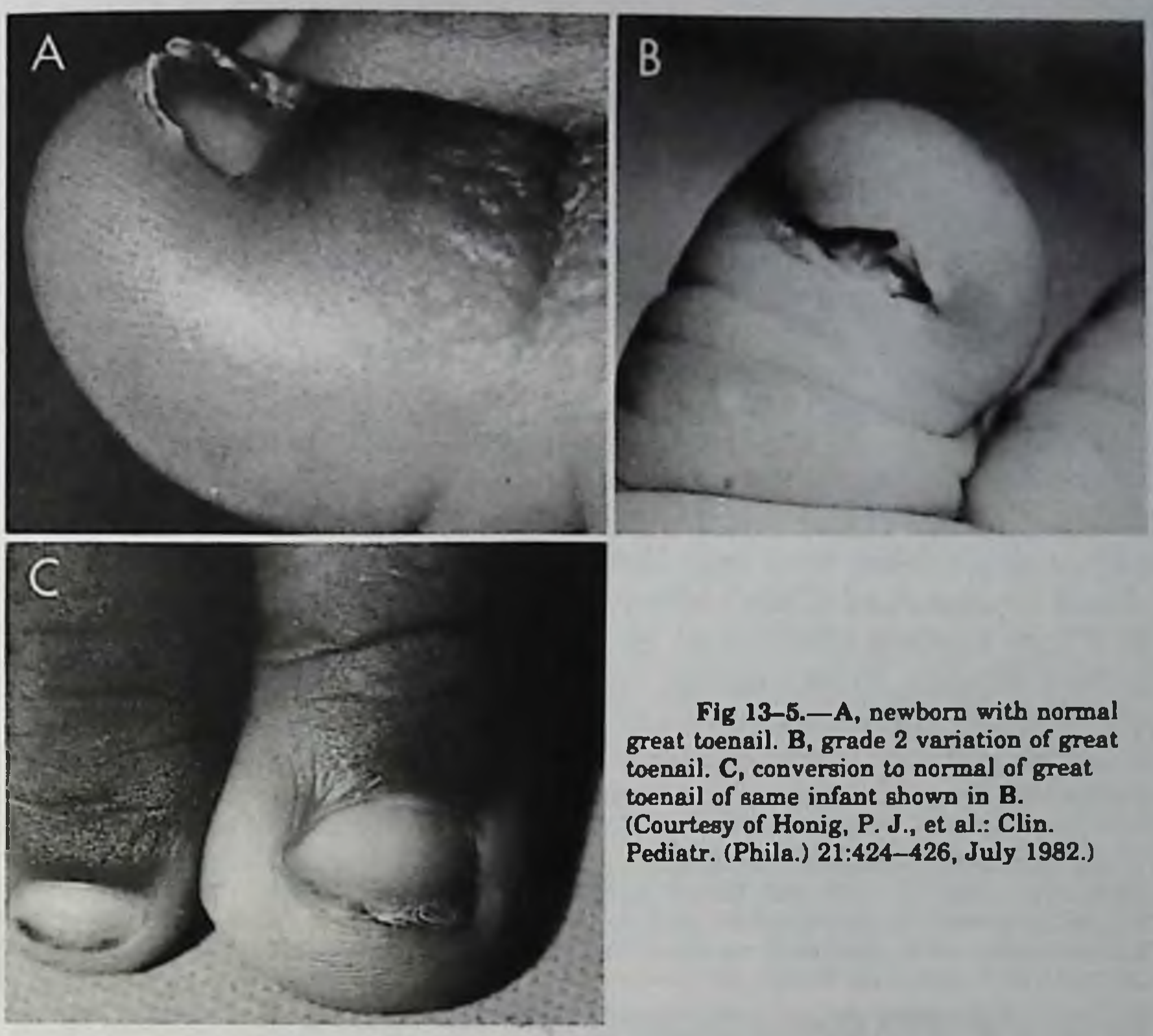


Fig 13–5.—A, newborn with normal great toenail. B, grade 2 variation of great toenail. C, conversion to normal of great toenail of same infant shown in B. (Courtesy of Honig, P. J., et al.: Clin. Pediatr. (Phila.) 21:424–426, July 1982.)

impedance by tissue; grade 1 variation from normal, with the nail plate curved at its distal end and growing up and over the tissue at the distal end of the great toe; and grade 2 variation (Fig 13–5, B), with the distal end of the nail plate appearing to be growing into the tissue at the distal end of the great toe.

Forty-eight male and 33 female infants (27%) had grade 1 variation, and 27 male and 25 female infants (17%) had grade 2 variation; 169 infants (56%) had normal great toenails. There was a decrease in

GRADE 2 TOENAIL VARIATION FOUND IN EACH WEIGHT CLASS

Weight (gms)	Total Infants	Grade 2 Variation	
		No.	%
2000–2500	32	13	40.6
2501–3000	78	21	26.9
3001–3500	117	14	12.0
3501–4000	59	3	5.0
>4000	16	1	6.3

(Courtesy of Honig, P. J., et al.: Clin. Pediatr. (Phila.) 21:424–426, July 1982.)

percentage of infants with grade 2 toenails with increasing birth weight (table).

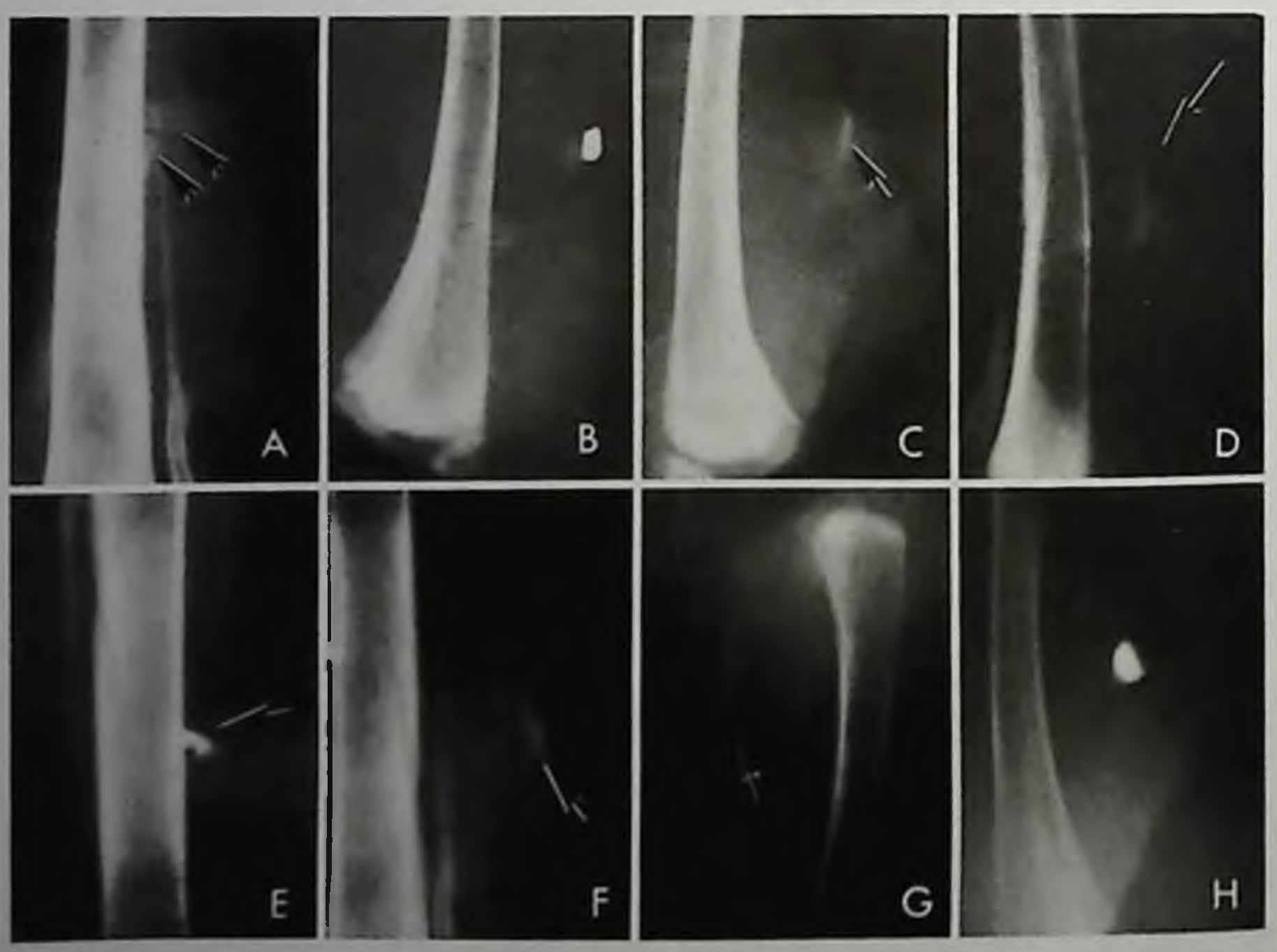
Forty-one infants who appeared to have great toenails impeded by tissue distally had follow-up for 12 months. Almost all infants had essentially normal nails (Fig 13–5, C) by age 6 months. None developed chronic paronychia.

The results suggest that the changes originally noted were variations in the normal development of the great toenail. These variations do not need surgical intervention and, with time, eventuate in a normally appearing nail.

► [File this report under "footnotes." It is worth keeping. I have always wondered what became of ingrown toenails in newborns. Now I know I haven't missed anything.—J.A.S., III] ◄

13–14 **Glass in the Hand and Foot: Will an X-Ray Film Show It?** Most physicians believe that only leaded or pigmented glass can be visualized on standard plain x-ray films, but a few workers suggest that any type of glass readily can be demonstrated. Dan Tandberg (Univ. of New Mexico, Albuquerque) examined various-sized fragments of 66 varieties of glass that were driven into the leg muscle of cadaveric chickens, which resembles the human thumb anatomically. Postero-anterior, lateral, and oblique roentgeonograms were obtained using

Fig 13–6.—Roentgenograms demonstrating detectability of several kinds of glass fragments in chicken-leg model. **A**, light bulb (clear); **B**, clinical thermometer; **C**, vanilla bottle (brown); **D**, beer bottle (green); **E**, peanut butter jar (clear); **F**, vinegar bottle (green); **G**, scotch bottle (clear); **H**, champagne bottle (green). (Courtesy of Tandberg, D.: *JAMA* 248:1872–1874, Oct. 15, 1982; copyright 1982, American Medical Association.)



(13–14) *JAMA* 248:1872–1874, Oct. 15, 1982.

a standard "hand" technique. No special soft tissue exposures were made.

All 66 specimens were seen easily on roentgenograms. The presence of lead or other heavy elements was not necessary for visualization. Glass fragments as small as 0.5 mm were detected easily if there was no overlying bone. Roentgenograms of several representative glass fragments are shown in Figure 13–6. Glass from a broken light bulb was the most difficult variety to visualize.

It is concluded that standard plain x-ray films of the injured hand or foot are useful in determining whether glass fragments are present in a wound. Fragments as small as 0.5 mm can be detected if there is no overlying bone, and fragments 2 mm or more in size can be seen even if overlying bone is present. Oblique or tangential views will help avoid the problem of obscuration of small glass fragments by overlying bone. The question of whether glass fragments in larger body regions are usually detectable remains open.

► [Most of us have been trained to believe that glass fragments cannot be detected easily on x-ray films unless they have leaded paint on them or other heavy metals within them. "Not so," says this clinical investigator. Tandberg has done a yeoman's job in compiling 66 different pieces of glass and imbedding them into the leg muscle of the *Gallus gallus*, or domestic chicken. This experimental model was chosen because of the resemblance in size and anatomical structure of the chicken "drumstick" to the human thumb. The various pieces of glass chosen for this study were picked because they "might reasonably be found as foreign bodies in the hands and feet of patients." This is the only part of the study that I don't believe. The author showed examples of windshield glass from 24 different automobiles, including a 1934 Plymouth and a 1947 Hudson. When was the last time you saw glass from either of those two relics in anybody's hand?

The unsung hero of this report is mentioned briefly in a footnote at the end of the article. He is "Tiny" Marsh of the Acme Wrecker Service in Albuquerque, New Mexico, who helped obtain the assorted pieces of automobile windshield glass. The readers of the YEAR BOOK applaud your efforts, Tiny.—J.A.S., III] ◄

13–15 **Circumferential Fingernail—Fingernail on the Palmar Aspect of the Finger** is described by Michael Kalisman and Harold E. Kleinert (Univ. of Louisville). The presence of a nail on the palmar aspect of the small finger is rare. In a previously reported case with involvement of both small fingers, an abnormality of chromosome 6 was the suggested cause.

Boy, aged 4 months, had a well-developed, totally circumferential nail on the left small finger. Both parents were healthy, and there was no family history of genetic or congenital disorder. The pregnancy had been uneventful. An abnormal palmar crease was also present on the left side. The tapered left small finger exhibited clinodactyly, and the finger was fixed in an extended position but retained full passive motion. Other deformities included a broad nasal bridge with telecanthus, down-slanting palpebral fissures, low-set ears, small mouth, hypospadias, left-sided hydrocele, broad great toes, and metatarsus varus deformity. Motor function was slightly subnormal, but sensory function was normal. A normal male karyotype was identified on chromosome analysis. X-ray films of the hands showed marked attenuation of the soft tissue and the distal and middle phalanges of the left small finger.

(13–15) J. Hand Surg. 8:58–60, January 1983.

This combination of anomalies does not appear to represent a recognizable syndrome. Reconstructive surgery is planned at a later time to improve the function of the affected finger. A flexor tendon graft, removal of the palmar nail, and reconstruction of the palmar distal phalangeal pad are anticipated.

14. Ophthalmology

14-1 **Ophthalmia Neonatorum Caused by Penicillinase-Producing *Neisseria gonorrhoeae*.** Strains of penicillinase-producing *N. gonorrhoeae* (PPNG) have been isolated from adults with gonorrhea in the United States with increasing frequency since 1976, but no cases of ophthalmia neonatorum (ON) have yet been reported. Harold S. Raucher, Michael J. Newton, and Roy H. Stern (Mount Sinai School of Medicine) encountered a case.

Boy, aged 19 days, was admitted with ON after vaginal delivery and intramuscular injection of 50,000 units of penicillin G a few minutes after birth. Mucoid ocular discharge had begun on day 3, and a conjunctival culture had yielded *Staphylococcus epidermidis*. The lids subsequently became extremely edematous, and discharge increased dramatically. Typical severe ON was present at admission. The father had been in Mexico 2 months before the infant's birth, and the mother had noticed a new vaginal discharge a week before delivery. Conjunctival culture yielded *N. gonorrhoeae* that was resistant to penicillin. Improvement occurred on intravenous and topical penicillin therapy, but the response was slower than expected. Gentamicin ophthalmic drops and intravenous cefazolin administration were followed by oral cephalexin therapy, and the eye disease resolved.

This infant presumably was infected with *N. gonorrhoeae* during vaginal delivery. It is the first failure of intramuscular penicillin prophylaxis at the authors' institution. Prompt parenteral treatment of gonococcal ON prevents corneal damage and blindness. Where PPNG is isolated from adults in significant numbers or the parent of an affected infant has had sexual contact with a person from an endemic region, penicillin and another drug with greater stability against the penicillinase of *N. gonorrhoeae* are indicated. Gonococcal isolates should be tested for penicillinase production in all cases of ON.

▶ [Dr. David B. Schaffer, Chairman, Pediatric Ophthalmology, Children's Hospital of Philadelphia, comments:

"In reporting the first known case of ophthalmia neonatorum from penicillinase-producing *Neisseria gonorrhoeae* (PPNG) in the United States, Raucher et al. raise some questions in regard to optimum care of the eyes of a neonate. What constitutes appropriate prophylaxis, diagnosis, and treatment of gonococcal ophthalmia neonatorum?

"The recommendations of the American Academy of Pediatrics and the National Society to Prevent Blindness Committee on Ophthalmia Neonatorum state that acceptable prophylactic agents for *N. gonorrhoeae* include 1% silver nitrate solution, 0.5% erythromycin ointment or drops, or 1% tetracycline ointment or drops instilled under the lids after cleaning the skin with sterile cotton moistened with sterile water. Irrigation following instillation should not be done even if a silver nitrate Credé ointment is employed. Full-term appropriate birth weight infants born to mothers with clinically apparent infection should receive a single dose of intravenous or intramuscular penicillin G, 50,000 units/kg body weight. Presumably, in this case intramuscu-

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(14-1) J. Pediatr. 100:925–926, June 1982.

lar penicillin was used because of a new vaginal discharge in the mother 1 week prior to delivery. However, the dose appears low.

"A second question arises from the evaluation of the infant when a discharge appeared at 3 days of age. At our institution (Children's Hospital of Philadelphia), any ocular discharge occurring before day 5 is gonococcal until proved otherwise. A rigorous conjunctival scraping is required, and both Gram and Giemsa stains are performed as well as immediate inoculation onto Thayer-Martin medium or chocolate agar. Vaginal and/or cervical scrapings from the mother (with a known discharge) would be examined similarly. Gentamicin eye drops or ointment, not one of the sulfa preparations, is instilled every 2 hours until the results of the culture and sensitivity are known, and then treatment is adjusted accordingly. Appropriate systemic therapy is always used with gonorrheal infections.

"In this report, lack of full response to less than optimum therapy led to the discovery of the first PPNG ophthalmia neonatorum in the United States. However, a proper evaluation at day 3 would have led to the same discovery and would have been more appropriate.

"The authors' recommendation that the antibiotic susceptibility be determined should be applauded and stressed. It is also the suggested approach to ophthalmia neonatorum recommended in the latest edition of the American Academy of Pediatrics' Guidelines for Perinatal Care."] ◄

14–2 **Oral Versus Topical Erythromycin Therapies for Chlamydial Conjunctivitis.** *Chlamydia trachomatis* is currently the most common cause of ophthalmia neonatorum; the infection is not prevented by administration of silver nitrate. Sustained nasopharyngeal carriage and pneumonia have occurred in infants treated with topical antibiotics for chlamydial conjunctivitis. Pisespong Patamasucon, Philip J. Rettig, Kathy L. Faust, Helen T. Kusmiesz, and John D. Nelson undertook a prospective trial comparing oral and topical erythromycin in 41 infants younger than age 4 months with chlamydial conjunctivitis. Nineteen infants were treated with 1% erythromycin ophthalmic ointment 4 times daily for 3 weeks. Twenty-two infants received erythromycin estolate, 20 or 30 mg/kg daily or erythromycin ethylsuccinate, 40 mg/kg daily, for 3 weeks. The orally treated infants included more girls and were older at the onset of symptoms. Nineteen infants had bilateral eye involvement. Culture results were comparable in the two groups.

Symptoms responded comparably in both groups, and chlamydial cultures became negative at similar rates. The finding of positive conjunctival antibody was similarly frequent in the two treatment groups. Relapse or reinfection occurred in 21% of topically treated infants and in 13.6% of those treated orally. All infants with relapse of chlamydial infection responded to a course of oral erythromycin therapy. Adverse effects were infrequent. Topical treatment was stopped in 1 child because of a papular rash about the eyes.

Orally administered erythromycin is microbiologically advantageous to ophthalmic ointment in eradicating *C. trachomatis* from the nasopharynx. Oral treatment is easier for the parents. Reported failure rates are presented in the table. Because chlamydial infection in the neonate carries the potential of later pulmonary infection, topical treatment of the ocular site may be inadequate. Erythromycin esto-

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(14–2) Am. J. Dis. Child. 136:817–821, September 1982.

COMPARATIVE FAILURE RATES IN THERAPY FOR CHLAMYDIAL CONJUNCTIVITIS

Method of Treatment	Duration, wk	No. of Failures*/ No. Treated (%)
Topical		
1% Tetracycline hydrochloride	2-3	21/25(84)
Tetracycline hydrochloride	2-4	6/24(25)
1% Tetracycline hydrochloride	3	2/7(29)
Erythromycin or a sulfonamide	. . .	2/4(50)
1% Tetracycline or 0.5% erythromycin	1-3	7/11(64)
10% "Sulfa drops"	2	2/2(100)
Tetracycline hydrochloride	2	6/34(18)
30% Sulfacetamide or 1% tetracycline hydrochloride	2-3	11/12(92)
1% Chlortetracycline hydrochloride ointment	4	1/12(8)
Oral		
Erythromycin estolate	2	0/4(0)
Combined oral and topical		
Oral erythromycin and topical tetracycline	2	2/10(20)
Oral erythromycin and topical chlortetracycline hydrochloride	2	1/22(5)

*Failures were defined as cases in which chlamydiae were cultured from the eye during or after therapy.
(Courtesy of Patamasucon, P., et al.: Am. J. Dis. Child. 136:817–821, September 1982; copyright 1982, American Medical Association.)

late can be given orally 2 or 3 times a day. The parents should be treated with tetracycline or another effective antibiotic for 2 weeks.

▶ [This report deals with the treatment of established neonatal conjunctivitis from chlamydial infection. As commented on in previous YEAR BOOKS, the goal of such treatment should be twofold. One would like to treat the conjunctivitis adequately, while at the same time completely eradicating the organism from the nasopharynx in order to prevent the later occurrence of chlamydial pneumonia. As many studies have shown, although control of local inflammation in the eye is possible with topically applied antibiotics, eradication of the organism from the nasopharynx is not predictable with this approach. The overwhelming body of data now indicates that we should be reserving topical antibiotics for prophylaxis, not for treatment of established conjunctivitis in the newborn. All children thought to have chlamydial conjunctivitis should be treated with orally administered antibiotics. Erythromycin preparations seem to be the most logical choice. Unfortunately, we still don't know the best design for the duration of oral therapy. The study from Doctor Nelson's group used a 3-week course and still found a 14% relapse or reinfection rate. This may not be because of an inappropriate length of treatment, but could be due to specific host factors or failure of compliance. Until the situation is clarified, the length of treatment probably should be 2 to 3 weeks.

The best treatment of chlamydial conjunctivitis in the newborn is not to treat it at all but, rather, to prevent its occurrence. How practical it is to screen all pregnant women is unclear, but studies of female adolescents have shown that about 10% of the sexually active girls at this age are infected with *Chlamydia trachomatis* (Fraser, J. J., et al.: *Pediatrics* 71:333, 1983). Most of them are asymptomatic; this does not mean that chlamydial infection is a totally benign process in the adolescent. Genital infection with this organism has been implicated in long-term sequelae, including cervical dysplasia and tubal infertility. For all of these reasons, greater efforts to identify and treat asymptomatic, as well as symptomatic, women infected with *C. trachomatis* are warranted. Obviously, this would serve to help eradicate chlamydial eye

infections in the newborn and the subsequent development of pneumonia. Tetracycline is probably the most commonly used drug to treat nonpregnant women, but you will have to rely on erythromycin if there is any likelihood that the woman is pregnant.

The funeral bells appear to be starting to ring finally for silver nitrate eye drops. A few more claps of the bell and this form of treatment may well become part of medical memorabilia. Everything that silver nitrate does for the prevention of *Neisseria gonorrhoeae* can be duplicated by tetracycline or erythromycin drops. The additional benefit of the latter is that prophylaxis of chlamydial conjunctivities also may take place. The only negative comment concerning the latter approach is the possibility of losing the warning sign of conjunctivitis in infants who may be harboring the organism also in the nasopharynx. Frankly, if these rational and cogent arguments for switching from silver nitrate don't drive the nail in the coffin of this old-timer medicinal, then the increasing number of parent requests for an alternative will. Erythromycin and tetracycline drops are, like Johnson's Baby Shampoo, ouchless to the eye. Making babies eyes red with silver nitrate also makes some parents red in the face and hot around the collar.—J.A.S., III] ◀

14–3 **Orbital Tuberculosis in Childhood.** A. Oakhill, K. J. Shah, A. G. Thompson, M. J. Stokes, and J. R. Mann report the case of an Indian girl living in England who had proptosis due to tuberculosis of the orbit.

Indian girl, 11, complained of intermittent headache for 2 months and protuberance of the left eye, fever, and a painful swelling above the left knee for 2 weeks. Her parents had been treated for tuberculosis 3 years previously, but she had not been given BCG immunization.

Chest film showed a paratracheal lobular mass without hilar involvement. Skeletal x-ray studies showed a destructive metaphyseal lesion on the lateral aspect of the left lower femoral shaft with periosteal reaction and soft tissue swelling. Computed tomography scan showed a soft tissue mass on the posterolateral and retrobulbar aspects of the left orbit, pushing the globe forward. A Mantoux test, 1:10,000, was strongly positive. Biopsy of the femoral lesion showed tuberculosis; *Mycobacterium tuberculosis* was cultured from this and early-morning urine specimens.

The patient was treated with streptomycin for 6 weeks and with rifampicin, isoniazid, and pyridoxine for 18 months. She made a complete recovery, and the proptosis regressed.

Orbital tuberculosis does not necessarily lead to proptosis; it also may present with sinus formation, keratitis, and ectropion. The course of the disease is typically slow. At presentation, there is nearly always evidence of widespread tuberculosis. Although malignancy, developmental anomalies, and nontuberculous infections are more common causes of proptosis, a tuberculin test should be included among the investigations of children with proptosis.

14–4 **Ocular Manifestations of Kawasaki Disease (Mucocutaneous Lymph Node Syndrome).** Kawasaki disease is an acute systemic disease of infants and young children. Six major diagnostic criteria established include fever for 5 or more days, bilateral conjunctival congestion, changes in the oral cavity mucous membranes, changes in the peripheral extremities, polymorphous exanthem, and acute nonsuppurative swelling of cervical lymph nodes. Five of these criteria must be present to establish the diagnosis.

In a prospective study of the ocular manifestations of Kawasaki

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(14–3) Br. J. Ophthalmol. 66:396–397, June 1982.
(14–4) Am. J. Ophthalmol. 93:713–717, June 1982.

disease in 11 boys and 7 girls, aged 5 months to 9 years, Shigeaki Ohno, Teruhide Miyajima, Makoto Higuchi, Atsushi Yoshida, Hidehiko Matsuda, Yoshito Sahecki, Ichimei Nagamatsu, Takehiro Togashi, and Shuzo Matsumoto (Sapporo, Japan) found bilateral injection of the bulbar conjunctiva in 16 children (medium-sized to large vessels of the bulbar conjunctiva were engorged and tortuous, whereas the palpebral conjunctiva showed minimal change), bilateral iridocyclitis (14), superficial punctate keratitis (4), vitreous opacities (2), papilledema (2), and subconjunctival hemorrhage (1). Except for subconjunctival hemorrhage, these symptoms were bilateral. Fellow eyes always had the same degree of inflammation.

There were significant correlations between ocular inflammation and erythrocyte sedimentation rate and C-reactive protein level. No serious ocular complications occurred.

Because bilateral iridocyclitis occurred in 78% of cases, it may be another important diagnostic criterion. Although bilateral congestion of the ocular conjunctiva is considered to be one of the six major diagnostic criteria, this study showed that the bilateral bulbar conjunctiva rather than the palpebral conjunctiva show injection in this disease; these lesions are not a form of conjunctivitis.

Although most forms of juvenile iridocyclitis associated with systemic disease are chronic, in Kawasaki disease, infants and young children have acute bilateral iridocyclitis. Kawasaki disease should be suspected in all children with acute bilateral iridocyclitis with bulbar conjunctival injection.

▶ [Kawasaki disease is now an established clinical entity. Red eyes are one of the main symptoms, and it may be for this problem alone that medical attention is initially sought. We have seen a few children who first presented to the ophthalmologist. Fortunately, they are becoming increasingly aware of the ocular manifestations of this disorder. Slit-lamp examination of the anterior chamber and ophthalmoscopy are useful means of diagnosis. The finding of nonexudative conjunctivitis and intraocular inflammation in a child with an eruptive febrile disease should make the ophthalmologist suspect Kawasaki disease.

After this report appeared from Japan and indicated that no serious ocular complications occurred during the course of Kawasaki disease, everyone felt more comfortable with this annoying, albeit cosmetically unpleasant, complication of the disorder. Unfortunately, just 3 months after the appearance of the study from Japan, our neighbors in Canada reported that they observed a child who had a much more complicated eye problem during the course of Kawasaki disease (Jacob, J. L., et al.: *Can. J. Ophthalmol.* 17:199, 1982). The patient who presented to them was a 4½-year-old boy who had fairly typical Kawasaki disease, including chorioretinal and vitreous inflammation. However, this progressed in a slow, discrete, and continuous process that ultimately resulted in a severe loss of vision. The authors speculated that this process was initiated by vasculitis and occlusion of a superficial retinal arterial vessel that led to ischemia and a secondary inflammatory process.

My ophthalmologist friends tell me that the eye manifestations of Kawasaki disease—uveitis and conjunctivitis—must be differentiated from the uveitis of juvenile rheumatoid arthritis and the conjunctivitis of Stevens-Johnson syndrome. In some respects these disorders look alike in certain of their manifestations, but it shouldn't be too difficult for us or the eye people to distinguish them.—J.A.S., III] ◀

14–5 **Soccer Ball-Induced Eye Injuries.** Miles J. Burke, James J. Sanitato, Paul F. Vinger, Lawrence A. Raymond, and Dwight R. Kulwin reviewed 24 cases of ocular contusion resulting from soccer ball im-

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(14–5) JAMA 249:2682–2685, May 20, 1983.

pact seen between 1976 and 1981. One patient had two separate eye injuries. Nineteen patients were male, with a mean age of 13 years. No subject used protective eye wear. Half the patients had hyphema, 29% had vitreous hemorrhage, and 21% had corneal abrasion. Angle recession was seen in 8%, and a retinal tear in 4%. Ten patients had both anterior and posterior chamber injuries. One patient later developed traumatic pigmentary retinopathy and an associated quadrantanopia. No cataract or choroidal rupture occurred. All patients but 2 had final acuities of 20/20. Only patients with hyphema were hospitalized. Three patients with hyphema had transient, mild elevations in intraocular pressure.

Soccer ball-related ocular injuries have increased substantially in number in recent years as the game has increased in popularity across the United States. Subjects in this series were predominantly boys in the early teenage years. No rebleeding occurred in the patients with hyphema, and in no case was the preinjury visual acuity affected. In soccer, the head often is used to strike the ball, and an eye protector must both dissipate the energy of the impacting ball before it is absorbed by the eye and be cushioned to prevent injury to areas of facial contact. The best protection can be provided by industrial-strength frames or sport-type eye guards with cushioned supports, fitted with impact-resistant polycarbonate safety lenses. Protective eye wear should be worn by all soccer players, even those who require prescription lenses.

► [I have to admit that I was not aware before seeing this study that soccer balls so commonly could cause eye injuries. My impression had been that it was the end of shoes or elbows that were causing such problems in soccer players. If you examine this report in detail, you can learn a great deal about how even a large object such as a soccer ball can cause damage to the eye. Smaller objects such as racket balls, squash balls, and tennis balls can hit the eye at any age. A tennis ball, for example, is 2⅞ in. in diameter. Once you get above 4 in. in diameter, round objects generally deliver most of their energy to the bony orbital rims. A soccer ball is 8 in. in diameter and normally would be expected to transmit most of its force to the bony orbit rather than to the globe. However, in younger children although the globe and orbital contents may have achieved adult size (this occurs by age 7), the bony orbit in no way has done this. Most preteenagers have flat orbital rims that give the globe a free reception to flying objects even if they are substantially large in size. Another uniqueness to the soccer ball is that it is often coming at the player from below eye level. The flatter inferior orbital rim affords less protection to the globe from a projectile coming at this angle. This study of Burke et al. is not the only one in the last year or so to caution us against the hazards of soccer balls. Berdaguer (*Am. J. Ophthalmol.* 93:145, 1982) reported 20 cases of traumatic retinal detachment caused by soccer balls. Twenty-five percent of this group had visual acuities of less than 20/200 resulting from this eye damage.

The National Society to Prevent Blindness estimates that 90% of sports-related eye injuries are preventable with appropriate eye protection. There will be a great deal of resistance, but we may be on the verge of seeing some pressure brought to bear to include soccer on the list of activities that should require headgear or some other form of eye protection for young participants (if not all). Before this recommendation will ever be accepted, it would be necessary to collect data to document how, how many, and what types of eye injury occur during soccer play. It would then be necessary to investigate what protective measures or equipment or rule changes would be necessary to prevent these injuries. Soccer is one of the unique sports in which the head is frequently and intentionally used to strike an object. Maybe it's time we all use our heads and try to figure out a way of keeping this sport safe for our children.—J.A.S., III] ◄

14-6 **Effects of Swimming Pool Water on the Cornea.** Ocular irritation from swimming pool water is well recognized, but corneal changes have not been well described. Jeffrey R. Haag and Richard G. Gieser (Loyola Univ. Med. Center, Maywood, Ill.) examined the eyes of 50 subjects of both sexes, aged 17 to 77 years, before and after they swam in a chlorinated pool without wearing protective lenses or goggles. The average swimming time was 34 minutes. The free chloride gas concentration was kept at about 1.0 to 1.5 ppm and the pH at about 7.5. Two thirds of subjects reported seeing rainbows, halos or both, around lights after swimming. All subjects but 3 had corneal epithelial erosions in a punctate or linear pattern on fluorescein staining and slit-lamp examination. No subject had a measurable decrease in visual acuity. None of the 3 subjects without corneal changes reported seeing rainbows or halos around lights after swimming.

Many factors may be responsible for the corneal changes seen in swimmers, including chlorine and chlorine-derived compounds, the pH and tonicity of the water, substances introduced by filtration, and mechanical disruption of the tear film and the corneal epithelium. Further studies are needed to determine the relative importance of these factors.

▶ [Everyone knows that swimming pools can cause eye irritation. This is among the first studies, however, that demonstrate that corneal alterations can occur. In fact, the development of corneal epithelial denudation can take place within 30 minutes of swimming in a chlorinated pool. The authors of this study suggest several etiologies for this transient eye damage. The least probable irritant is chlorine itself. Low pH seems to be much more of a problem. Hypotonicity of the pool water also can be a factor. This is one of the reasons why swimming in the ocean rarely produces similar problems. Finally, one of the most important factors causing eye irritation in swimmers could be chloramines. Chlorine combines with ammonia, which is introduced into the water by swimmers to form monochloramine and dichloramine. Chloramines are weak disinfectants that may collect as insoluble gases over the surface of the pool and enter the eye of the swimmer. Adjustment of pH can be helpful in limiting the concentration of these compounds. The only other thing that would work would be trying to get the kids (and others) to stop introducing substances into the water that generate ammonia. Unfortunately, the likelihood of being able to do that is about as great as trying to get your cat to stop peeing in the bathtub (in order to carry on the vendetta against cats established by prior editors of the YEAR BOOK, the following are eight annoying things that cats do, as published in the *Book of Lists*, No. 3, William Morrow & Company, Inc., New York, 1983, p. 451:

"1. Sleep on your face.

"2. Pee in the bathtub.

"3. Sit on the dinner plates.

"4. Lay across newspapers, books or magazines you are trying to read.

"5. Shed on all your black, brown, and navy clothes.

"6. Stare at your face until you wake up—usually at 5:30 A.M.

"7. Try to steal roast beef, ham, and turkey roll out of your hero sandwich (Hoagles, for our Philadelphia readers).

"8. Wack a plastic ball against the bathroom tiles at 2:00 A.M.")

The obvious preventive measure for irritation of the eyes when swimming, if all else fails, is to wear goggles. Even these are not truly safe, as witnessed by two letters to the editor of the *New England Journal of Medicine* this past year. R. I. Jacobson (*N. Engl. J. Med.* 308:1363, 1983) notes that he experienced pain in the supraorbital ridge area of the face after wearing tight-fitting swim goggles. Apparently, pressure

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(14–6) JAMA 249:2507–2508, May 13, 1983.

of the goggles caused a supraorbital neuralgia. A. Petstronk (ibid., pp. 226) developed migraine headaches when he started using "Mark Spitz"-type swim goggles. The headaches stopped when the goggles were no longer used and started again when they were reintroduced. These phenomena are similar to the observation in the same journal that large sunglasses can cause numbness about the nose and the upper teeth. This is caused by compression of the infraorbital branch of the trigeminal nerve. So, now to "giggle micturition," we must add "sunglass dentition" and "goggle mentation."—J.A.S., III] ◀

14–7 **Abnormal Immune Responses in Ocular Presentation of Wiskott-Aldrich Syndrome.** Wiskott-Aldrich syndrome is an X-linked disorder characterized by thrombocytopenia, eczema, and recurrent infections. Survival into the second decade was rare until recently, when better understanding and earlier recognition of the syndrome and newer treatments of infectious and hemorrhagic disorders improved survival. Robert B. Guss and James P. McCulley (Stanford Univ.) encountered 3 youths, aged 15 to 19 years, who had eczema of the eyelids, episcleritis, marginal keratitis, and blepharitis in association with the syndrome. These ophthalmologic findings reflect the change in survival of patients with Wiskott-Aldrich syndrome.

Boy, 15, had eczema at age 2 months, thrombocytopenia at 9 months, and spontaneous rectal bleeding at 1 year. Asthma and respiratory tract infections have recurred since early life. The diagnosis of Wiskott-Aldrich syndrome was made at age 4 years. The immunoglobulin profile showed high IgA and IgE, normal IgG, and low IgM concentrations. Transfer factor, first administered at age 7 years, resulted in transient amelioration of symptoms. Renal insufficiency was diagnosed at age 13 years. Since age 10, four episodes of episcleritis in one or both eyes have occurred. At age 12 years, staphylococcal blepharitis with marginal keratitis and adjacent episcleritis of one eye was observed. Topical treatment with antibiotics and intensive lid hygiene resulted in improvement in the keratitis and resolution of the episcleritis. At age 13 years, a bacterial ulcer adjacent to an area of marginal keratitis in one eye responded promptly to topical and oral antibiotic therapy coupled with vigorous lid hygiene (warm compresses followed by baby shampoo scrubs of the lids twice a day). Vision has remained at 6/6 in each eye. The lids have shown various degrees of eczema in parallel with the generalized eczema. No specific long-term therapy other than lid hygiene has been prescribed. Corticosteroids have not been used topically for eczema of the lids.

(14–7) Ann. Ophthalmol. 14:1058–1060, November 1982.

15. Neurology and Psychiatry

15–1 **Convulsions Following Birth Asphyxia/Birth Trauma: Are Long-Term Anticonvulsants Necessary?** Infants who are asphyxiated or have traumatic delivery often convulse in the early neonatal period. Prolonged anticonvulsant therapy has been considered necessary in only a minority of cases. Geoffrey L. Gillam (Royal Children's Hosp., Parkville, Australia) examined the need for long-term anticonvulsant medication beyond the neonatal period in a review of data on 38 infants seen in 1974–1978 with signs of fetal distress during labor or evidence of birth trauma, depression at birth requiring active resuscitation, and seizures in the early neonatal period. All lived to age 1 year. Infants of less than 36 weeks' gestational age were not included in the study.

Seizures first occurred before age 3 days in 34 cases. In 6 cases seizures continued for longer than 72 hours. Anticonvulsants were withdrawn before discharge except in 3 cases. One of these infants had continued seizures and another had a family history of seizures. Ten infants behaved abnormally at the time of discharge; 3 of these had continued convulsions. Eight infants had a recurrence of seizures in the first year of life. Five of these had major neurologic sequelae. Four of them had mental retardation and cerebral palsy. Seven infants were receiving anticonvulsants by age 1 year. Eight of the 10 infants with abnormal behavior at discharge were developmentally abnormal at age 1 year.

It is recommended that anticonvulsant medication not be continued beyond the neonatal period for infants who have stopped convulsing and are feeding well and behaving normally. It is reasonable to stop medication 3–4 days after the last seizure, so that anticonvulsant therapy can be reinstituted before discharge if seizures recur. There is about a 50% risk of seizures recurring if a persistent neurologic deficit is present. Long-term anticonvulsant therapy could be considered for these infants.

▶ [We are pleased, and fortunate, to have our annual contribution from Dr. Joseph Volpe. We save the toughest commentaries for him. Doctor Volpe, The Stein Professor of Developmental Neurology, Professor of Pediatrics, Neurology and Biological Chemistry, Washington University in St. Louis writes:

"Gillam's report addresses the issue of the appropriate duration of long-term anticonvulsant therapy in infants with neonatal seizures secondary to perinatal asphyxia. The work should be placed in the context of important recent observations concerning *the management and prognosis of neonatal seizures*. These two aspects will be the focus of this commentary; a detailed discussion of other aspects of neonatal seizures is available elsewhere (see Volpe, J.: *Neurology of the Newborn*, W. B. Saunders Co., Philadelphia, pp. 111–137).

"The first issue concerning management of neonatal seizures is recognition of *the*

(15–1) Aust. Paediatr. J. 18:90–91, June 1982.

urgency of treatment and *the deleterious effects of seizures*. It is easier, though inappropriate, to ignore the newborn quietly exhibiting continuous subtle seizures than the older child jerking violently in a generalized tonic-clonic seizure. Repeated seizures, even if subtle in type, may disturb ventilation and cause hypoxemia and hypercapnia. Transcutaneous monitoring of respiratory gases has documented this point clearly. Hypoxemia can cause brain injury directly or, by provoking cardiovascular failure, can lead to ischemic brain injury. In addition, and especially important in the preterm infant, continuous monitoring of blood pressure has shown that abrupt increases regularly accompany subtle seizures (Lou and Friis-Hansen: *Acta Paediatr. Scand.* 68:803, 1979; Goldberg et al.: *Pediatrics* 69:583, 1982; and Perlman and Volpe: *J. Pediatr.* 102:288, 1983). This pressor response, when coupled with certain other accompaniments of seizures, i.e., impaired autoregulation, hypercapnia, and elevated cerebral lactate levels (secondary to enhanced glycolysis), may lead to dangerous increases in cerebral blood flow (Perlman and Volpe: ibid.) and, perhaps, intraventricular hemorrhage or hemorrhagic infarction. Finally, seizures per se, separate from the disturbances of ventilation and perfusion just described, may lead to brain injury, at least in experimental studies of neonatal as well as mature animals (see, for review, Wasterlain: *Neuropaediatrie* 9:213, 1978; and Soderfelt et al.: *Acta Neuropathol.* 54:219, 1981).

"The second issue concerning management is the *mode of treatment*. The initial optimal approach is to establish an intravenous line, determine blood glucose on the first drops of blood (Dextrostix), and treat with glucose if hypoglycemia is present. If hypoglycemia is not present, we proceed to administration of anticonvulsant drugs. (Other metabolic causes for neonatal seizures and the appropriate treatments are discussed elsewhere [Volpe, J.: *Neurology of the Newborn*, W. B. Saunders Co., Philadelphia, 1981, pp. 111–137].)

"*Phenobarbital* is the drug of first choice in neonatal seizures. We administer the drug intravenously in two 10-mg/kg increments, each administered over 5 to 10 minutes, i.e., a total loading dose of 20 mg/kg, with careful attention to respiration. As shown by Painter et al., this dose results in a therapeutic blood level of approximately 20 μg/ml (*J. Pediatr.* 92:315, 1978). The response of this dose depends on the etiology of the seizure, but, in general, approximately one half to two thirds of infants will respond. If more anticonvulsant medication is necessary, we recommend additional 5- to 10-mg/kg increments of phenobarbital, administered over 5 to 10 minutes, to a maximum dose of 40 mg/kg. With this approach, only approximately 10% of infants will require a second anticonvulsant drug (Gal et al.: *Neurology (NY)* 32:1041, 1982).

"*Phenytoin* is our choice for second drug. We administer phenytoin directly into the intravenous line (phenytoin will precipitate if added to the usual intravenous solutions) and follow the injection with a small amount of normal saline (the pH of the parenteral preparation is 12 and is irritating to the vein). A dose of 20 mg/kg will achieve an appropriate blood level of 15 to 20 μg/ml (Painter et al.: *J. Pediatr.* 92:315, 1978).

"With the regimen just described, the need for a *third drug* in control of neonatal seizures is rare. Moreover, it is often more dangerous to attempt to stop every remaining remnant of seizure activity by adding more medication. Nevertheless, occasionally we have utilized rectal or intravenous administration of paraldehyde. Gamstorp and Sedin (*Upsala J. Med. Sci.* 87:143, 1982) have recommended continuous, intravenous infusion of diazepam in the term infant.

"Maintenance of anticonvulsant drug therapy and total duration of therapy are the next issues in management. The *maintenance* dose of phenobarbital is 3 to 4 mg/kg/day. Intravenous, intramuscular, or oral administration is satisfactory. This dose achieves a blood level of approximately 20 to 25 μg/ml (Fischer et al.: *Neurology (NY)* 231:1042, 1981) and prevents the drug accumulation observed at approximately 7 to 10 days with higher maintenance doses (Painter et al.: *J. Pediatr.* 92:315, 1978). The dose requirement may increase over the next several weeks because of an increase in the rate of drug elimination. The initial maintenance dose of phenytoin is similar to that for phenobarbital, but careful attention to blood levels is especially important, because of considerable interpatient variability in pharmacokinetics, especially in the first week of life, and a marked, threefold increase in elimination rate over the next 3 weeks ($T_{1/2}$ in first week = 57.3 ± 48.2 hours, and in fourth week = 19.7 ± 1.3 hours) (Bourgeois and Dodson: *Neurology (NY)* 33:173, 1983). In addition, intravenous ad-

ministration is preferred over either intramuscular (erratic absorption, danger of muscle necrosis) or oral (deficient absorption) administration.

"*Duration of therapy* relates principally to the likelihood of recurrence of seizure if the drugs are discontinued. What is the risk of subsequent epilepsy in infants with neonatal seizures? The overall incidence of subsequent epilepsy after neonatal seizures has varied from study to study between approximately 10% and 25%. This overall range can be refined to the individual patient if one considers: (1) the cause of the neonatal seizures, (2) the neonatal neurologic findings, and (3) the neonatal EEG. The first of these is very critical determinant. Thus, the risk of subsequent epilepsy after neonatal seizures secondary to perinatal asphyxia was 29% in the series of Watanabe et al. (*Brain Dev.* 4:341, 1982) and 21% in the above-abstracted report of Gillam. Neonatal seizures secondary to cortical dysgenesis carry a risk of epilepsy of 81%. However, the risk is 0% with simple, late-onset hypocalcemia. The second determinant, the neonatal neurologic examination, is similarly important. For example, in Gillam's study of asphyxiated infants, there was an approximately 50% risk of recurrence of seizures if the neurologic examination at discharge was abnormal. The third determinant, the EEG, was useful in the study of term infants by Watanabe et al.; thus, of 54 asphyxiated infants with seizures and a neonatal interictal sleep EEG that was normal and showed only "minimal" or "mild depression," none developed subsequent epilepsy. In contrast, 15 of 37 (41%) with "marked depression" developed subsequent epilepsy.

"We recommend that these three factors be assessed carefully in each newborn with seizures to determine duration of therapy. In practice, we discontinue phenytoin almost invariably during the neonatal period, usually when intravenous lines are removed. Phenobarbital is discontinued in the neonatal period also if the neurologic examination is normal. In questionable cases, the EEG may be particularly useful. If the infant is discharged receiving phenobarbital, we reassess the neurologic examination and development at 2 to 3 months of age and, if the neurologic status is normal, discontinue phenobarbital (over 4 weeks). If the infant is not normal, a sleep EEG is useful, and, if not overtly paroxysmal, we believe it is reasonable to taper and discontinue the phenobarbital."] ◄

15–2 **Characteristic EEG Pattern in Neonatal Herpes Simplex Encephalitis.** Eli M. Mizrahi and Barry R. Tharp (Stanford Univ.) obtained EEGs on 6 infants with localized type 2 herpes simplex virus (HSV) encephalitis. Clinical symptoms first were noted in these previously well infants between 14 and 20 days of age. Fever and lethargy were common, but the major disorder was partial motor seizures refractory to anticonvulsants. Initial computed tomography in 5 patients was normal or nonspecifically abnormal. In 1 case, a focal temporal lobe radiolucent abnormality suggested HSV infection.

The first EEG (obtained within the first week of illness) in 4 infants showed a unique multifocal periodic or quasiperiodic pattern, with recurrent slow waves or sharp slow-wave complexes; in 1 infant, a periodic pattern subsequently replaced the quasiperiodic pattern. A fifth infant developed a quasiperiodic pattern on the eighteenth day (Fig 15–1). All these infants died or were left with severe encephalopathy. Therapy with adenine arabinoside was begun in 1 of these patients after the periodic pattern was noted in the EEG on the third day of illness.

In a sixth infant, acyclovir therapy (30 mg/kg/day) was begun on day 2. The periodic pattern did not appear in any of the EEGs of this infant, and at age 8 months he showed only moderate motor delay.

A periodic EEG in a young infant with partial motor seizures and

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(15–2) Neurology (NY) 32:1215–1220, November 1982.

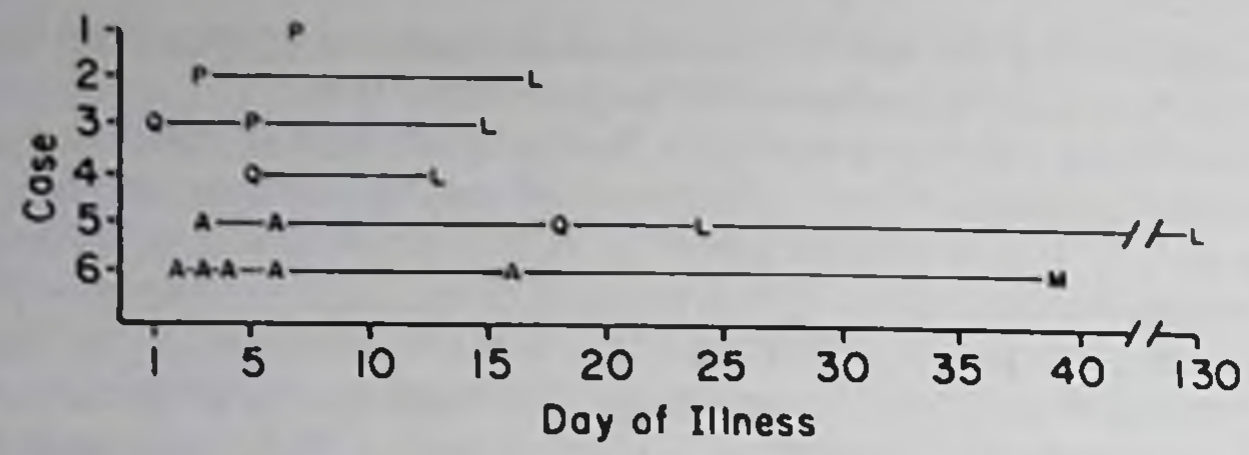

Fig 15–1.—The EEG findings in 6 cases of type 2 herpes simplex virus encephalitis. *P*, periodic activity; *L*, low-voltage or isoelectric EEG; *Q*, quasiperiodic activity; *A*, abnormal EEG (multifocal sharp waves, bursts of negative theta activity in central regions, absence of normal background rhythms); *M*, mildly abnormal EEG. (Courtesy of Mizrahi, E. M., and Tharp, B. R.: Neurology (NY) 32:1215–1220, November 1982.)

cerebrospinal fluid lymphocytic pleocytosis is virtually diagnostic of HSV encephalitis.

▶ [It would be wonderful if this observation can be confirmed. A prompt diagnosis of herpes simplex virus encephalitis would enable the institution of therapy that might produce a better neurologic outcome. All 6 of the infants in this report presented with fits and none had signs of mucocutaneous involvement. It is estimated that approximately 50% of infants with central nervous system disease will have no dermatologic manifestations (see Arvin, A. M., et al.: *J. Pediatr.* 100:715, 1982). For more on the unusual skin lesions in this disease during the newborn period, see this edition of the YEAR BOOK, Chapter 3, "Allergy and Dermatology."—F.A.O.] ◀

15–3 **Hazard of Video Games in Patients With Light-Sensitive Epilepsy.** Neil R. Dahlquist, James F. Mellinger, and Donald W. Klass (Mayo Clinic and Found.) present the case of a boy in whom playing video games precipitated seizures.

Boy, 15, was well and had played video games for 1 year. While playing a video game, a friend noticed that he was in a daze and that his hand twitched. At home shortly thereafter, his mother noticed he had lost his glasses, was uncharacteristically belligerent, and had slow mentation. Later that month he fell in the shower and was found on the floor in an extremely agitated and belligerent state and with the right arm twitching briefly; afterward he transiently was confused.

Six weeks after the initial episode, while playing a video game, the patient had a generalized tonic-clonic seizure lasting several minutes. A postictal state lasted 2 hours. Results of neurologic examination were otherwise normal. A waking EEG showed a burst of spike-and-wave activity during photic stimulation. Phenytoin sodium, 300 mg per day, was prescribed. The boy had three more generalized seizures, always associated with bright, early morning sunlight.

Examination 5½ months after the initial episode showed normal neurologic findings. An EEG while awake and during hyperventilation was normal, but photic stimulation consistently elicited diffuse bursts of high-amplitude, bilaterally synchronous spike and slow-wave complexes that were sometimes accompanied by generalized myoclonus. The next day, an EEG contained no paroxysmal abnormalities during photic stimulation, viewing of different geometric patterns, or playing a video game. The patient was advised to taper the dosage of phenytoin and to begin to take 250 mg of valproic acid four times daily. In the next month he avoided playing video games and had no further seizures.

(15–3) JAMA 249:776–777, Feb. 11, 1983.

Seizures induced by playing video games are similar to those induced by watching television; the latter are well recognized in epileptic patients sensitive to flickering lights or geometric patterns. Spontaneous fluctuations in threshold for photosensitivity are also well-known, accounting for the patient being extremely photosensitive one day but not the next. Time of day probably also had an influence. This patient was tested in the afternoon on the second day, whereas his history showed most seizures occurring in the morning, and the previous EEG contained spontaneous epileptiform abnormality only after the patient was aroused from sleep.

▶ [This boy first became glassy-eyed while playing "Combat," and "Pac-Man" finally did him in. Previous provokers have included "Space-Invaders" (*Lancet* 1:501, 1981) and "Dark Warrior" (*Br. Med. J.* 284:1751, 1982). If the game is incapable of producing a fit, it is not worth playing at all. No hazard—no fun.—F.A.O.] ◀

15–4 **Childhood Brain Tumors Presenting as Chronic Uncontrolled Focal Seizure Disorders.** Warren T. Blume, John P. Girvin, and John C. E. Kaufmann (Univ. of Western Ontario) found tumors in 16 of 35 patients undergoing surgical resection of an epileptogenic focus between 1974 and 1980. All patients were younger than age 21 and had uncontrolled seizures, despite thorough medical treatment, most or all of them arising from a resectable area, or radiologic evidence of a neoplasm. Patients seen primarily with a progressive neurologic deficit or elevated intracranial pressure were not included in the series. Twelve of the 16 tumor patients had astrocytomas. Most of the other patients had neuronal or architectural abnormalities, glial scars, or cortical malformations.

Mean ages at onset of seizures were 9 years for tumor patients and 7 years for the others, and the respective mean durations of seizure disorder before operation were 6 and 9 years. The neurologic findings were more often normal in the group with tumor. All but 2 of 15 tumor patients but only 8 of 18 patients without tumor had an IQ greater than 79. When a plausible reason for intractable focal seizures was identified, only 2 of 16 patients were found to have a tumor. A tumor was found in 10 of 14 patients with persistent delta EEG activity in most records. The nature of seizures and EEG spikes were not helpful in distinguishing the two groups of patients. Seven of 8 patients who had "complete" tumor removal have been free from seizures on follow-up for 8 to 38 months after operation, and the other patient has had fewer attacks. Four of 6 patients who had incomplete removal of tumor have had significantly fewer seizures, and the other 2 are free from seizures. Most tumor patients are using less anticonvulsant than before operation, and none is using more.

Tumor was a frequent cause of uncontrolled focal epilepsy in children in this series who were candidates for operation. Tumor was the most common cause of seizures when the neurologic findings or intelligence, or both, were normal, focal EEG delta activity was present in most recordings, or there was no other plausible cause for seizures.

(15–4) Ann. Neurol. 12:538–541, December 1982.

15–5 **Chronic Toxicity in Epileptic Patients Receiving Single-Drug Treatment.** The relative importance of various anticonvulsants in producing chronic toxic effects is difficult to assess because most studies have been done in patients receiving polypharmacy. D. I. Dellaportas, S. D. Shorvon, A. W. Galbraith, M. Laundy, E. H. Reynolds, W. J. Marshall, and I. Chanarin prospectively compared chronic metabolic effects in 30 patients treated with phenytoin alone and effects in 33 patients taking carbamazepine alone. Measurements were made before and after 2 years of therapy in previously untreated patients who had tonic-clonic or partial seizures or both.

In both groups, mean cell volume rose significantly. In the phenytoin group, both serum and red blood cell concentrations of folate fell significantly; a similar trend in the carbamazepine group was not significant. With both drugs, there was a significant fall in serum calcium ($P < .05$) and phosphate ($P < .01$) concentrations and a rise in alkaline phosphatase ($P < .005$) concentrations. Bilirubin concentration dropped in both groups, significantly with carbamazepine, but not with phenytoin. Reductions in hemoglobin were slightly significant and total protein concentrations were highly significant with carbamazepine but not with phenytoin. Seventy-five percent of patients on carbamazepine had mean drug concentrations in the optimum range compared with 37% of those on phenytoin (table).

The clinically insignificant metabolic changes noted contrast with more widespread and florid abnormalities reported in chronic epilepsy. Polypharmacy may be unnecessary and undesirable. These findings suggest that chronic toxicity can be reduced by careful monitoring of single-drug treatment.

► [These changes are not striking, but demonstrate that a price is paid for any medication. Polypharmacy should be avoided whenever possible. E. Fischbacher (*Br. Med. J.* 285:423, 1982) describes an attempt to reduce the number of anticonvulsants used to treat epilepsy in an institution for the mentally handicapped. At least one drug was withdrawn successfully from 20 of 36 patients without loss of seizure control—and, in each instance, the well-being of the patient was improved significantly.

Barbiturate anticonvulsants may be a cause of depression (Ferrari, M., et al.: *J. Psychiatry* 140:112, 1983) and will increase requirements for theophylline in patients who have the misfortune of having both asthma and epilepsy (Paladino, J. A., et al.: *Ther. Drug Monit.* 5:135, 1983).

Close to 50% of patients receiving valproic acid will have asymptomatic hyperammonemia (Murphy, J. V., et al.: *Arch. Neurol.* 39:591, 1982).—F.A.O.] ◄

15–6 **Submersion Accidents in Children With Epilepsy.** James P. Orlowski, A. David Rothner, and Hans Lueders (Cleveland Clinic Found.) reviewed data on 100 children who drowned or nearly drowned between 1972 and 1979; 6 children had known underlying seizure disorders that probably had caused their accidents. All 6 were boys, as were 75% of the entire series. Five patients had major motor seizure disorders of the tonic-clonic type, and 1 had complex partial seizures. The disorder was not fully controlled by anticonvulsant therapy in any of the 6. Three patients had an IQ of 75 of less. In 3 patients the most recent preaccident drug levels were in the subther-

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(15–5) Br. Med. J. 285:409–410, Aug. 7, 1982.
(15–6) Am. J. Dis. Child. 136:777–780, September 1982.

INDICES OF CHRONIC TOXICITY BEFORE AND AFTER TWO YEARS OF TREATMENT WITH A SINGLE DRUG

	Phenytoin				Carbamazepine			
	No of patients	Before treatment	After two years' treatment*	p	No of patients	Before treatment	After two years' treatment*	p
Haemoglobin (g/dl)	22	14·2 ± 0·3	14·4 ± 0·3	NS	22	14·0 ± 0·3	13·9 ± 0·3	< 0·05
Mean cell volume (fl)	20	86·0 ± 1·0	89·0 ± 1·0	< 0·001	20	85·0 ± 1·0	88·0 ± 1·0	< 0·005
Serum folate (µg/l)	18	4·6 ± 0·3	3·2 ± 0·3	< 0·005	23	6·7 ± 0·8	5·4 ± 0·7	NS
Red cell folate (µg/l)	15	443·0 ± 47·0	318·0 ± 32·0	< 0·05	19	396·0 ± 44·0	338·0 ± 31·0	NS
Total protein (g/l)	19	73·0 ± 1·0	72·0 ± 1·0	NS	18	75·0 ± 1·0	72·0 ± 1·0	< 0·05
Albumin (g/l)	19	42·0 ± 1·0	44·0 ± 1·0	NS	19	44·0 ± 1·0	45·0 ± 1·0	NS
Total bilirubin (µmol/l)	17	8·0 ± 1·0	6·0 ± 1·0	NS	19	9·0 ± 1·0	5·0 ± 1·0	< 0·0005
Calcium (mmol/l)	17	2·47 ± 0·02	2·42 ± 0·02	< 0·05	20	2·54 ± 0·02	2·42 ± 0·05	< 0·05
Phosphate (mmol/l)	16	1·08 ± 0·06	0·95 ± 0·05	< 0·01	18	1·12 ± 0·04	1·00 ± 0·04	< 0·01
Alkaline phosphatase† (IU/l)	13	61·0 ± 4·0	78·0 ± 5·0	< 0·005	13	68·0 ± 8·0	82·0 ± 17·0	< 0·0005

*Percentage of patients with mean drug concentrations in optimum range: phenytoin 37%, carbamazepine 75%.
†Patients younger than age 18 years were excluded.
NS, not significant.
(Courtesy of Dellaportas, D. I., et al.: Br. Med. J. 285:409–410, Aug. 7, 1982.)

Submersion Accidents in Patients With Seizure Disorders

Source, yr	Fatal Submersion Accidents: Total No.	Fatal Submersion Accidents: No. (%) With Seizure Disorder	Nonfatal Submersion Accidents: Total No.	Nonfatal Submersion Accidents: No. (%) With Seizure Disorder
Peam et al, 1978	31	0(0)	109	4(3.7)
Adams, 1966	163	4(2.5)	0	0(0)
Chun et al, 1973	347	16(4.6)	0	0(0)
Dietz and Baker, 1974	117	4(3.4)	0	0(0)
Peam, 1977	25	2(8.0)	86	4(4.7)
Present study	26	2(7.7)	74	4(5.4)
Total	**709**	**28(4.0)**	**269**	**12(4.5)**

(Courtesy of Orlowski, J. P., et al.: Am. J. Dis. Child. 136:777–780, September 1982; copyright 1982, American Medical Association.)

apeutic range for one drug. Seizures precipitating the submersion event were witnessed in 3 instances. No toxic anticonvulsant drug levels were found. Three patients survived and returned to their previous levels of functioning. One patient remains semicomatose, and 2 died of drowning or its sequelae.

The reported occurrence of seizure disorders in those who experience drowning or near-drowning accidents is given in the table. The proportion averages 4% for fatal submersion accidents and 4.5% for nonfatal accidents. The major risk groups among children are teenage boys, both swimmers and nonswimmers, and unsupervised toddlers. Patients with seizure disorders constitute another risk group. The increased risk appears related to seizures occurring while the person is in the water as well as to mental retardation. All of the 6 boys described probably had a seizure that precipitated the accident, and 3 of the 6 were mentally dull or retarded. Mentally subnormal children may be allowed to swim if they are well controlled by medication and are supervised properly in the water. Children with poorly controlled epilepsy and subtherapeutic or unstable anticonvulsant drug levels, and poorly compliant patients, probably should be encouraged to seek other forms of play and exercise until the problems can be resolved. Epileptic persons should swim only under close supervision by a lifeguard trained in cardiopulmonary resuscitation.

► [I am delighted to have this comment from Dr. N. Paul Rosman, Professor of Pediatrics and Neurology, Boston University. Doctor Rosman writes:

"There has long been discussion of what restrictions, if any, should be imposed on physical activities of children with epilepsy. Since 1% of our population has epilepsy and most affected persons are children or adolescents, who tend to be physically active, such discussion is important. Most would agree that potentially hazardous endeavors (such as mountain climbing) or unusually exhausting sports (such as marathon running) should be avoided. Many advise that collision sports, such as football, also should be avoided. Most agree that contact sports, such as basketball, need not be avoided; and most will not try to prevent the epileptic child from swimming if seizures are well-controlled and if adequate supervision is insured. In general, physical activity would appear to be more advantageous than disadvantageous for the epileptic child, for exercise has been shown to raise seizure threshold, perhaps secondary to exercise-induced metabolic acidosis.

"The study by Orlowski *et al.* does heighten one's concern about the advisability of swimming by epileptic children, since the frequency of drowning or near-drowning in their population was four times greater than in nonepileptic children. Analysis of their 6 cases of submersion accidents suggests, however, that probable explanations for the occurrence of the drowning or near-drowning could be provided in each instance.

"In Case 1, the child's postaccident phenytoin level was subtherapeutic. In Case 2, no seizure was observed and the child had an intercurrent illness (amebic meningoencephalitis), ultimately fatal, that could have caused the event. In Case 3, a boy of borderline intelligence, preaccident and postaccident phenytoin blood levels were subtherapeutic and no seizure was witnessed. In Case 4, a mildly retarded boy, a preaccident phenytoin level was subtherapeutic. In Case 5, a mildly retarded boy, a preaccident phenytoin blood level was above therapeutic, while postaccident phenytoin and phenobarbital levels were subtherapeutic. In Case 6, a boy of borderline intelligence, a preaccident carbamazepine level was subtherapeutic and no seizure was seen. Of note, in only 3 of the 6 cases were the children swimming in the presence of lifeguards. It is also noteworthy that despite incomplete seizure control in all 6 children, in 4 of the 6 cases the preaccident EEG did not show seizure discharges.

"This study does indicate that swimming poses a greater potential hazard to epileptic than to nonepileptic children, particularly when seizure control is incomplete, when the child has cognitive limitations, when anticonvulsant levels are subtherapeutic, and when there is inadequate supervision in the swimming area. In the absence of adverse factors such as these, the authors' suggestion that the epileptic child should be permitted to swim, if closely supervised by responsible personnel, seems most reasonable."] ◀

15–7 **Persistent Toe-Walking in Children: A Comprehensive Clinical Study of 28 Cases.** Toe-walking is not part of the usual developmental sequence of learning to walk. According to previous studies, it can, however, be a normal temporary phase in a minority of children. This tendency may be familial. Toe-walking often is observed in childhood autism and psychosis.

F. Furrer and Th. Deonna (Lausanne, Switzerland) studied perinatal and postnatal history, details of locomotor development, and the evolution of toe-walking in 28 children with persistent toe-walking age 1–16 years in whom no etiologic diagnosis was evident originally. A detailed neurologic and orthopedic examination was performed, and the level of motor maturation was evaluated.

Three major clinical findings emerged: pyramidal tract signs, motor retardation, and limitation of ankle dorsiflexion (Fig 15–2). Based on the absence or presence of these findings, 4 tentative diagnostic categories were defined: (1) minimal spastic diplegia (5 children who were constant toe-walkers with clear-cut pyramidal tract signs; all with limitation of ankle dorsiflexion, and 4 of the 5 with motor retardation); (2) habitual toe-walking (9 children who were intermittent toe-walkers and had no limitation of ankle dorsiflexion, motor retardation, or pyramidal tract signs who tended to walk early, run more than walk, and were very active); (3) congenital short tendo calcaneus (STC) (4 children with limitation of ankle dorsiflexion of much the same degree in flexed or extended knee position but normal motor level and no pyramidal tract signs who stood on their toes before walking); and (4) mixed or unclassified (10 children). A detailed reevaluation of the latter group enabled them to be reclassified in one

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(15–7) Helv. Paediatr. Acta 37:301–316, 1982.

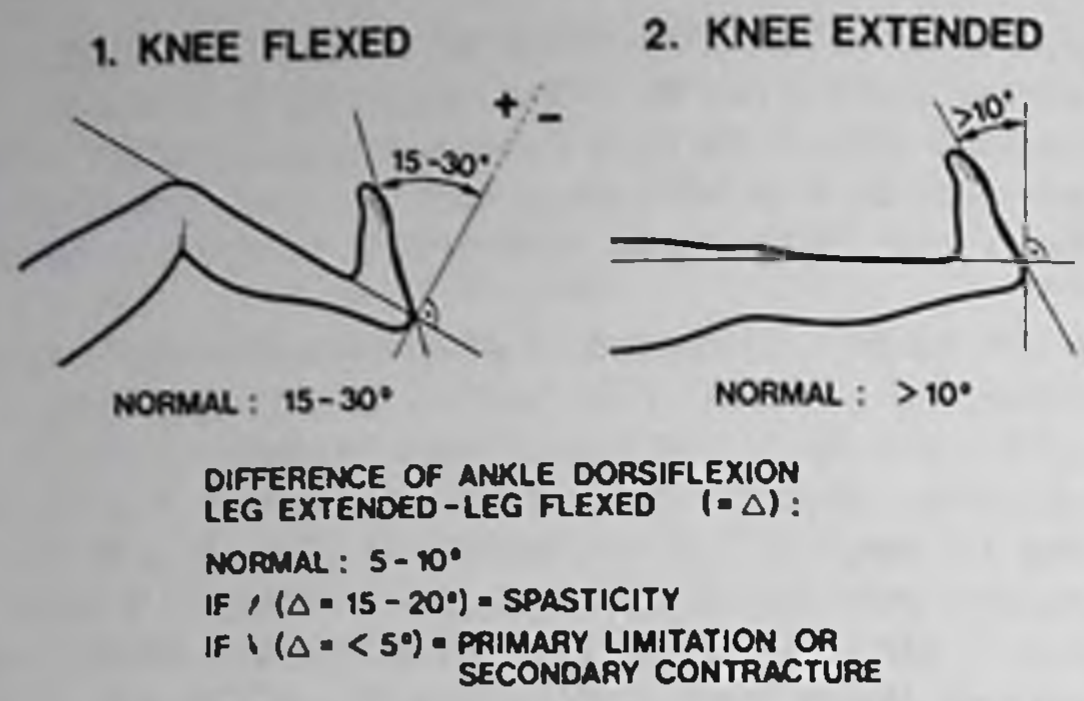

Fig 15–2.—Measurement of ankle dorsiflexion (passive). (Courtesy of Furrer, F., and Deonna, Th.: Helv. Paediatr. Acta 37:301–316, 1982.)

of the three major categories, even if in some cases several factors seemed to play a role in the toe-walking.

The influence of persistent toe-walking on the range of ankle dorsiflexion is an important question, and it might be argued that some children of the STC group might be habitual toe-walkers with secondary contracture. It appears that only a longitudinal evaluation of these children could better document the existence of the two separate entities.

In toe-walkers with spasticity, active and passive exercises can be performed to increase range of movement at the ankle joint and improve motor performances. Surgical lengthening of the tendo calcaneus can be done if indicated in these children or in those with an isolated short tendo calcaneus. Special investigations (e.g., nerve conduction velocities, electromyography, enzyme studies) are indicated only in children in whom muscle weakness cannot be ruled out clinically and when toe-walking appears after a period of normal gait, mainly to exclude neuropathy or myopathy.

15–8 **Vitamin E Deficiency and Neurologic Disease in Children With Cholestasis: Prospective Study.** Children with chronic cholestasis may develop a progressive disabling neurologic disorder related to vitamin E deficiency. Mary Anne Guggenheim, Virginia Jackson, John Lilly, and Arnold Silverman (Univ. of Colorado) assessed the neurologic and vitamin E status of 48 children with previously recognized cholestasis and 23 others with either noncholestatic malabsorption or progressive ataxia. The children with cholestasis had biliary atresia, neonatal hepatitis, or Alagille syndrome. Forty had had a Kasai-type enterostomy. Eleven controls had noncholestatic malabsorption, usually cystic fibrosis, and 12 had familial ataxic syndromes without evidence of hepatobiliary disease.

Three fourths of the group with cholestasis and 18% of the control children with other types of malabsorption were vitamin E-deficient. Five children with cholestasis were taking supplemental vitamin E. Two children with cholestasis had low serum vitamin E concentrations when their portoenterostomies were externally drained but normal values after closure of the stomas and reinstitution of enteric

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(15–8) J. Pediatr. 102:577–579, April 1983.

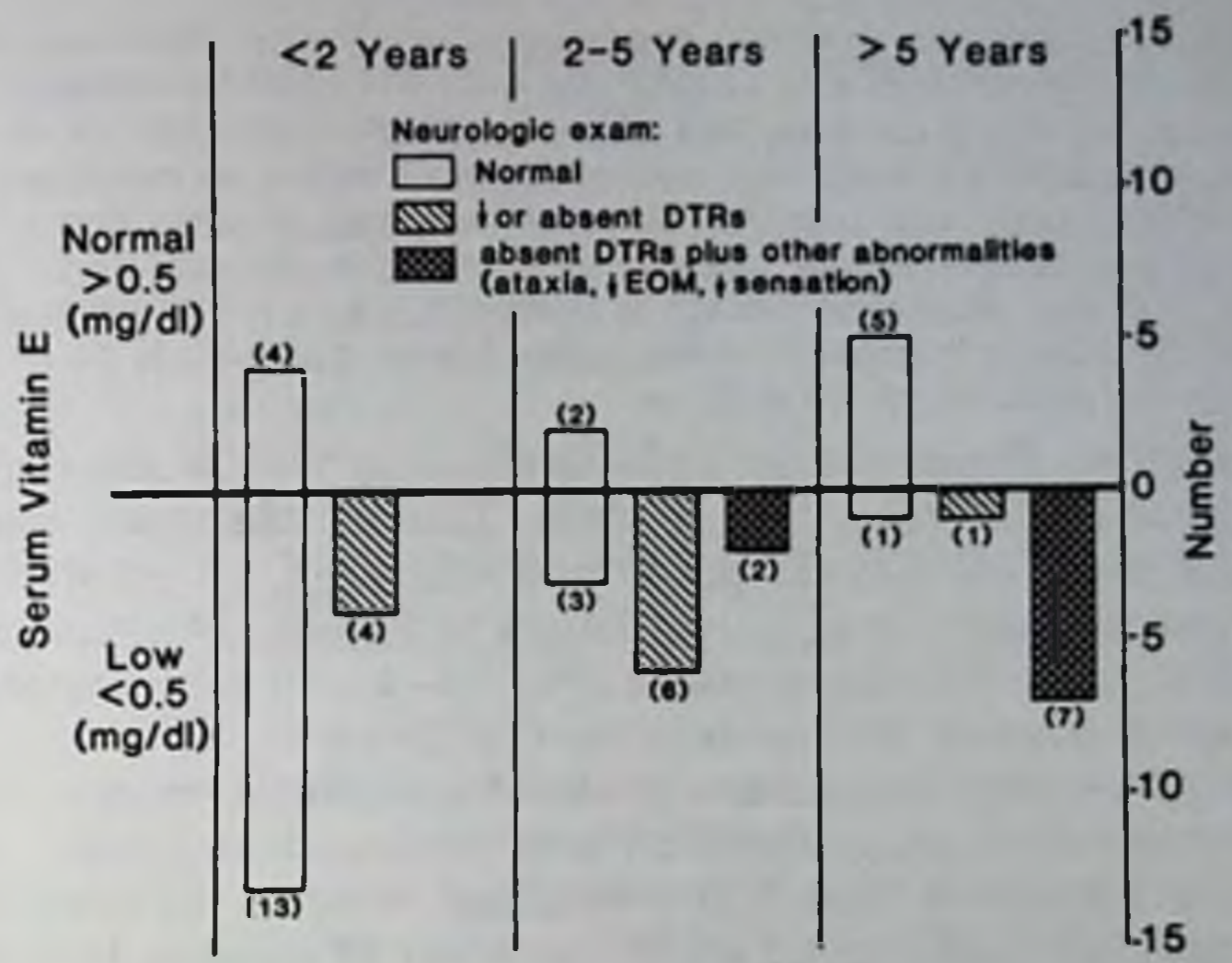


Fig 15–3.—Correlation of age, serum vitamin E concentrations, and neurologic status in 48 children with chronic cholestasis. *EOM*, extraocular movement; *DTR*, deep tendon reflex. (Courtesy of Guggenheim, M. A., et al.: J. Pediatr.) 102:577–579, April 1983.)

biliary flow. Vitamin E-deficient children were likelier to have neurologic abnormalities with advancing age (Fig 15–3). Areflexia was the earliest abnormality. Eighty percent of vitamin E-deficient children older than age 5 years had clinically significant neurologic impairment.

The neuropathologic abnormalities associated with malabsorption states, especially cholestasis, progress with age and are identical with the changes seen in chronically vitamin E-deficient animals. The neurologic abnormalities seen in the children in this study with chronic cholestasis and vitamin E deficiency are consistent with the neuropathologic substrate of neuraxonal changes and demyelination of the posterior columns and brain stem. Correction of vitamin E deficiency in children with cholestasis can lead to partial improvement in the neurologic abnormalities, but parenteral vitamin E administration may be necessary. Attempts to reverse the deficiency with large oral doses of vitamin E deserve trial, but they are not always successful.

► [To get an overview of this problem, I suggest that you take a look at the 1980 YEAR BOOK (p. 299), the 1981 YEAR BOOK (pp. 389–390), and the 1983 YEAR BOOK (pp. 406–410).

This study by Guggenheim and associates puts the clinical problem of vitamin E deficiency into perspective and defines the risk of the neuromuscular disturbance developing in patients with fat malabsorption. All patients with fat malabsorption are at risk, and patients with cholestatic liver disease, abetalipoproteinemia, and cystic fibrosis are the most likely to turn up with the problem.

The primary manifestations of the neuromyopathy produced by longstanding vitamin E deficiency include: areflexia, truncal and limb ataxia, superior ophthalmoplegia, facial weakness, and decreased proprioception and fibratory sense. The deep tendon reflexes appear to be the first to go. The ultrastructural and histochemical abnormalities of skeletal muscle in patients with chronic vitamin E deficiency resemble those seen in vitamin E-deficient animals and are the end result of intracellular lipid peroxidation (Neville, H. E., et al.: *Neurology (NY)* 33:483, 1983).

How early can histologic changes be observed? R. J. Sokol and co-workers have demonstrated alterations in the histology of the sural nerve as early as age 6 months.

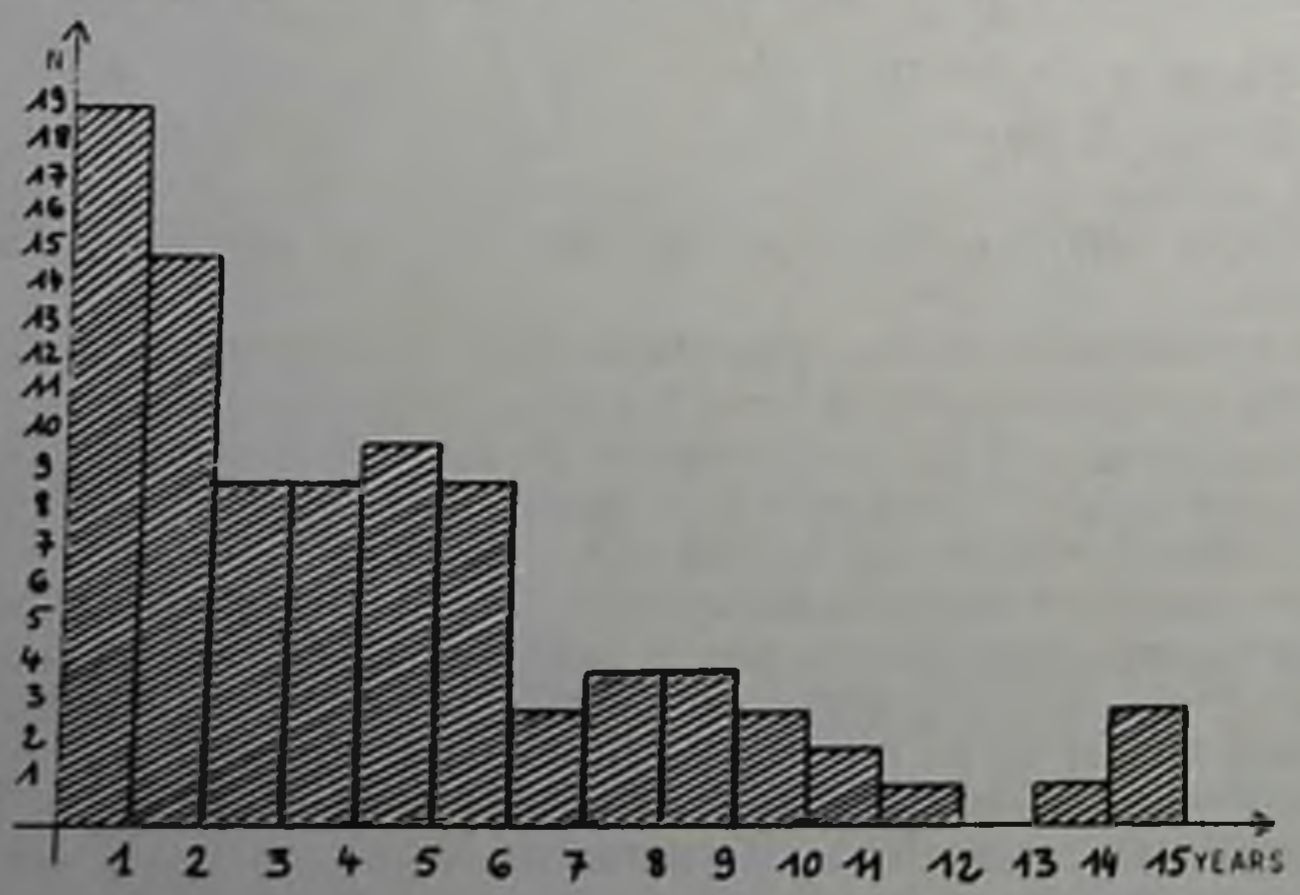
A degenerative axonopathy involving large-caliber myelinated fibers was present (*J. Pediatr.* 103:197, 1983). Sokol et al. recommend early and aggressive vitamin E therapy to prevent the neurologic damage. This means supplementation with up to 150 IU/kg/day of α-tocopherol orally to achieve normal vitamin E status, as measured by serum vitamin E to lipid ratios and hydrogen peroxide hemolysis. If correction of vitamin E deficiency by oral supplementation cannot be accomplished by age 18 to 24 months, Sokol et al. feel that parenteral therapy is indicated. There is still no approved parenteral form of vitamin E available in the United States. You have to go to Europe or borrow it from a veterinarian.—F.A.O.] ◄

15–9 **Intracranial Pressure in Craniostenosis** was studied by Dominique Renier, Christian Sainte-Rose, Daniel Marchac, and Jean-François Hirsch (Necker Hosp. for Sick Children, Paris) with an epidural sensor for periods of 12–24 hours in 92 patients, aged 6 weeks to 15 years, with craniosynostosis (Fig 15–4); all had premature fusion of one or several cranial sutures (Table 1).

Preoperative recordings were grouped into three categories (Table 2); the intracranial pressure (ICP) was obviously increased in 23 patients. Table 3 shows that ICP recordings vary in different types of craniosynostosis and depend on the number of sutures involved (Fig 15–5). The recordings were abnormal (15 mm Hg or greater during slow-wave [SW] sleep) in 14% of patients with involvement of one suture and in 47% of patients with involvement of several sutures. Fifty-eight children were operated on, in most cases by the classic surgical technique—free flaps, extensive craniectomies. Postoperative recordings indicated the ICP to be lower after surgery. Thus, taken 6 months postoperatively, the final mean decrease from preoperative levels of ICP during SW sleep was 6 mm Hg ($P < .001$) and that of waves of increased ICP during rapid-eye-movement (REM) sleep was 16 mm Hg ($P < .001$).

This study considered ICP to be normal when it was below 10 mm Hg, abnormal above 15 mm Hg, and borderline in between. Waves of increased ICP during REM sleep were regarded as abnormal when they were sustained. Sustained waves of increased ICP during REM

Fig 15–4.—Age at time of intracranial pressure recording in 92 patients with craniosynostosis. (Courtesy of Renier, D., et al.: J. Neurosurg. 57:370–377, September 1982.)



(15–9) J. Neurosurg. 57:370–377, September 1982.

TABLE 1.—TYPES OF CRANIOSYNOSTOSIS IN 92 PATIENTS

Type	No. of Cases
scaphocephaly	25
plagiocephaly	10
trigonocephaly	5
brachycephaly	9
oxycephaly	27
Apert's syndrome	12
Crouzon's disease	4

(Courtesy of Renier, D., et al.: J. Neurosurg. 57:370–377, September 1982.)

TABLE 2.—PREOPERATIVE INTRACRANIAL PRESSURE IN 75 CASES OF CRANIOSYNOSTOSIS

Preop ICP Groups	Mean ICP (mm Hg)		REM Sleep (no. of cases)	
	SW Sleep	REM Sleep	Sustained Waves	Phasic Waves
increased ICP (23 cases)	21	48	17	6
borderline ICP (22 cases)	14	35	7	15
normal ICP (30 cases)	9	27	5	25

*ICP, intracranial pressure; *SW*, slow-wave; *REM*, rapid-eye-movement.
(Courtesy of Renier, D., et al.: J. Neurosurg. 57:370–377, September 1982.)

TABLE 3.—INTRACRANIAL PRESSURE (ICP) IN DIFFERENT TYPES OF CRANIOSYNOSTOSIS

Type	Slow-Wave Sleep ICP			Total
	> 15 mm Hg	11–15 mm Hg	≤ 10 mm Hg	
scaphocephaly	3	4	16	23
plagiocephaly	2	4	3	9
trigonocephaly		1	4	5
brachycephaly	3	2	2	7
oxycephaly	10	9	4	23
Apert's syndrome	3	2	1	6
Crouzon's disease	2			2
total	23	22	30	75

(Courtesy of Renier, D., et al.: J. Neurosurg. 57:370–377, September 1982.)

sleep are due to increased cerebral blood volume. They are found in cases of hydrocephalus, subdural hematomas, craniosynostosis and space-occupying lesions.

This study suggests that, over the long term, there seems to be a relationship between moderately increased ICP and a low IQ level. The ICP was usually elevated when craniosynostosis involved several sutures, and it is known that IQ is often low in these patients. Table 4 indicates that the longer craniosynostosis and its associated in-

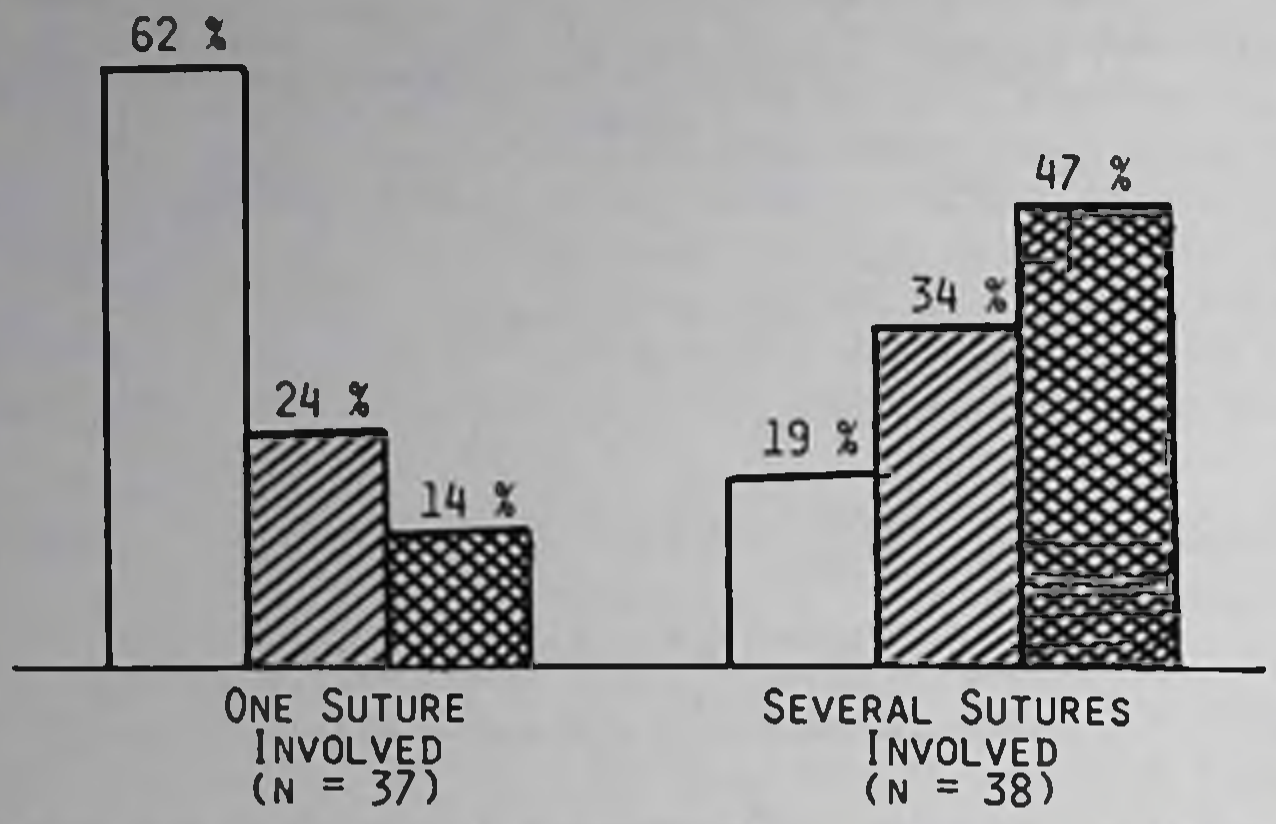


Fig 15–5.—Distribution of intracranial pressure values according to number of fused sutures. *White columns*, ≤10 mm Hg; *diagonally ruled columns*, 10–15 mm Hg; *cross-hatched columns*, more than 15 mm Hg. (Courtesy of Renier, D., et al.: J. Neurosurg. 57:370–377, September 1982.)

creased ICP persist, the lower the mental level of the patient. The decrease of ICP in children older than age 6 may indicate a progressive development of cerebral atrophy likely related to chronic intracranial hypertension.

► [Dr. Harold J. Hoffman, Professor of Surgery, University of Toronto Faculty of Medicine, and Director of Neurosurgery, The Hospital for Sick Children, kindly provided us with the following comment:

"Although R. Virchow (*Verh. Phys.-Med. Ges. Wurzburg*. 2:230, 1852) in 1852 first described craniosynostosis, the modern treatment for craniosynostosis did not begin until the historic paper of H. K. Faber and E. B. Towne (*Am. J. Med. Sci.* 173:701, 1927) in 1927. These two pioneers advised early operation in the cases of craniosynostosis with the explicit purpose of preventing blindness and mental deficiency.

"Although the early arguments for treatment of craniosynostosis were to improve mental function, the emphasis subsequently shifted toward the cosmetic benefits of surgery. By the latter half of this century, the doctrine of operating on craniosynostosis early in infancy in order to prevent gross cosmetic deformity was widely accepted. However, controversy has continued to swirl about the concept that closed sutures can be a threat to mental normality. Furthermore, some authors (Hemple, D. J., et al.: *J. Pediatr.* 58:324, 1961; and Freeman, J. M., and Berkowf, S.: *Pediatrics* 30:57, 1962) have questioned the value of any surgical treatment of craniosynostosis.

"However, as early as 1956, H. Anderson and S. P. Johnson (*Acta Paediatr. Scand.* 57:47, 1968) documented 19 cases with raised intracranial pressure (ICP) due to an isolated sagittal suture synostosis. The group in the Necker Hospital for Sick Children in Paris have very conclusively shown that craniosynostosis can produce raised ICP. Even in cases of isolated closure of the sagittal suture, they found some patients with pathologic levels of ICP with pressures during REM sleep greater than 15 mm of

TABLE 4.—RELATIONSHIP OF IQ AND AGE AT TIME OF MEASURING INTRACRANIAL PRESSURE*

Age (yrs)	IQ ≥ 90	IQ < 90
≤ 3	22	5
> 3	9	19

*IQ, intelligence quotient, including development quotient in children younger than age 2½ years. Significance: $P < .001$.

(Courtesy of Renier, D., et al.: J. Neurosurg. 57:370–377, September 1982.)

mercury. After surgical correction of craniosynostosis, the pathologic levels of pressure dropped to normal.

"Furthermore, they found a very significant relationship between IQ levels and the level of ICP. They found improved IQs after treatment of the craniosynostosis and reduction of ICP to normal levels. Improvement of IQ after corrective procedures on craniosynostosis have been recorded by other authors (Powazek, M., and Ballmeister, G. J.: *Am. J. Dis. Child.* 133:151, 1979). However, this group of authors have gathered the largest series of children with craniosynostosis for careful evaluation of ICP and IQ both before and after surgery.

"The cranial sutures allow for the rapid expansion of brain mass during infancy and childhood. The human brain grows more rapidly during the first 6 months of life than it does during the remainder of life. It is brain growth that determines the growth and shape of the overlying skull vault. When a cranial suture is closed, expansion of the cranial vault becomes uneven, leading to the cosmetic abnormality, and brain growth is restricted, leading to bouts of raised ICP.

"The study conducted by the group at Necker Hospital for Sick Children in Paris has conclusively shown that treatment of synostosis not only improves appearance, but also prevents the deleterious effect of raised ICP on intellectual function. We therefore can conclude that the earlier that craniosynostosis is diagnosed and promptly treated, the better the results will be not only for cosmesis, but also for intelligence."] ◄

15–10 **Abdominal Complications of Ventriculoperitoneal Shunts, With Emphasis on the Role of Imaging Methods.** Ventriculoperitoneal shunting of cerebrospinal fluid (CSF) is the most common method used to relieve increased intracranial pressure. A wide range of complications may attend this procedure. Farooq P. Agha, Marco A. Amendola, Khalil K. Shirazi, Beatriz E. Amendola, and William F. Chandler (Univ. of Michigan) reviewed data on 155 female and 125 male patients who had 400 ventriculoperitoneal shunt procedures for intracranial problems between 1976 and 1981. The 280 patients were aged 1 month to 52 years. All had computed tomographic (CT) studies of the head and routine x-ray examinations of the chest and abdomen, and some patients also had radionuclide clearance and pressure mon-

TABLE 1.—CONDITIONS REQUIRING VENTRICULOPERITONEAL SHUNTS IN 280 PATIENTS

Diseases	*No. of patients*
Congenital hydrocephalus	140
Communicating hydrocephalus	50
Posterior fossa cysts	10
Cerebellar tumors	10
Increased intracranial pressure, secondary to sepsis	15
Subarachnoid hemorrhage with hydrocephalus	15
Meningomyelocele	18
Meningoencephalitis	8
Aqueduct stenosis	5
Brain stem contusion	4
Third ventricular astrocytoma	4
Myeloschisis and myelodystrophy	1
Total	280

(Courtesy of Agha, F. P., et al.: Surg. Gynecol. Obstet. 156:473–478, April 1983.)

(15–10) Surg. Gynecol. Obstet. 156:473–478, April 1983.

TABLE 2.—Abdominal Complications in 400 Ventriculoperitoneal Shunts

	No. of patients	*Per cent*
Shunt malfunction,		
Mechanical	28	7
Occlusion of tube tip	40	10
Infected shunt	25	5
CSF, loculations and pseudocyst formation	7	1.75
Intestinal obstructions	2	0.5
Migration of shunt tip	1	0.25
Perforation of viscera	1	0.25
Intractable ascites	1	0.25
Total No. of complications	100	25

(Courtesy of Agha, F. P., et al.: Surg. Gynecol. Obstet. 156:473–478, April 1983.)

itoring studies, ultrasonography, contrast CT of the abdomen, contrast study of the shunt, and fine-needle aspiration of a suspected CSF collection. The indications for shunting are listed in Table 1.

The 100 complications related to the abdominal end of the shunt (Table 2) required 120 surgical revisions. Common complications included mechanical malfunction and tip occlusion due to fibrous encasement. Twenty-five shunts were infected. Forty patients required more than one shunt revision.

Abdominal complications of ventriculoperitoneal shunting are listed in Table 3. Plain roentgenography can evaluate the position of the tubing and identify tube disconnection, a broken or kinked tube, and peritoneal pseudocysts and fluid loculations. Combined pressure measurement and radionuclide clearance study are useful in evaluating patients with suspected shunt malfunction. Ultrasonography can accurately localize abdominal fluid loculations, and fine-needle aspiration can show the type of collection that is present. Computed tomography is helpful in showing the relation of a cyst or fluid loculation to the shunt catheter. Intestinal perforation by a shunt can be demonstrated by contrast opacification of the shunt. Despite the many complications that may occur, ventriculoperitoneal shunting is the treatment of choice for long-term relief from increased intracranial pressure.

15–11 **Spinal Cord Injury Without Radiographic Abnormalities in Children.** Cord injury in children often occurs without evidence of fracture or dislocation. The inherent elasticity of the vertebral column in infants and young children renders the spine highly vulnerable to deforming forces. Dachling Pang and James E. Wilberger, Jr. (Univ. of Pittsburgh) reviewed findings in 24 children seen from 1960 to 1980 with closed spinal cord injuries and no radiographic evidence of fracture or fracture-dislocation. The mean age was 7.2 years. Follow-up ranged from 8 months to 20 years. Causes of injury are listed

(15–11) J. Neurosurg. 57:114–129, July 1982.

TABLE 3.—REPORTED ABDOMINAL COMPLICATIONS OF VENTRICULOPERITONEAL SHUNTS

Malfunction
  Mechanical—Disconnection, breaking and kinking
    blockage and tube shortening
  Occlusion—Tip occlusion by fibrous encasement or omental clog-
    ging
Infection
  Infected shunt
CSF loculation, pseudocyst formation and abdominal mass
  Peritoneal pseudocyst
  Omental cyst
  Intractable/recurrent ascites
  Subphrenic CSF loculation
  Lesser sac CSF loculation
  Inflammatory pseudotumor of mesentery
  Inguinal hernias and hydroceles
Intestinal obstruction—secondary to adhesions
  Tube wrapped around intestine
  Knot around intestine
  Herniation through site of shunt insertion
  Volvulus
  Torsion of omental cyst
Perforation of viscera
  Intestine
  Urinary bladder
  Uterus and vagina
  Rectum
  Gallbladder
Migration of shunt
  Within peritoneal cavity to a nonabsorption area
  Outside peritoneal cavity to:
    thorax—pleural effusion and pneumothorax
    abdominal wall—through umbilicus
    through hernial sac into scrotum
Metastatic tumor spread by way of the ventriculoperitoneal shunt

  Abdominal mass
  Malignant ascites

(Courtesy of Agha, F. P., et al.: Surg. Gynecol. Obstet. 156:473–478, April 1983.)

in Table 1. Hyperextension and flexion injuries were most frequent, but flexion-compression and longitudinal distraction injuries also occurred; there was 1 direct crush injury with possible hyperextension.

Five lesions involved the upper cervical cord, 15 the lower cervical cord, and 4 the thoracic region. The neurologic syndromes noted at presentation are listed in Table 2. Children aged 8 and younger had much more serious neurologic injuries than older patients had. The mechanism of injury is related to the severity of neurologic damage in Table 3. Thirteen patients had a delayed onset of neurologic deficit after injury (Table 4). The radiographic tests performed are listed in Table 5. Patients with high cervical cord lesions required prolonged ventilation and intensive care unit management. The most common complications developing in the acute treatment period were frequent respiratory and urinary tract infections. No delayed spinal deformity

TABLE 1.—Cause of Injury in 24 Children

Cause of Injury	Cases	
	No.	Percent
hit by car	4	16.7
run over by car (chest)	1	4.2
automobile accident	5	20.8
motorcycle accident	1	4.2
fall from height	5	20.8
fall down steps	2	8.3
football tackle	1	4.2
diving	1	4.2
object fell on head	1	4.2
sled accident	1	4.2
wrestling	1	4.2
child abuse	1	4.2

(Courtesy of Pang, D., and Wilberger, J. E., Jr.: J. Neurosurg. 57:114–129, July 1982.)

TABLE 2.—Types of Neurologic Syndromes in 24 Children

Neurological Syndromes	No. of Cases	Percent of Total
complete cord transection	7	29.1
central cord, severe	4	16.7
central cord, mild	6	25.0
partial cord, severe	3	12.5
partial cord, mild	3	12.5
Brown-Séquard	1	4.2

(Courtesy of Pang, D., and Wilberger, J. E., Jr.: J. Neurosurg. 57:114–129, July 1982.)

TABLE 3.—Correlation Between Mechanism of Injury and Severity of Neurologic Injury

Mechanism of Injury	Severity of Injury		
	Complete	Severe	Mild
hyperextension	3	1	6
flexion	2	4	2
flexion-extension	0	1	0
longitudinal distraction	1	1	0
direct crush injury	1	0	0
flexion-compression	0	0	2

(Courtesy of Pang, D., and Wilberger, J. E., Jr.: J. Neurosurg. 57:114–129, July 1982.)

was observed. The outcome is presented in Table 6. The long-term prognosis was poor. The chief prognostic factor appeared to be the initial neurologic status. Only 2 of 14 children with initially complete or severe cord syndromes made satisfactory progress; 7 of 10 less se-

TABLE 4.—DELAYED NEUROLOGIC SIGNS IN 13 CHILDREN

Case No.	Age (yrs)	Mechanism of Injury	Initial Transient Symptoms	"Latent Period"	Neurological Manifestations	Myelography	Final Outcome
1	2	flexion	mother noted child not moving limbs immediately after injury; cleared quickly	2 days	severe C-6 central cord	normal	severe deficits
2	4	longitudinal distraction	paresthesia, both arms & legs	2 days	severe C-5 central cord		severe deficits
3	8½	extension	subjective feeling of paralysis	2 days	mild C-5 central cord		normal
4	10	flexion-compression	lightning sensation; paresthesia, both hands; subjective feeling of paralysis	24 hrs	mild C-5 central cord		normal
5	10	flexion-compression	paresthesia both hands, subjective weakness	4 hrs	mild C-5 central cord		mild deficits
6	11	extension	paresthesia, both legs	12 hrs	severe T-5 partial cord	normal	severe deficits
7	14	extension	paresthesia, both hands & legs	12 hrs	mild central cord	normal	normal
8	15	extension	paresthesia, both hands	6 hrs	mild C-6 central cord		normal
9	½	flexion		4 days	severe C-3 partial cord	normal	moderate deficits
10	1½	direct crush injury		24 hrs	T-6 complete cord transection	normal	complete cord transection
11	2½	extension		4 days	C-7 complete cord transection	normal	complete cord transection
12	9	flexion		30 min	mild C-5 central cord		mild deficits
13	16	extension		24 hrs	mild C-5 central cord		normal

(Courtesy of Pang, D., and Wilberger, J. E., Jr.: J. Neurosurg. 57:114–129, July 1982).

severely damage patients recovered completely, and the rest are only minimally disabled.

Initial radiographic evaluation of these children should include tomography and, occasionally, myelography. The long-term prognosis

TABLE 5.—Radiographic Tests Performed in 24 Patients

Radiography	Cases	
	No.	Percent
plain spine films	24	100
tomography	20	83.3
myelography	12	50
dynamic studies		
acute	18	75
delayed	24	100
computerized tomography of spine	1	4.2

(Courtesy of Pang, D., and Wilberger, J. E., Jr.: J. Neurosurg. 57:114–129, July 1982.)

TABLE 6.—Outcome in 24 Children

Initial Neurological Status	No. of Cases	Final Neurological Status				
		Death	Complete Cord Syndrome	Severe Deficits	Mild/ Moderate Deficits	Normal
complete cord syndrome	7	1	6			
severe cord syndrome	7			5	2	
mild cord syndrome	10				3	7

(Courtesy of Pang, D., and Wilberger, J. E., Jr.: J. Neurosurg. 57:114–129, July 1982.)

is poor for patients with cord injury without abnormalities apparent on radiography. Only children with initially mild lesions have hope of satisfactory recovery.

▶ [It is always a delight to elicit a comment from Dr. Luis Schut, Professor of Neurosurgery, University of Pennsylvania, and Director, Division of Neurosurgery, Children's Hospital of Philadelphia. Doctor Schut writes:

"More than 5,000 years ago, the Edwin Smith Surgical Papyrus from Egypt described spinal cord injuries and commented that these type of ailments should not be treated. This pessimistic attitude toward trauma to the spinal cord has persisted to this day, and a nihilistic attitude has prevailed to the very recent past.

"For the past 2 decades, improvements in the understanding of the pathophysiology of trauma to the spinal cord from the mechanical, physiologic, electrophysiologic and biochemical changes have enhanced our understanding of changes in the spinal canal and spinal cord. To enhance this newly found knowledge, spinal cord injury centers have been established in major medical centers throughout the United States and are beginning to bear fruit from their research and clinical efforts.

"In this paper, Doctors Pang and Wilberger have undertaken a massive review of the available literature on spinal cord injuries to children in which no obvious disruption of the bony elements are visible, either in clinical examination or on radiologic studies. While this phenomenon has been recognized in the past, the authors are to be commended for putting together the available material and for trying to make sense of the several different types of classification that have been used in the past.

"The authors also coin a new term, 'SCIWORA,' an acronym for "spinal cord injury without radiographic abnormality." In the course of their very thorough review of the cases seen at the Children's Hospital of Pittsburgh, they provide the reader with a useful classification of neurologic syndromes in these children (Table 2), namely,

complete cord transection; central cord, severe, central cord, mild; partial cord, severe; partial cord mild; and Brown-Séquard.

"What perhaps is not very well underlined in this comprehensive review is the very little function that surgery has in alleviating the damage to neural elements in this type of injury, or, indeed, in much of the severe spinal cord injuries at any age.

"I would like to recommend that readers refer to the excellent articles of Ducker and Lucas, as well as Bohlman, who have done extensive work in this subject. Ducker, in particular, has statistically proved that surgical intervention, such as laminectomies for spinal cord injuries, provides very little help, with the possible exception of patients with central cord syndromes in association with narrow spinal canals. He also was able to prove statistically that steroids have practically no influence in the recovery of injured patients and that early laminectomy was not helpful in improving the dismal statistical recovery of patients with complete cord section.

"I believe that the lesson to be learned from this very scholarly paper is simply that much of the efforts of the medical profession should be geared toward prevention and education on spinal cord injuries and a better understanding of the physiopathology of the trauma itself and the physiologic changes that occur in the cord after trauma. However, trying to find a surgical cure after the event will be a bitter disappointment to most of us, with the very few exceptions where compressive masses within the spinal canal, such as bony fragments or epideral hematomas, will be found."] ◀

15–12 **Parental Negative Self and Adolescent Suicide Attempts.** Carl L. Tishler and Patrick C. McKenry (Ohio State Univ., Columbus) compared the parents of 46 adolescent suicide attempters with parents of 46 adolescents who had not attempted suicide to determine differences in factors descriptive of self-image. Both groups of families were in a lower middle-class socioeconomic group. Instruments for the study consisted of a demographic background information questionnaire, Rosenberg Self-Esteem Scale (Rosenberg, 1965), the depression and anxiety subscales of the SCL-90 (Brief Symptom Inventory) (Derogatis et al., 1973), and scaled questionnaire items measuring suicidal ideation and alcohol use.

Results indicated that fathers of the attempters were significantly more depressed, had significantly lower self-esteem, and consumed significantly more alcohol than fathers of nonattempters. However, both self-esteem and depression means for fathers of attempters were within normal limits established for the instruments.

Mothers of adolescent attempters were significantly more anxious, experienced significantly greater suicidal ideation, and consumed significantly more alcohol than mothers of nonattempters, but the anxiety mean of the mothers of attempters was within a "normal" range established for the instrument.

Alcohol use was not great in any subgroup. The significant differences between the fathers of attempters and those of nonattempers in depression and self-esteem and the significant differences between mothers of attempters and those of nonattempters in anxiety were accounted for only by parents of daughters.

Caution must be used in interpreting these preliminary findings. The use of a small, nonrandom sample precludes generalization to a wider sample of parents of suicidal adolescents. Because a noncausal, correlational design was used, it could be possible that the parents of adolescent suicide attempters were reacting to the crisis of the moment.

(15–12) J. Am. Acad. Child Psychiatry 21:404–408, July 1982.

15–13 **Suicide Attempts in Children and Adolescents.** In a review of pediatric hospital emergency room admissions over 7 years, Barry D. Garfinkel, Art Froese, and Jane Hood (Hosp. for Sick Children, Toronto) found 505 children and adolescents who had attempted suicide.

There were 3 times as many girls as boys; the boys were significantly younger (girls, aged 15.3 years, vs. boys, aged 14.7 years). Features that distinguished them from matched controls were religion, living situation, substance abuse, current psychiatric illness, prior psychotherapy, and current medical illness. Their families had more medical and psychiatric illness (primarily drug or alcohol abuse), suicide, paternal unemployment, and paternal and maternal absence than the families of controls (table).

Suicide attempts usually occurred in the winter, after school or in the evening, at home with someone nearby, and by drug overdose (usually a household pain reliever). The index group had more somatic symptoms than did controls. Symptoms of major and minor depression, hostility, and situational disturbance were common; rates of neurotic symptoms and psychotic phenomena were low. Emergency room clinicians observed rage in the form of aggressive symptoms, often directed toward others. One to 9 years after the index admis-

INDIVIDUAL AND FAMILY CHARACTERISTICS SIGNIFICANTLY DIFFERENT BETWEEN CHILDREN AND ADOLESCENTS WHO ATTEMPTED SUICIDE AND CONTROLS

	Suicide Attempters			Controls					
		With Characteristic			With Characteristic		Significance		
Characteristic	Available N	N	%	Available N	N	%	χ^2	df	p
Individual									
Religion	428			473			11.12	3	.05
Catholic		170	39.7		217	45.9			
Protestant		228	53.3		206	43.6			
Jewish		13	3.0		29	6.1			
Prior substance abuse	482	179	37.2	440	24	5.5	145.6	1	.01
Housing	208			160			49.87	3	.001
Private		45	21.6		75	46.9			
Rental		72	34.6		60	37.5			
Public		15	7.2		13	8.2			
Group		76	36.5		12	7.5			
Current psychiatric diagnosis	479	327	68.3	452	73	16.1	255.64	1	.01
Current medical illness	469	255	54.4	479	205	42.7	12.25	1	.01
Previous contact with psychosocial services	486	307	63.2	421	75	17.8	188.48	1	.01
Family									
History of mental illness	442	228	51.6	452	74	16.4	122.3	1	.01
History of medical illness	445	229	51.5	468	208	44.5	3.96	1	.05
History of suicide	443	37	8.3	442	5	1.1	23.95	2	.01
Suicide attempts		26	5.9		5	1.1			
Completed suicide		11	2.5		0				
Employment									
Father	242			193					
Employed		208	85.9		180	93.3			
Unemployed		34	14.1		13	6.7	6.89	1	.01
Mother	264			202					
Employed		131	49.6		72	35.6			
Unemployed		32	12.1		20	9.9			
Homemaker		101	38.3		110	54.5	12.9	2	.01
Parental presence	442			437					
Both present		209	47.4		366	83.8			
Father absent		110	24.8		52	12.0			
Mother absent		11	2.4		5	1.2			
Both absent[a]		112	25.4		13	3.0	129.3	3	.001

[a]Group or foster home placement.

(Courtesy of Garfinkel, B. D., et al.: Am. J. Psychiatry 139:1257–1261, October 1982.)

(15–13) Am. J. Psychiatry 139:1257–1261, October 1982.

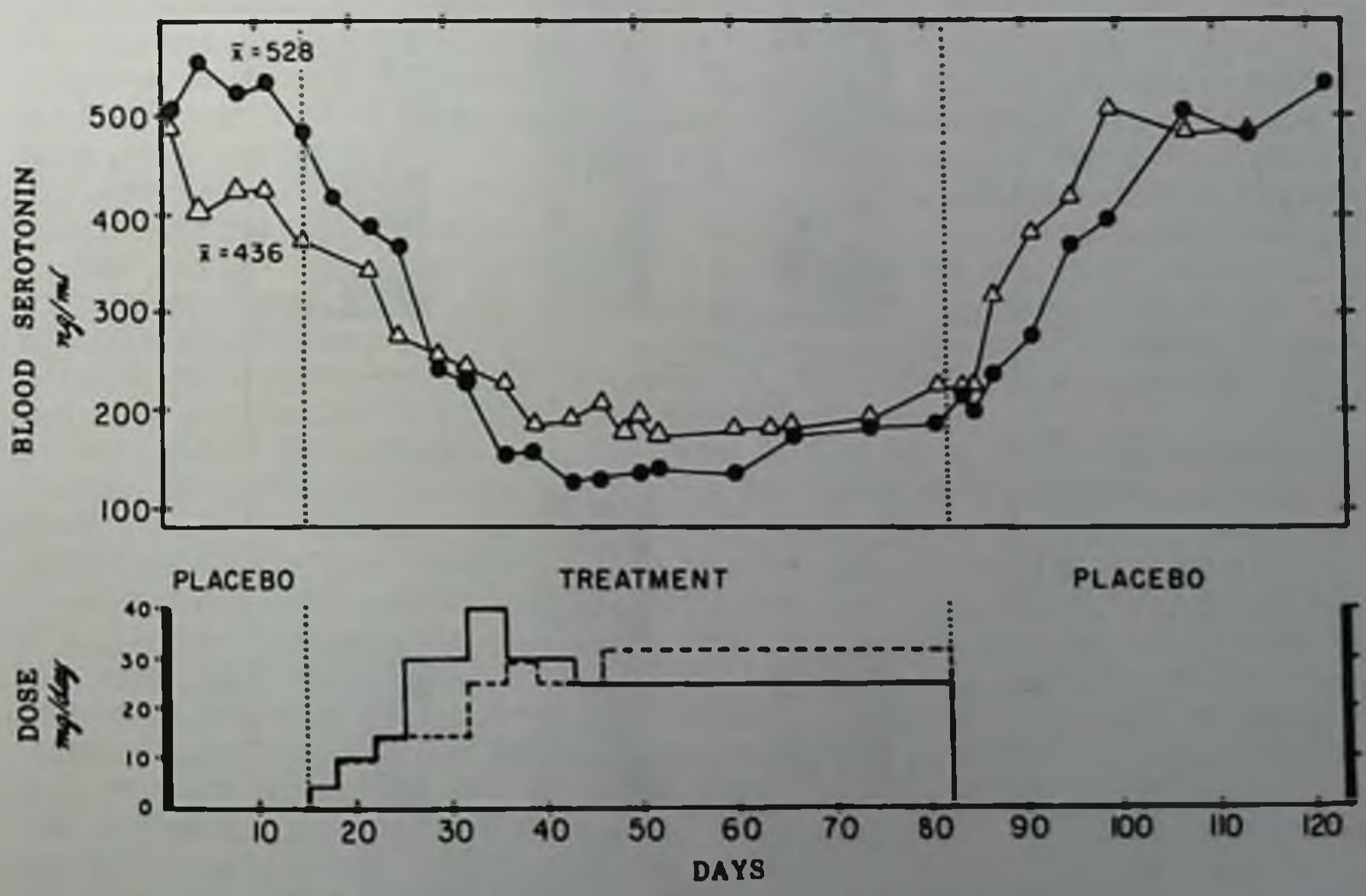
sion, 8 of those who had attempted suicide were dead of hanging (4), motor vehicle accidents (3), and drug overdose (1).

Parents must be able to recognize early signs of depression and be knowledgeable about their children's after-school activities and the whereabouts and use of medications in their homes. Attempted suicide is on a continuum with completed suicide. More education for hospital staff in poison control measures, evaluation of adolescent depression, and crisis intervention with families and adolescents is required to increase the efficacy of management of such cases.

▶ [Deliberate self-poisoning in adolescents often results in differences of opinion between the adolescent and the care-giver as to the reasons behind the attempt. K. Hawton and associates (*Br. J. Psychiatry* 141:286, 1982) conducted a systematic study of 50 adolescents who had taken drug overdoses. Most adolescents indicated that they had been feeling lonely or unwanted or angry with someone and had taken the overdose to either alleviate or demonstrate this distress. Only one-third said they wanted to die. In contrast, the clinicians attributed the overdose to punitive or manipulative reasons in 43 of the 50 instances. The adolescents rarely indicated that they had taken the overdose in order to get help. You figure all this out.—F.A.O.] ◀

15–14 **Preliminary Observations on the Effect of Fenfluramine on Blood Serotonin and Symptoms in Three Autistic Boys.** It now generally is agreed that a subgroup of autistic persons (perhaps as many as 40%) have elevated blood serotonin levels as compared with normal persons of the same age and sex. Edward Geller, Edward R.

Fig 15–6.—Serotonin response to fenfluramine treatment. Triangles and dashed line indicate values in patient 1; solid circles and solid line indicate values for patient 2. Placebo or 20-mg fenfluramine hydrochloride tablets (split in quarters, when necessary) were given twice a day, usually at 8 A.M. and 4 P.M. On days when serotonin was measured, morning dose was delayed until noon and afternoon dose was delayed until 8 P.M. For serotonin determination, blood obtained during fasting was collected in ethylenediamine tetra-acetic acid tubes; for platelet counting and sizing, blood was collected in citrate tubes. (Courtesy of Geller, E., et al.: N. Engl. J. Med. 307:165–169, July 15, 1982.)



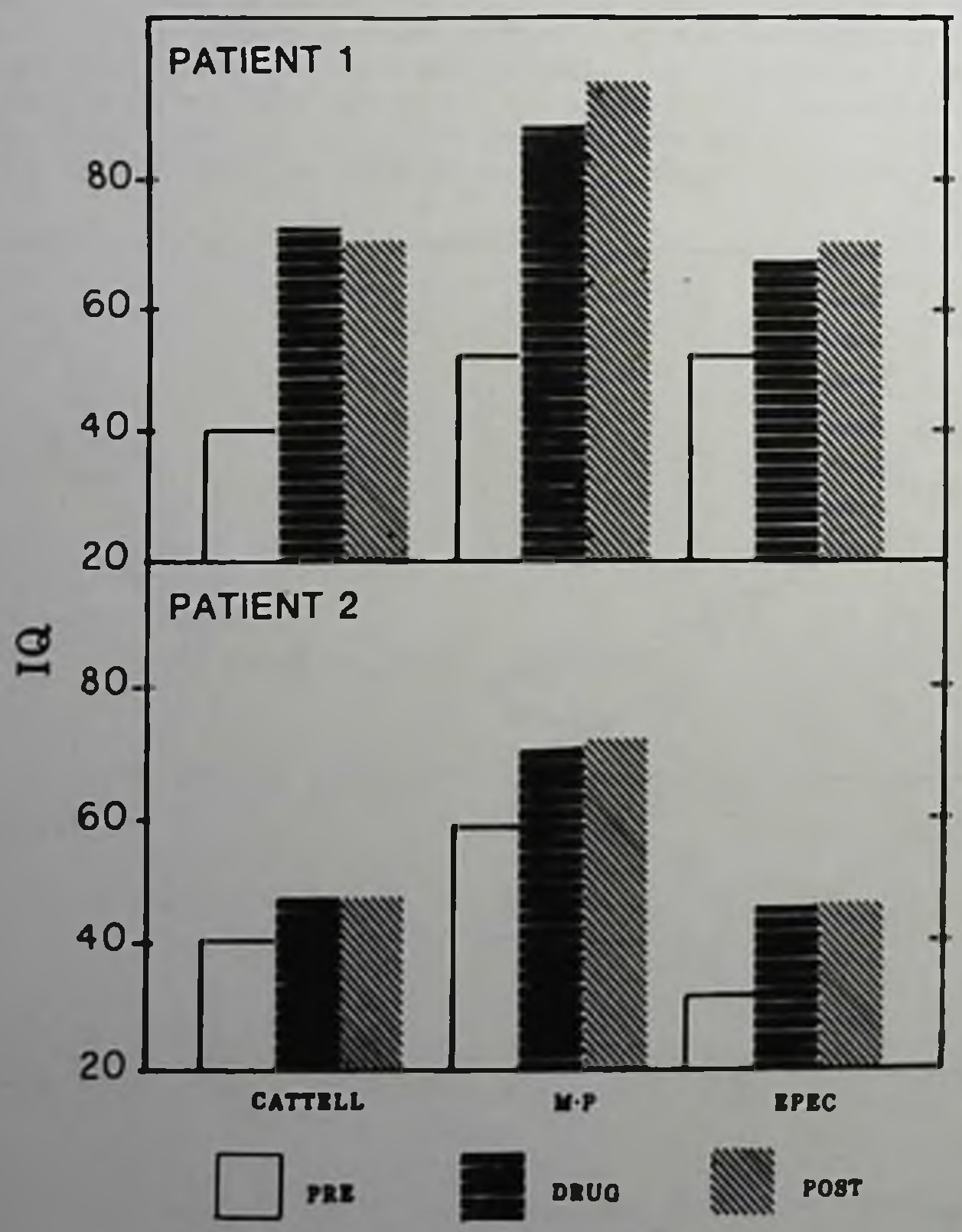
(15–14) N.Engl. J. Med. 307:165–169, July 15, 1982.

Ritvo, Betty Jo Freeman, and Arthur Yuwiler (Los Angeles) have hypothesized that serotonin levels in the central nervous system also may be elevated in this subgroup and that this abnormality may be related to certain clinical features. They have attempted to manipulate brain serotonin levels by using an anorexigenic drug, fenfluramine, which produces a long-lasting, reversible decrease in brain serotonin levels in animals. Three young boys selected for testing had extensive autistic symptoms and high blood levels of serotonin. Although it is not known whether fenfluramine lowers the level of serotonin in the brain of human beings, the drug reduces the level of 5-hydroxyindoleacetic acid in cerebrospinal fluid.

In the first patient, fenfluramine was begun at a dose of 10 mg/day and was increased by 10 mg/day every 4 days. The blood serotonin level fell rapidly to 43% of baseline at 40 mg/day. After a short lag when fenfluramine was tapered and discontinued, blood serotonin levels began rising and returned to baseline within 2 weeks.

In 2 other patients, the dose of fenfluramine was adjusted to keep the blood serotonin level at about 150 to 200 ng/ml; this phase lasted about 3 weeks and was followed by 8 weeks of unchanged dosage.

Fig 15–7.—Effect of treatment on IQ scores. Tests were administered to both boys before beginning of fenfluramine administration, at end of treatment period, and 6 weeks after cessation of drug. Cattell, the Cattell test; *M-P*, Merrill-Palmer test; and *EPEC*, Evaluation and Prescription for Exceptional Children. (Courtesy of Geller, E., et al.: N. Engl. J. Med. 307:165–169, July 15, 1982.)



Blood levels of serotonin were quite responsive to variations in dosage (Fig 15–6), but there appeared to be some spontaneous elevation of serotonin level when dosage was stable during the final weeks of administration.

No side effects of fenfluramine were noted. The reduction in blood serotonin concentrations induced by the drug was accompanied by improvement in behavior and cognitive function. Some of these beneficial effects were retained for several weeks after drug administration. Each of 2 boys tested substantially improved his performance on three IQ tests (Fig 15–7); the improvement was about the same on each test. An identical autistic twin brother of 1 patient showed no change in test results. The gains of both patients were sustained during the 6-week posttreatment period. Tests conducted 3 months after treatment showed a considerable loss of effect had occurred.

Studies in rats have shown that although blood serotonin returns to pretreatment levels within days after fenfluramine administration is stopped, serotonin concentrations in the brain remain depressed for several weeks. It is not known whether the alteration of serotonin levels in the blood and presumably in the brain is related directly to the improvement noted in the patients in this study or whether it only appears to be related because this change is what was monitored. This study is only preliminary; more work is needed to establish whether fenfluramine is of substantial value.

▶ [Dr. Herbert Schneiderman, Associate Professor of Pediatrics, State University of New York at Syracuse, prepared the following comment:

"I read this article with a mixture of great interest and concern. The authors have avoided the pitfalls that make almost worthless so many studies of drug treatment in autism, i.e., inclusion of subjects who do not meet clear and widely accepted criteria, imprecise observations of behavior, and lack of "double-blinded" treatment protocols, etc. However, as they themselves stress, the study is preliminary and will need to be repeated with larger numbers of children for longer periods of time in naturalistic settings. Their observations raise a number of fascinating questions about fenfluramine, serotonin, and autistic behavior. Fenfluramine injected into rats lowers the level of serotonin in the brain. Is that happening in human beings? Normal levels of serotonin in the blood occur in at least 60% of autistic persons. What would be the effect of fenfluramine on this group? Fenfluramine also affects catecholaminergic neurotransmitters in animals. Could its effects on the boys in this study be unrelated to serotonin levels? Even if the effect of fenfluramine is due primarily to lowering of brain levels of serotonin, how do high brain levels of serotonin relate to autistic behaviors and performance on IQ tests? We are barely in infancy in our understanding of the relationship between brain biology and complex behaviors such as autism, and this study will certainly stimulate further efforts in this area.

"My concern about the article is due to no fault of the authors. After exposure in the popular press, parents undoubtedly will be calling their physicians to treat or even "cure" their autistic children with fenfluramine. Casual use of this drug in uncontrolled clinical situations may lead to dashed expectations, at the least. But it could do even worse. Although many adults have taken this drug for weight control and have had no determinable problems, fenfluramine does produce neurotoxicity in rats (Messing, R. B.: *Ann. N.Y. Acad. Sci.* 305:480, 1978). In human beings there have been case reports of (reversible) dyskinesias, pulmonary hypertension, and nightmares. Depression, occasionally quite severe, has followed the withdrawal of this drug in controlled studies. And in predisposed persons, case reports suggest that the use of fenfluramine may have precipitated paranoid or schizophreniform symptoms (Myler, L.: *Side Effects of Drugs* [9th ed.], Williams & Wilkins Co., Baltimore, 1983, pp. 12–13; and *Side Effects of Drugs Annual 1982*, Elsevier North-Holland, Inc, New York, 1982, pp. 9–10)."] ◀

15–15 **Intellectual and Emotional Sequelae of Reye's Syndrome.** The increasing survival of patients with Reye's syndrome has focused attention on the quality of life of surviving patients. Pauline Y. Benjamin, Morris Levinsohn, Dennis Drotar, and Elizabeth E. Hanson (Case Western Reserve Univ., Cleveland) examined the neurologic, emotional, and intellectual status of 16 survivors of Reye's syndrome, as well as the impact on their families, after treatment in 1974–1979. Reye's syndrome had been treated with such measures as exchange transfusion, intraventricular pressure monitoring, controlled hyperventilation, osmotherapy, and dexamethasone therapy. Febrile patients were cooled to prevent hyperthermia. Venting of cerebrospinal fluid was attempted in patients refractory to osmotherapy.

No children had severe neurologic or physical sequelae. All but 2 had an IQ within the low-normal to bright range (table). The exceptions had been diagnosed as retarded before the onset of Reye's syndrome. Nine (56%) children had emotional problems that lasted more than 3 months after discharge. Nearly all mothers reported having been anxious or depressed or exhibiting overprotective behavior for as long as 5 years after their child's illness. Only 2 families indicated that psychological or social work intervention might have been helpful in the acute phase of illness, while 12 mothers would have liked an opportunity to examine their emotional reactions at a later time, possibly in the context of medical follow-up visits.

FOLLOW-UP DATA

Subject	Verbal IQ	Performance IQ	Full-scale IQ	Achenbach Child Behavior Profile*	Emotional sequelae children†	Emotional sequelae mothers†	Previous losses†
1			88	NA		X	
2			92	NA		X	X
3	88	82	84	SC,U,OC,SW, H,ACT	X	X	
4	111	104	108	U	X		
5	109	88	100	SC	X	X	X
6	125	121	126	SC	X	X	
7	113	98	106	WNL		X	X
8	101	100	101	WNL		X	X
9	108	101	105	SC	X	X	X
10	112	97	105	WNL		X	
Mean ± SD	108.4 ± 10.61	98.9 ± 11.52	102.2 ± 11.52				
11	113	124	119	WNL		X	X
12	96	123	108	NA	X	X	X
13	107	113	110	NA		X	X
14	124	133	130	NA	X	X	X
Mean ± SD	110 ± 11.69	123.3 ± 8.18	116.7 ± 10.05				
Mean ± SD of subjects 1–14	108.83 ± 10.47	107.00 ± 15.71	105.86 ± 13.11				
15	52	45	44	ACT,SOC,S	X	X	
16	73	85	77	SC,UC,OC,S	X	X	X
					9/16	15/16	10/16

*Abbreviations: A, aggressive; ACT, decreased activities; H, hyperactive; NA, not administered; OC, obsessive-compulsive; S, school problems; SC, somatic complaints; SOC, decreased social participation; SW, social withdrawal; U, uncommunicative.

†As reported by mother.

(Courtesy of Benjamin, P. Y., et al.: Crit. Care Med. 10:583–587, September 1982.)

(15–15) Crit. Care Med. 10:583–587, September 1982.

The significant emotional problems of these children and their families contrasted with the relatively good intellectual and academic recovery observed. In many respects, the parents suffered more and longer than their children. Evening or weekend appointments should be offered to enhance paternal participation. Future research should include independent corroboration of parental reports, perhaps by teacher ratings, direct psychological assessment of survivors, or comparison by surviving children with sibling controls.

▶ [Children who recover from Reye's syndrome are perfect candidates for the "vulnerable child" syndrome (Green, M., and Solnit, A. J.: *Pediatrics* 34:58, 1964). The vulnerable child syndrome occurs in the setting where a child recovers from a potentially fatal illness. The disturbance in parent-child relationships may manifest itself by difficulty with separation, infantilization, bodily overconcerns, and school underachievement. It is very difficult to overcome the continued anxiety of the parents because we still don't know what causes Reye's syndrome and we must acknowledge that second attacks can occur.—F.A.O.] ◀

15–16 **Mass Hysteria Among Schoolchildren: Early Loss as a Predisposing Factor.** Gary W. Small and Armand M. Nicholi, Jr. (Harvard) report that on May 21, 1979, an outbreak of illness spread swiftly among elementary school students in a Boston suburb. Of 224 children at an assembly, 34 were hospitalized with severe dizziness, weakness, hyperventilation, headache, nausea, abdominal pain, and chills (Table 1) after a sixth-grade boy fell from the stage and bled from a chin laceration.

Despite evacuation of the building and isolation of afflicted students, the symptoms struck a new child every few minutes. There were 40–50 mildly symptomatic children. As physicians reassured patients, symptoms began to subside. Several children had transient blood pressure elevations.

Sudden remission of the epidemic (within 4 hours), preponderance of girls afflicted, and failure of an extensive epidemiologic investigation to detect an organic cause indicated mass hysteria. The students in the sixth grade anticipated a number of imminent losses: the re-

TABLE 1.—DIFFERENCES BETWEEN HOSPITALIZED AND NONHOSPITALIZED GROUPS OF CHILDREN

	Hospitalized Children (N = 34), No. (%)	Nonhospitalized Children (N = 148), No. (%)	P*
Parental divorce	16 (47)	15 (10)	< .00005
Death within the family	25 (74)	57 (39)	< .0005
Chronic medical illness	3 (9)	18 (12)	NS
Recent acute illness	3 (9)	10 (7)	NS
Absent from school day after outbreak	10 (29)	28 (19)	NS
Child's belief that organic factors caused outbreak	13 (38)	45 (30)	NS

*One-tailed χ^2, $df = 1$. *NS*, not significant.

(Courtesy of Small G.W., and Nicholi, A.M., Jr.: Arch. Gen. Psychiatry 39:721–724, June 1982; copyright 1982, American Medical Association.)

(15–16) Arch. Gen. Psychiatry 39:721–724, June 1982.

spected principal was to be transferred, graduation was impending, and a camping trip was to follow graduation, where many would sleep away from home for the first time. To test the hypothesis that previous loss influenced a child's vulnerability to current loss and predisposed that child to mass hysteria during this outbreak, the incidence of family disruption in the hospitalized children was compared with that in the nonhospitalized children.

A significantly higher rate of parental divorce ($P < .00005$) and death within the immediate and extended family ($P < .0005$) occurred among hospitalized children. The rates of early loss for the nonhospitalized group with mild, transitory symptoms were similar to those of the asymptomatic group and significantly lower than those of the hospitalized group with more severe symptoms (Table 2). When rates of early loss for all symptomatic children were compared with those of asymptomatic children, the differences remained statistically significant (Table 3). Hospitalized children were older and experienced

TABLE 2.—SYMPTOMS OF THE 34 CHILDREN HOSPITALIZED

Symptom	No. (%)
Dizziness	23 (68)
Weakness	23 (68)
Increased respiratory rate	22 (65)
Paresthesia	22 (65)
Headache	20 (59)
Trembling or shaking	16 (47)
Nausea	15 (44)
Abdominal pain	14 (41)
Shortness of breath	12 (35)
Chills	11 (32)
Chest pain	5 (15)
Urge to defecate	3 (9)
Cough	3 (9)

(Courtesy of Small, G. W., and Nicholi, A. M., Jr.: Arch. Gen. Psychiatry 39:721–724, June 1982; copyright 1982, American Medical Association.)

TABLE 3.—RATES OF EARLY LOSS AMONG HOSPITALIZED SYMPTOMATIC, NONHOSPITALIZED SYMPTOMATIC, AND ASYMPTOMATIC CHILDREN

	Children		
	Hospitalized Symptomatic (N = 34), No. (%)	Nonhospitalized Symptomatic (N = 38), No. (%)	Asymptomatic (N = 110), No. (%)
Parental divorce*	16 (47)	4 (11)	11 (10)
Death within family*	25 (74)	15 (40)	42 (38)

*$P < .01$ for comparisons of the two symptomatic groups: nonsignificant P values for comparison of nonhospitalized groups (one-tailed χ^2, $df = 2$).

(Courtesy of Small, G. W., and Nicholi, A. M., Jr.: Arch. Gen. Psychiatry 39:721–724, June 1982; copyright 1982, American Medical Association.)

TABLE 4.—RATES OF EARLY LOSS AMONG SYMPTOMATIC* AND ASYMPTOMATIC CHILDREN

	Children		
	Symptomatic (N = 72), No. (%)	Asymptomatic (N = 110), No. (%)	P†
Parental divorce	20 (28)	11 (10)	< .01
Death within family	40 (56)	42 (38)	< .05

*Includes both hospitalized and nonhospitalized symptomatic children.
†One tailed χ^2, $df = 1$.
(Courtesy of Small, G. W., and Nicholi, A. M., Jr.: Arch. Gen. Psychiatry 39:721–724, June 1982; copyright 1982, American Medical Association.)

symptoms earlier than nonhospitalized children. There were no significant differences between groups in variables such as rate of chronic illness, recent acute illness, or absenteeism from school the day after the outbreak (Table 4).

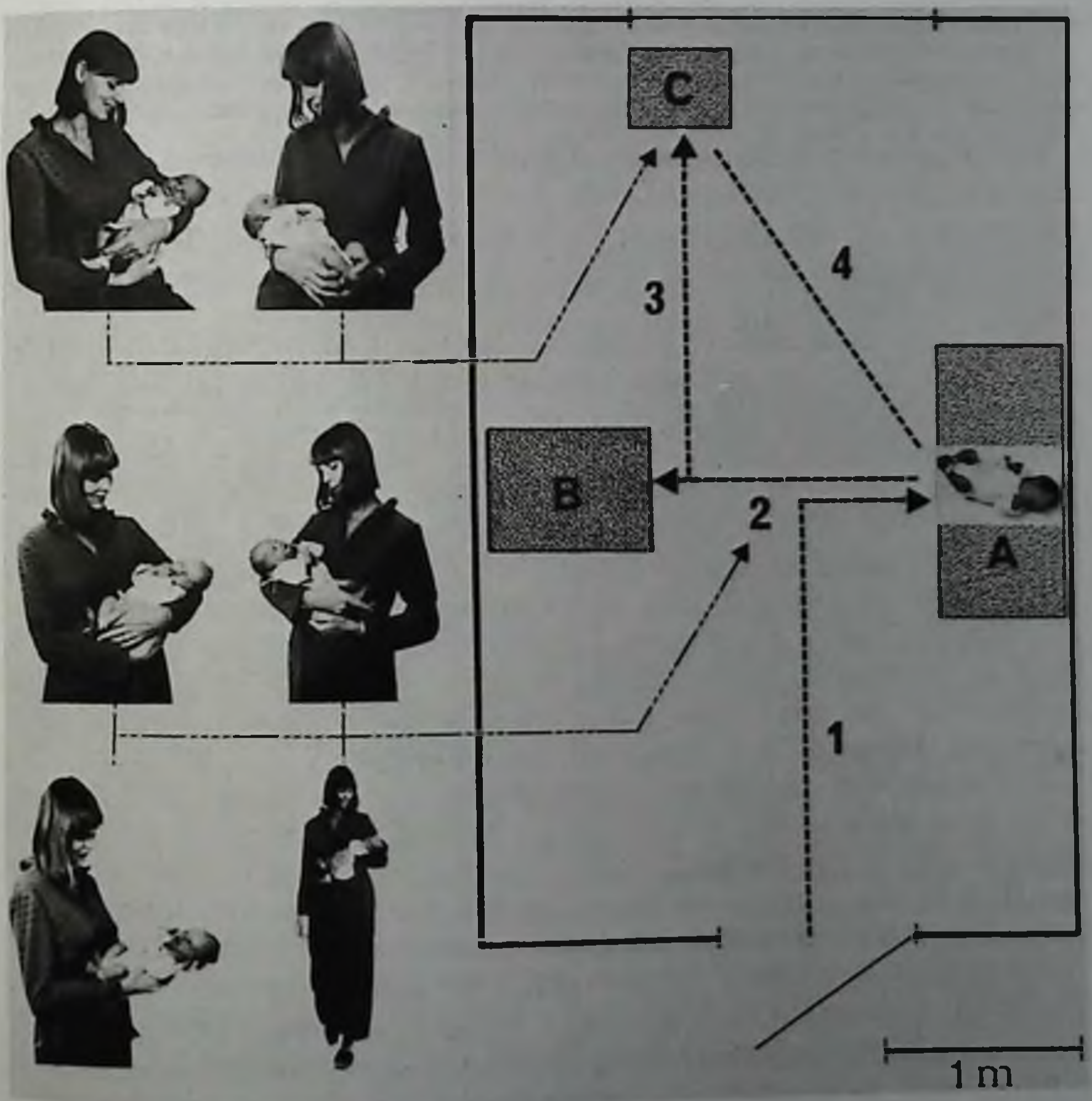
The findings suggest a relationship between childhood loss and susceptibility to mass hysteria.

▶ [If the authors' hypothesis is correct, episodes of mass hysteria will become more common in view of the very high divorce rate in the United States today. I am not a sexist, but—with all the talk about sexual equality—I find it reassuring, in a nostalgic way, to read that mass hysteria is still more common in females—even young girls.—F.A.O.] ◀

16. Child Development

16–1 **Left-Side Preference for Holding and Carrying Newborn Infants: Parental Holding and Carrying During First Week of Life.** Most newly delivered mothers hold their infants to the left of the body midline, and the proportion declines with separation of the mother and infant in the neonatal period. Peter de Château (Karolinska Inst., Stockholm) examined holding and carrying behavior in the

Fig 16–1.—Room in which observations were made contained a nursing table *(A)*, crib *(B)*, and chair *(C)*. Arrows 1–4 indicate subjects' position and passage through the observation room; 2 = recording how subject carried the (own) infant (left, right, "in hands"). At *C*, record was made of the side of the body on which the parent held the infant (left, right). Examples of infant holding *(upper left)* and carrying and walking *(middle* and *lower left)* are shown. (Courtesy of de Château, P.: J. Nerv. Ment. Dis. 171:241–245, April 1983.)



(16–1) J. Nerv. Ment. Dis. 171:241–245, April 1983.

first week after delivery in 66 first-time and second-time mothers, the 66 fathers, 43 other fathers with children older than age 1 year, and 41 men without children of their own. All of the parents were healthy and right-handed. All study participants were aged 20–35 years. The design of the study is shown in Figure 16–1.

Of the mothers, 80% held their infants to the left of the body midline, as did 84% of the fathers. Side preference was a stable phenomenon for both holding and carrying. No differences in side preference were found between fathers with older children and new parents. Men without children of their own exhibited significantly less left-side preference in holding than did parents. No significant group differences were noted in side of carrying.

Both newly delivered mothers and fathers, as well as fathers with older infants, exhibit a significant preference for holding infants to the left of their bodies, apart from handedness, parity, and infant sex. Individual mother-father pairs tend to hold their infants on the same side of the body. Right-holding increases in separated mothers and is related to greater prenatal and postnatal anxiety in the relationship to their infants.

► [I was skeptical of this report until I got out an old doll and tested this observation on some of my friends. Sure enough, most cradled the doll in the left arm if they ever had babies of their own. There must be some simple explanation of this phenomenon. And who was it who said, "I'd rather be right than president"?—F.A.O.] ◄

16–2 **Developmental Deficits in Iron-Deficient Infants: Effects of Age and Severity of Iron Lack.** Betsy Lozoff, Gary M. Brittenham, Fernando E. Viteri, Abraham W. Wolf, and Juan J. Urrutia studied mental and motor development in iron-deficient Guatemalan infants aged 6–24 months.

The nonanemic control group (40 babies) had hemoglobin values ≥12 gm/dl. The iron-deficient anemic group (28 patients) had hemoglobin values ≤10.5 gm/dl; iron deficiency was indicated by at least two of three biochemical measures—ferritin ≤12 μg/L, transferrin saturation ≤10%, free erythrocyte protoporphyrin >100 μg/dl packed red blood cells. Within anemic and nonanemic groups, children randomly were assigned orally administered iron or placebo treatment. The Bayley Scales of Infant Development were administered by a Guatemalan tester unaware of hematologic status before and after 1 week of treatment. Items passed or failed by <10% of a given age group were excluded. The association between developmental test score and degree of iron depletion was determined.

The motor and mental development scores of the nonanemic babies at all ages were within normal range according to the United States norm of 100 ± 16, although mental scores decreased somewhat with age (Fig 16–2). Anemic babies in each age range scored lower than controls in motor development; there were no age-related changes between groups and there was no significant difference within any age group. Mental scores in the anemic group decreased markedly from normal in infants younger than 19 months to a mean of 73.4 in the

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(16–2) J. Pediatr. 101:948–952, December 1982.

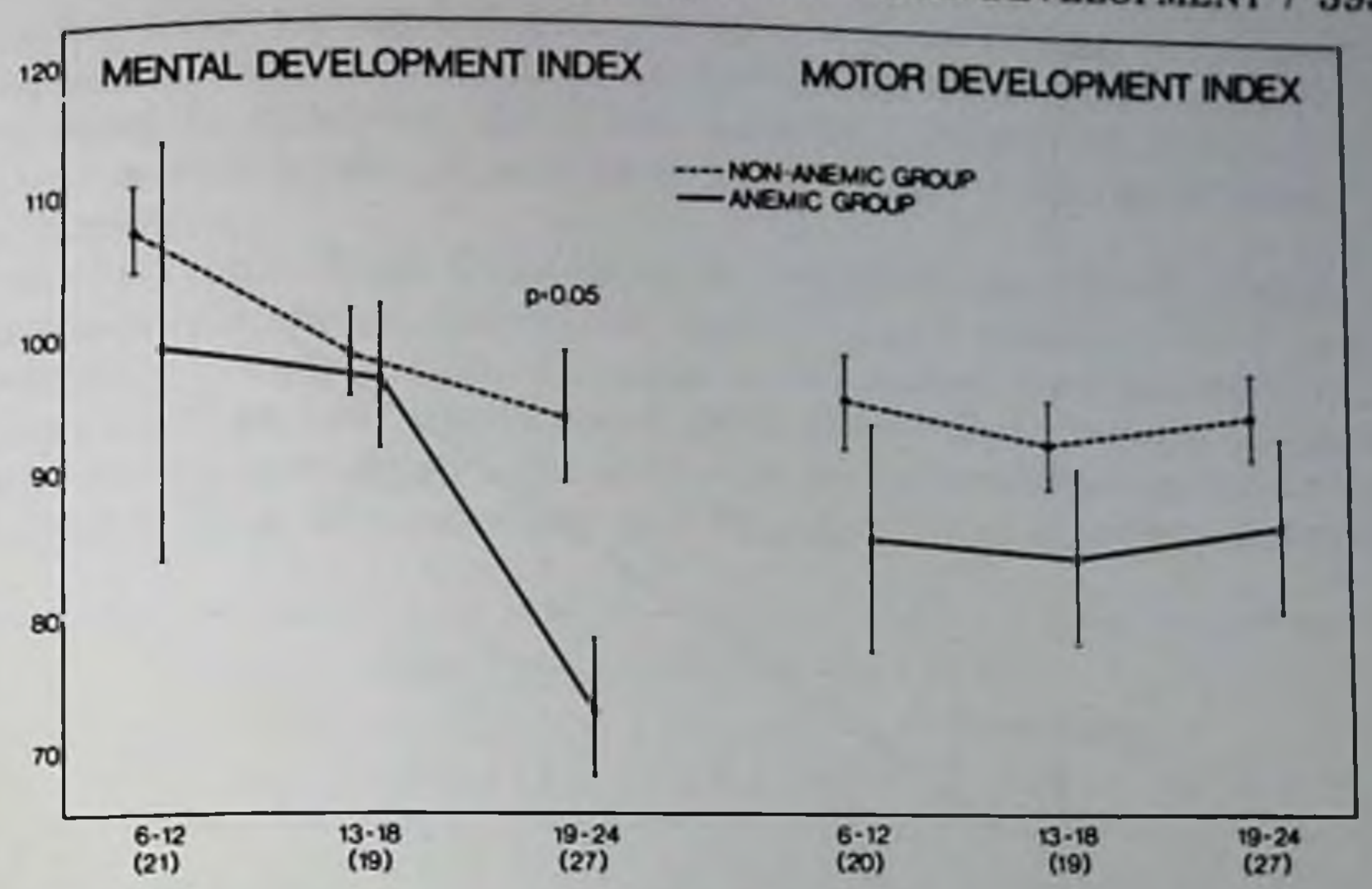


Fig 16–2.—Initial mental and psychomotor development indices in anemic and nonanemic infants by age. Values are means ± SEM. Differences between age groups were significant only for Mental Development Index in older babies. Because the study hypothesized that anemic infants would have lower developmental test scores than normal babies, one-tailed tests of significance were used. (Courtesy of Lozoff, B., et al.: J. Pediatr. 101:948–952, December 1982.)

oldest age range; the difference in Mental Development Index (MDI) between older anemic and nonanemic groups was statistically significant at the 0.05 level. Short-term oral iron therapy did not change test scores.

Older anemic infants weighed less than nonanemic controls. The test scores of malnourished anemic infants were not lower than those of adequately nourished anemic peers.

Iron status was highly correlated with mental developmental test performance among older infants (Fig 16–3); the more severe the iron deficiency, the more severe the developmental deficit. The correlation between iron status and psychomotor test scores was not statistically significant at the 0.05 level, nor did hemoglobin levels correlate with MDI in the anemic or nonanemic group. Anemic infants seemed to have disproportionate difficulty with language items.

The results suggest that both the timing and severity of iron deficiency influence developmental test score deficits.

▶ [Lozoff and Wolf have extended these observations and reached the conclusion that the poor developmental test performance recorded in these infants is mediated by disturbances in behavior such as abnormal affect and task orientation (*Pediatr. Res.* 17:100A, 1983). Evidence continues to mount that incriminates iron deficiency, even iron deficiency in the absence of anemia, as a cause of poor performance in the Mental Development Index of the Bayley Scales of Infant Development. T. Walter and co-workers (*J. Pediatr.* 102:519, 1983) reported, in a study from Chile, that both infants with iron deficiency anemia and infants with biochemical evidence of iron deficiency without anemia had significantly lower scores in the Mental Development Index than did controls. In contrast to the findings of Lozoff et al., they found that after 11 days of oral iron therapy there was significant improvement in these scores. The

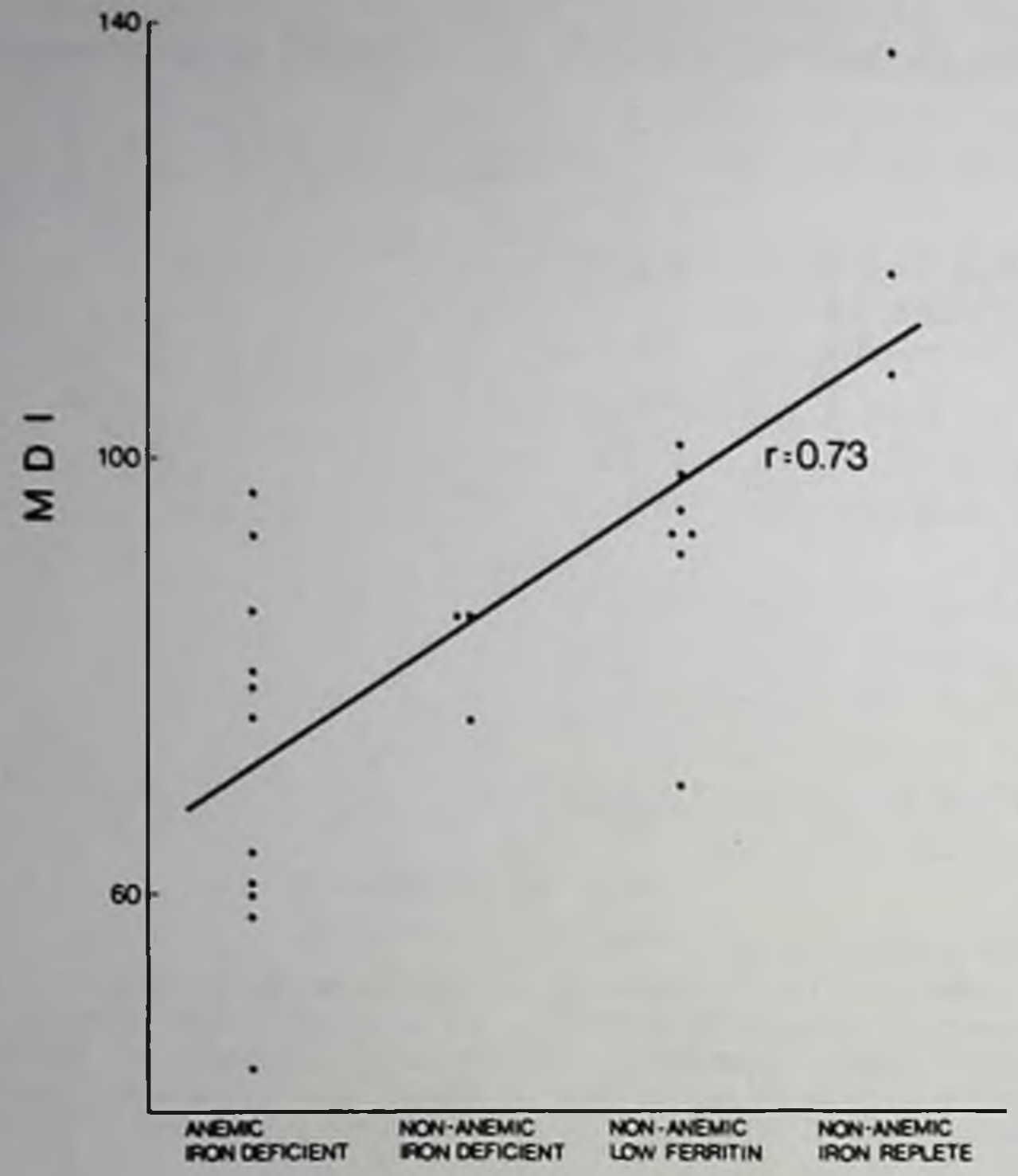


Fig 16–3.—Iron status and Mental Development Index *(MDI)* in infants aged 19–24 months. (Courtesy of Lozoff, B., et al.: J. Pediatr. 101:948–952, December 1982.)

rise in scores was associated with improvement in attention span and cooperativeness. In a similar fashion, we have documented (*Pediatrics* 71:877, 1983) that iron deficiency in the absence of anemia in infants aged 9–12 months also is associated with significantly poorer performance on the Mental Development Index. One week after the intramuscular administration of iron, the scores of these infants improved by approximately 20 points. My co-worker, Alice Honig, was able to characterize these iron-deficient infants as being "solemn" and that this solemnity improved with iron therapy.

There are several lessons in all of this. Never accept the results of the Bayley Development Index without some knowledge of the iron status of the infant as well as the behavior of the infant during the examination. Always suspect iron deficiency in the unhappy and uncooperative infant. Remember that a normal hemoglobin or hematocrit value does not exclude the possibility that the infant may be iron deficient. And finally, when you encounter a cranky menarchal female, realize that she has a 20% to 50% chance of being iron deficient.—F.A.O.] ◄

16–3 **Validation of an Early Language Milestone Scale in a High-Risk Population.** Pediatricians often must evaluate young children for possible developmental disability, but despite the presumption that speech-language delay in the first 3 years often indicates underlying developmental disorder, few tests of early language development are available. James Coplan, John R. Gleason, Rita Ryan, Michael G. Burke, and Margaret L. Williams (Syracuse, N.Y.) carried out detailed language evaluations by interviewing the parents of 191

(16–3) Pediatrics 70:677–683, November 1982.

healthy children, aged 3 and younger, and by testing the children themselves. Normative data were derived for 41 language milestones and used to construct the Early Language Milestone Scale (ELM Scale), a brief language assessment tool designed for use by general pediatricians.

For individual ELM Scale items that resemble previously described language milestones, emergence ages obtained with the ELM Scale normative sample compared closely with reported descriptions of language development. Use of the ELM Scale by physicians to evaluate 119 children considered to be at high risk of developmental disability showed it to be 97% sensitive and 93% specific in detecting develop-

EARLY LANGUAGE MILESTONE SCALE ITEMS

Item*		Normative Data†			
	Set by	25%	50%	75%	90%
I. Auditory expressive (AE)					
AE1 Coos	H	NB	0.1	1.7	3.2
AE2 Reciprocal vocalization	H	NB	0.4	1.5	2.6
AE3 Laughs	H	1.1	2.1	3.0	4.0
AE4 Blows bubbles (gives "raspberry")	H	1.7	3.5	5.4	7.3
AE5 Monosyllabic babbling	H	4.2	6.1	8.1	10.0
AE6 Polysyllabic babbling	H	5.4	7.2	9.0	10.8
AE7 Mama/dada: nonspecific usage	H	4.8	6.6	8.4	10.1
AE8 Mama/dada: correct usage	H	7.0	9.3	11.7	14.0
AE9 First word beyond mama/dada	H	8.4	11.3	14.2	17.0
AE10 4–6 single words	H	10.9	15.1	19.3	23.5
AE11 Tells 2 or more wants	H	15.2	17.2	19.0	20.8
AE12 2-word sentences	H	17.3	19.3	21.2	23.2
AE13 50 or more single words	H	17.6	20.3	22.9	25.6
AE14 Any use of "me" or "you"	H	18.2	21.8	25.3	28.8
AE15 Uses prepositions	H	23.0	26.8	30.5	34.2
AE16 Holds brief conversations	H	24.7	27.9	31.1	34.3
AE17 Gives name and use of two objects	T	27.3	29.7	32.0	34.4
AE18 Correct use of pronoun "I"	H	22.3	31.2	>36	>36
II. Auditory receptive (AR)					
AR1 Alerts to voice	H	NB	NB	NB	1.0
AR2 Turns laterally to voice	H	0.4	1.2	2.1	2.9
AR3 Recognizes certain sounds	H	0.5	1.3	2.2	3.1
AR4 Turns laterally to bell	T	2.0	3.0	4.0	5.0
AR5 Turns laterally then downward to bell	T	3.8	5.3	6.7	8.2
AR6 Inhibits to command "no"	H	5.3	6.9	8.5	10.1
AR7 Turns diagonally downward to bell	T	6.4	8.3	10.2	12.1
AR8 Follows 1-step commands	H	8.3	10.1	11.8	13.5
AR9 Points to 1 or more body parts	H	12.8	15.4	18.1	20.8
AR10 Follows 2-step commands	H	14.1	17.8	21.4	25.1
AR11 Points to named object	T	16.5	20.0	23.5	27.0
AR12 Points to objects described by use	T	23.5	26.5	29.6	32.6
AR13 Follows prepositional commands	T	25.8	29.6	33.3	>36
III. Visual (V)					
V1 Smiles	H	NB	0.5	1.0	1.5
V2 Recognizes parents	H	1.1	1.7	2.3	2.9
V3 Recognizes objects	H	0.7	1.6	2.5	3.4
V4 Responds to facial expression	H	0.7	2.0	3.4	4.7
V5 Visual tracking	T	1.3	2.4	3.6	4.7
V6 Blink to threat	T	1.7	2.8	3.9	4.9
V7 Imitates gesture games	H	5.9	7.0	8.0	9.1
V8 Follows gestural commands	H	5.9	7.6	9.3	11.0
V9 Initiates gesture games	H	7.3	8.9	10.4	12.0
V10 Points to desired objects	H	10.0	12.5	15.1	17.7

*H, history, testing; NB, newborn.

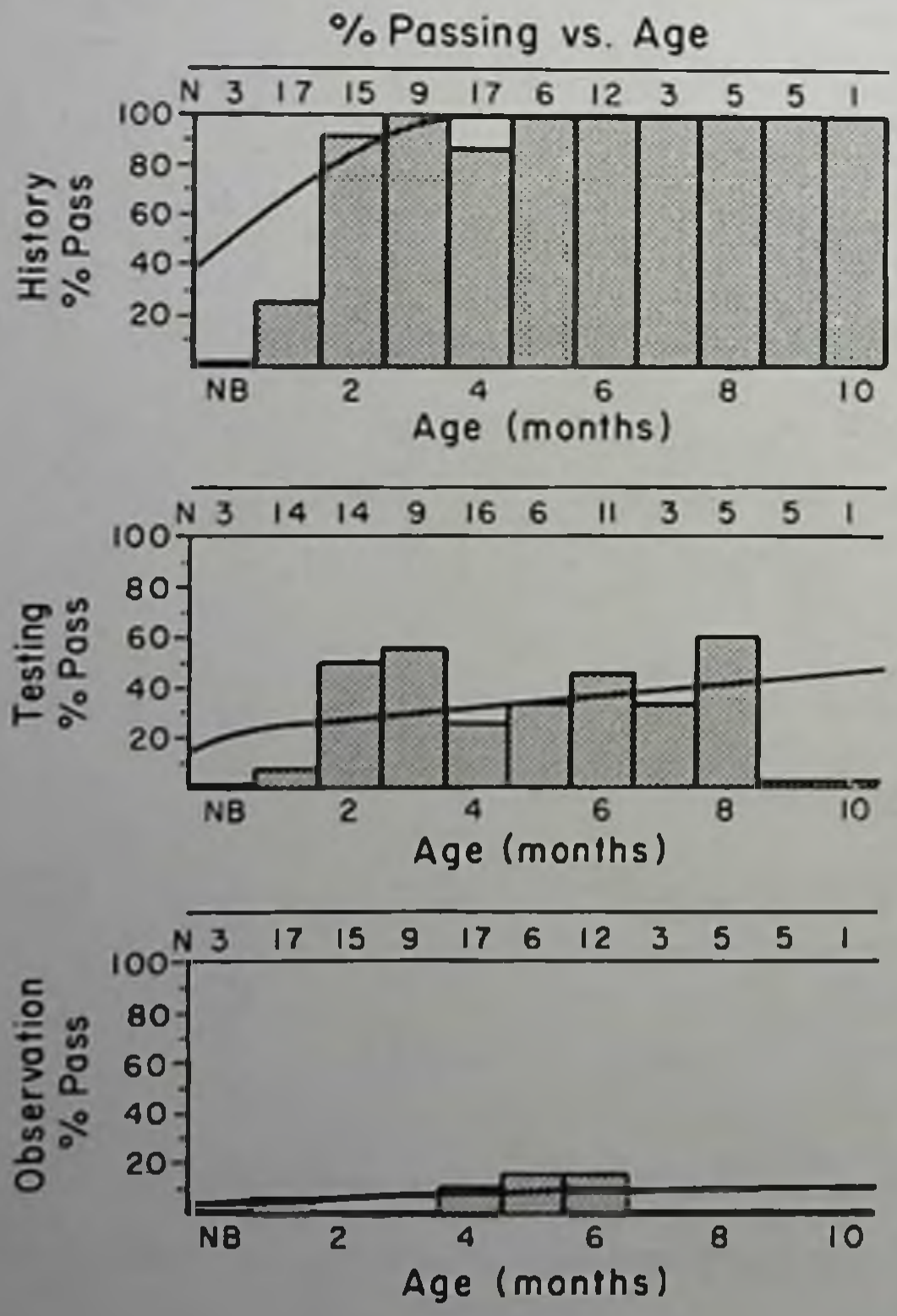
†Complete description of each item and specific manner of elicitation are contained in separate directions. Ages are given in months.

(Courtesy of Coplan, J., et al.: Pediatrics 70:677–683, November 1982. Copyright American Academy of Pediatrics 1982.)

mentally delayed children, compared with more formal developmental measures as applied by a clinical psychologist or speech pathologist. The ELM Scale items are listed in the table. For items that could be elicited by both history and testing, the emergence age by testing always followed that by history by several months, and emergence ages based on incidental observation were always later still (Fig 16–4). The ELM Scale was validated both by comparing emergence ages for each item with those from published reports and by applying passing and failing criteria, based on performance of children in the normative sample, to children referred for evaluation of possible developmental delay.

Early language milestones are a sensitive indicator of developmental integrity, and the delayed achievement of these milestones strongly suggests significant developmental disability. The ELM Scale is a valid measure of developmental status in children at high risk of developmental disability. The ELM Scale is highly specific for language or intellectual delay and is unaffected by physical handicap other than dysarthria. Children younger than age 3 years who ex-

Fig 16–4.—Compiled data for one item (AE2, reciprocal vocalization): *N*, number of subjects tested in each 1-month age block; *NB*, newborn; stippled bars indicate percent passing at each age; smooth curve represents logistic model fit of pass versus age at testing. Note that apparent emergence age is earliest by history, somewhat later by testing, and essentially indeterminate based on incidental observation. (Courtesy of Coplan, J., et al.: Pediatrics 70:677–683, November 1982. Copyright American Academy of Pediatrics 1982.)



hibit delayed language milestones should undergo formal developmental assessment.

▶ [This is a powerful screening test and has the added advantage that it can be administered in 1 to 3 minutes' time in the office setting. The Denver Developmental Screening Test, a popular examination with pediatricians, has been known to have weak agreement with reference tests such as the Bayley Scales of Infant Development or the Cattell Infant Intelligence Scale during the first 2 years of life. The Denver test can miss as many as 50% of infants with developmental delay. The Early Language Milestone Scale may be the better mousetrap that we have been looking for.—F.A.O.] ◀

16–4 **Motor Development of Fat Babies.** Although fat babies might be expected to be slow in motor development, there is minimal objective evidence for this. Michael Jaffe and C. Kosakov (Rothschild Univ. Hosp., Haifa, Israel) evaluated psychomotor function in 136 healthy infants aged 6–18 months. Posture, gross and fine motor function, speech, social behavior, vision, hearing, and neurologic status were assessed. One normal-weight infant was retarded and was excluded from the study. All other infants had normal fine motor, adaptive, social, and language development. The relationship of gross motor function to body weight is shown in Table 1. Fat babies showed significantly delayed motor development, especially those who were

TABLE 1.—RELATIONSHIP OF GROSS MOTOR FUNCTION TO BODY WEIGHT

		Motor Development	
Body Weight	Total Infants	Normal Function	Gross Delay
Normal	79	72 (91%)	7 (9%)
Fat	56	39 (70%)	17 (30%)
Overweight	45	32 (71%)	13 (29%)
Obese	11	7 (64%)	4 (36%)

(Courtesy of Jaffe, M., and Kosakov, C.: Clin. Pediatr. 21:619–621, October 1982.)

TABLE 2.—FAT BABIES AT 1-YEAR FOLLOW-UP

	Reexamination	
Number of Babies	Weight	Motor Development
10 (71%)	Normal	Normal
1 (8%)	Overweight	Normal
3 (21%)	Fat	Motor delay
(2 overweight)		
(1 obese)		

(Courtesy of Jaffe, M., and Kosakov, C.: Clin. Pediatr. 21:619–621, October 1982.)

(16–4) Clin. Pediatr. 21:619–621, October 1982.

obese rather than merely overweight. Findings at follow-up of fat babies a year later are given in Table 2. Most were of normal weight and were developing normally at follow-up, but 3 subjects were still fat and motor delayed. One infant remained overweight but had caught up in motor development.

A correlation does exist between excessive weight in infants and gross motor delay. The greater the degree of excessive weight, the greater is the probability of the delay becoming manifest. Both body weight and motor development tend to revert to normal over the ensuing year in most cases. Most fat infants have normal motor development. Comprehensive medical and neurodevelopmental assessment is indicated before motor delay is attributed to obesity, because mental retardation, neuromuscular disturbance, or a general medical condition such as hypothyroidism may be responsible.

▶ [While we are on the subject of obesity, are you familiar with Owen's law? It goes like this: "All humans will defend, on moral grounds, that which fattens their wallets" (from G. Owens, in the *Baltimore Evening Sun*, May 9, 1979).—F.A.O.] ◀

16–5 **Sleeping Patterns in Upper-Middle-Class Families When the Child Awakens Ill or Frightened.** Using a questionnaire, Alvin A. Rosenfeld, Anne O'Reilly Wenegrat, Diane K. Haavik, Brant G. Wenegrat, and Carole R. Smith (Stanford Univ.) surveyed 415 upper-middle-class parents of 576 children. Parents were asked if, when their child awoke ill or frightened, they took the child into their bed.

The results indicate that when a child is ill or frightened, parents of upper-middle-class 2- to 10-year-old American children commonly let the child come into their beds; 68% of the children were said to come to their parents' bed under these circumstances, and 92% of these parents allowed the children to come into their bed.

Boys and girls were equally likely to come to the parents' bed. Younger children came to their parents' bed more often than older children. Once children came to their parents' bed, those allowed to stay (63% of the total sample) remained for varying lengths of time (table). There were no significant differences between the sexes or younger and older children in length of stay.

Parents of boys and of younger children visit the children's bedrooms during the night more often than do parents of older children and of girls. A sizable percentage of parents did not stay in the child's bedroom; another large number stayed until the child fell asleep.

At no age did children show a clear preference for lying beside one parent or the other. About 29% of each age group reported a preference for lying near the mother; about 5.5% of children were reported as preferring to lie near the father. Single parents reported that their children came to their beds more often, and children of single parents were allowed to stay longer than children of married parents. No significant differences were found between children of married parents and those of single parents in the frequency of the child's awaking ill or frightened at night. Mothers older than age 32 years at the time of the child's birth reported fewer nighttime visits by their children.

(16–5) Arch. Gen. Psychiatry 39:943–947, August 1982.

LENGTH OF CHILD'S STAY IN PARENTS' BED*

Length of Stay	No. (%) Boys	Girls
Does not stay	62 (31.8)	53 (30.5)
Few minutes	17 (8.7)	21 (12.1)
Half hour	54 (27.7)	36 (20.7)
Until asleep	60 (30.8)	62 (35.6)
Rest of night	2 (1.0)	2 (1.1)
Total	195 (100)	174 (100)

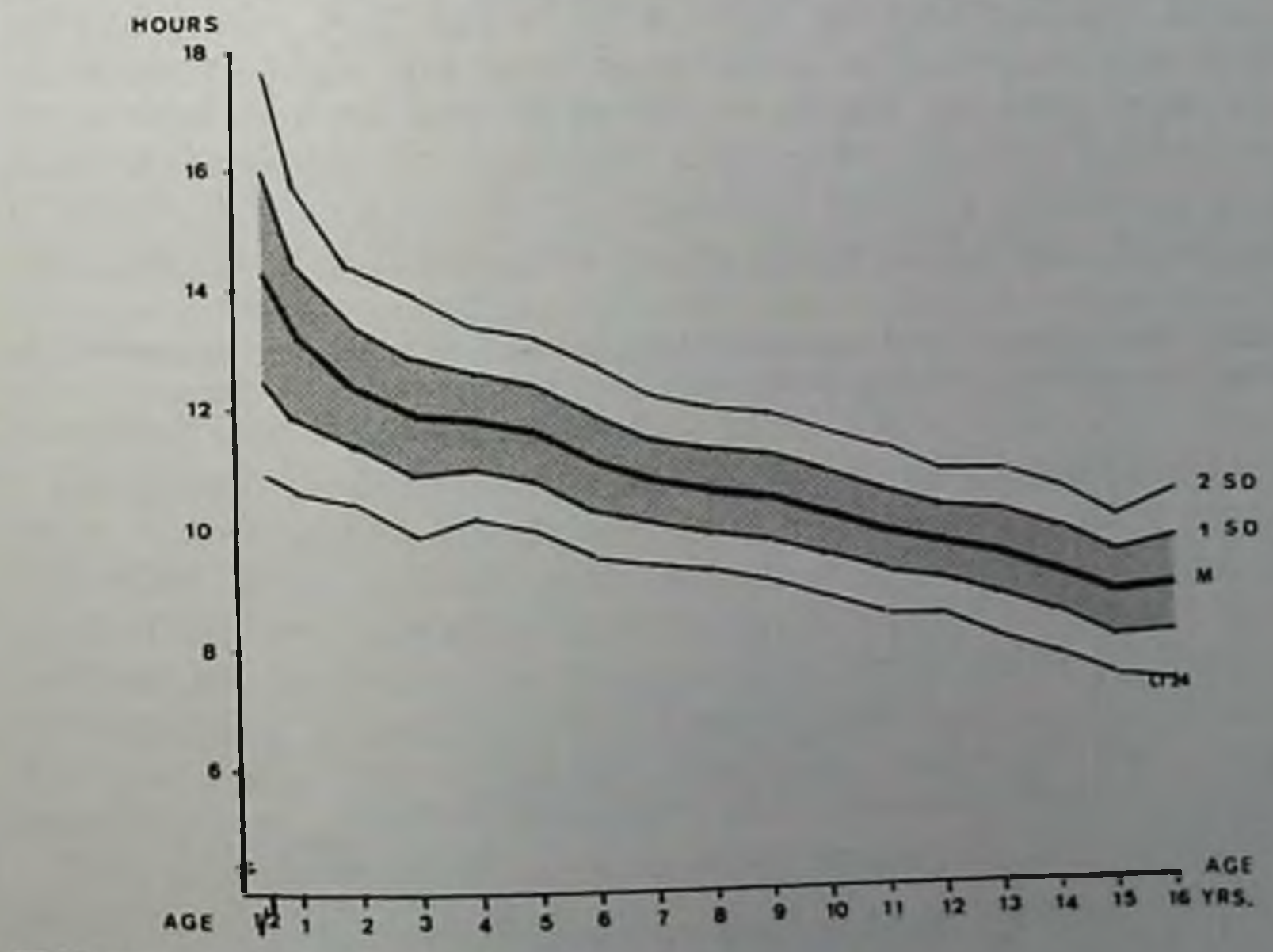
*Twenty-five parents did not answer the question, and 182 reported that the child did not come to their bed.

(Courtesy of Rosenfeld, A. A., et al.: Arch. Gen. Psychiatry 39:943–947, August 1982; copyright 1982, American Medical Association.)

If, in any given case, a child's being in the parental bed gives rise to psychopathology, clinicians must consider whether being in bed with the parent is per se the cause, or whether the child's being in the bed reflects deeper problems in family relationships, ego defects in the child, or the parents' use of the child for their own ends.

16–6 **Sleep Behavior Studied Longitudinally: Data From 4 to 16 Years on Duration, Night-Awakening, and Bed-Sharing.** Gunnar Klackenberg (Karolinska Hosp., Stockholm) undertook a prospective longitudinal study of children up to age 16 to learn whether disturbed sleep in the preschool years influences later sleep disturbances. Initially about 200 children, randomly selected, were

Fig 16–5.—Duration of sleep (day + night) at various ages. Mean *(M)* and standard deviation *(SD)*. (Courtesy of Klackenberg, G.: Acta Paediatr. Scand. 71:501–506, May 1982.)



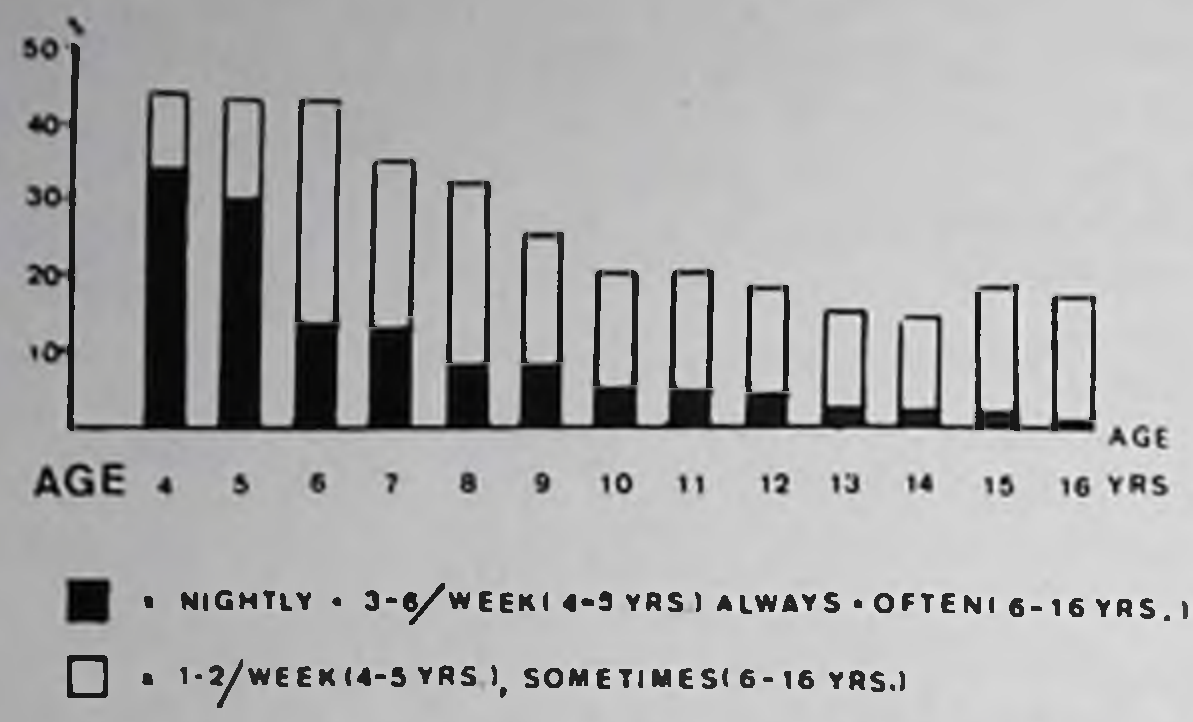


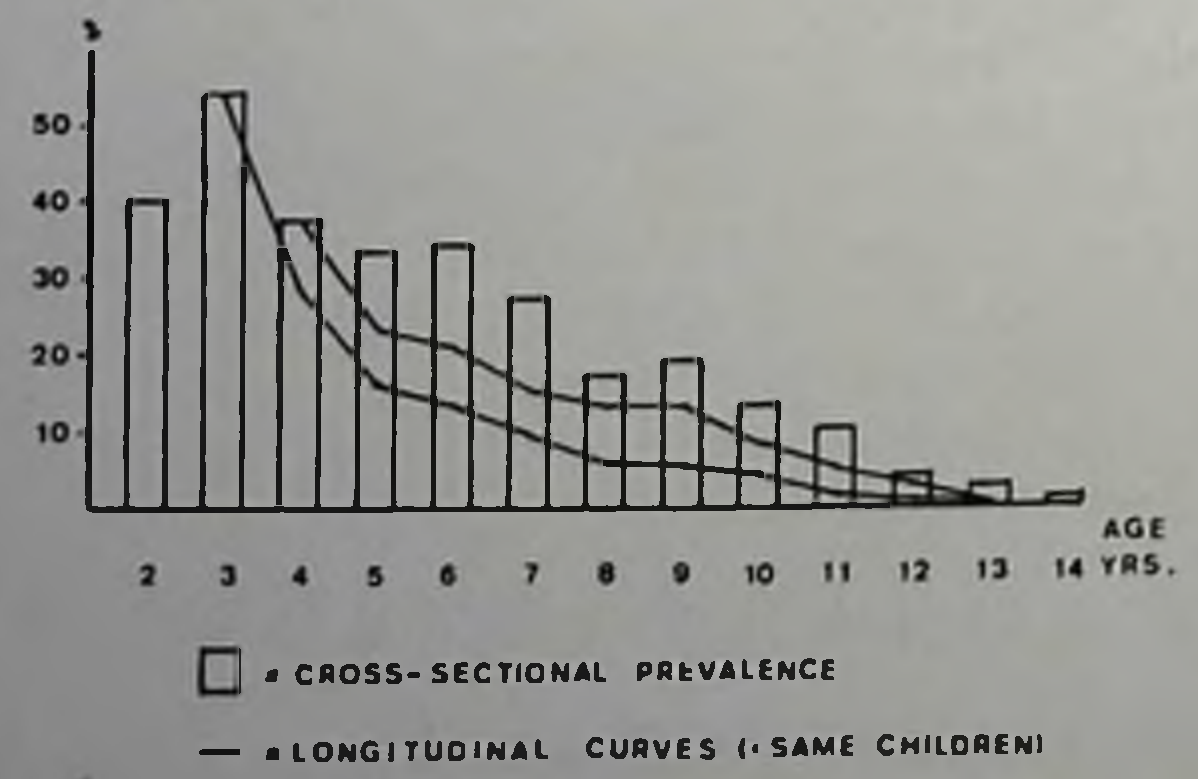
Fig 16–6.—Prevalence of night-awakening. (Courtesy of Klackenberg, G.: Acta Paediatr. Scand. 71:501–506, May 1982.)

admitted to the study and had annual somatic and psychologic evaluations.

The duration of sleep at different ages is shown in Figure 16–5. The time of awakening became more uniform at the start of school. The prevalence of night-awakening is shown in Figure 16–6. The tendency to awaken during the night persisted, but awakening even several times was not always perceived as poor sleep at age 4 or 5 years. Poor sleepers more often had a nervous or mentally ill parent, one with alcohol problems, or parents with marital difficulties. This was the case at all ages. The poor sleep of 66% of children aged 1 to 5 years and 46% of those at school age, however, could not be attributed to these findings. The prevalence of bed-sharing up to age 14 years is shown in Figure 16–7. Children of all ages who feared the dark tended to be bed-sharers more often than others.

Frequent night-awakening appears to be the chief sleep variable causing future anxiety. The duration of sleep and night awakenings at age 4 years were not highly predictive of conditions at later ages, but the habit of sharing the parents' bed, particularly at school age, was more difficult to give up. Bed-sharing was not a good predictor of marital instability in this study. Apart from the reason for awaken-

Fig 16–7.—Sharing parents' bed: prevalence and persistence. (Courtesy of Klackenberg, G.: Acta Paediatr. Scand. 71:501–506, May 1982.)



ing, it is natural for the child to seek reassurance from the parents, and the reinforcement gained is presumably a reason why the habit may persist for several years.

▶ [Dr. William Carey, a member of the Pediatric faculty at the University of Pennsylvania and a superb practicing pediatrician, comments as follows:

"The two accompanying papers by Klackenberg and by Rosenfeld et al. illustrate some important points about sleep behavior in infants and children.

Despite some recent technical advances (Anders, T. F., and Keener, M. A., in Levine, M. D., et al. (eds.): *Developmental-Behavioral Pediatrics*, W. B. Saunders Co., Philadelphia, 1983) our present understanding of commonplace phenomena is rich in theory but rather poor in data. Well-designed, useful studies of the ordinary variations and deviations in sleep behavior are not numerous. These two are helpful.

"An important methodologic obstacle in such studies is defining the matter to be observed. For example, if night-awakening is the subject, does one count all episodes of wakefulness or only those accompanied by crying, attempts to enter the parents' bed, or other annoyances that brought it to the parents' attention? How many episodes of waking per night, during what hours, and for how many nights must these occur to constitute the phenomenon under consideration? If the researcher and parent disagree as to whether it is a problem, how is it rated? Such lack of precision is troublesome.

"Data available so far concerning common variations in sleep behavior indicate that a number of factors are involved in their incidence and their evaluation by parents: the child's physical and neurologic status, his developmental level, temperament and behavioral adjustment, the parent-child relationship, and other environmental circumstances such as housing arrangements. Studies of correlations between single factors and sleep disturbances are not likely to yield high correlations. Also, as Klackenberg demonstrated, predictions from one age to another are not of a high order.

"The modest extent of our knowledge about sleep problems should discourage clinicians from being dogmatic when dispensing advice to parents. For example, most pediatricians probably follow the teachings of Spock and strongly discourage letting children sleep with their parents even when frightened. Yet, the majority of the parents studied by Rosenfeld et al. allowed the practice. Where is the evidence that this is harmful? As these authors say in their conclusion, "Until we develop a better picture of normative family life, we will be unable to specify what precisely is aberrant in troubled families."

"The need for more research is abundantly clear. Moreover, I should like to stress that this is an area in which pediatric practitioners have a unique opportunity to make a contribution (Carey, W. B.: *Pediatrics* 62:424–425, 1978). Studies of sleep behavior are ideally situated in settings of ongoing contact with normal populations of children. Although one needs clear definitions, good research design, and careful data collection and analysis, there is no requirement for complicated equipment or additional personnel. The practitioner can obtain valuable data on incidence, prevalence, associated factors, and various programs of management for a variety of sleep problems with a small amount of additional questioning and record keeping. Such surveys would be of great theoretical and practical value."] ◀

16–7 **Sleep and Bedtime Behavior in Preschool-Aged Children.** Antonio U. Beltramini and Margaret E. Hertzig (New York Hosp.-Cornell Univ. Med. Center) analyzed age-stage-specific changes in patterns of bedtime and sleep behavior in normally developing preschool children in the New York Longitudinal Study of Temperament and Development. A total of 109 children from middle-class families in the New York City region were included. Interviews were conducted annually from ages 1 to 5 years.

Over two thirds of the children shared a room some time in their first 5 years (Table 1). Maternal supervision of bedtime activities was

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(16–7) Pediatrics 71:153–157, February 1983.

TABLE 1.—SLEEP ARRANGEMENTS AND ADULT SUPERVISION AT BEDTIME

	Year 1 N (%)	Year 2 N (%)	Year 3 N (%)	Year 4 N (%)	Year 5 N (%)	Ever N (%)	Cochran Q	df	P
Shares bedroom	32 (29)	43 (39)	53 (49)	59 (54)	56 (49)	78 (72)	33.97	4	<.001
Father regularly participates in bedtime routine	7 (6)	13 (12)	21 (19)	16 (15)	18 (17)	35 (32)	19.01	4	<.001

(Courtesy of Beltramini, A. U., and Hertzig, M. E.: Pediatrics 71:153–157, February 1983. Copyright American Academy of Pediatrics 1983.)

the predominant pattern in the preschool period, but paternal participation was reported in one third of cases at some time in the first 5 years. Paternal participation increased with advancing child age. A regular bedtime routine was followed by all children at all ages. Selected bedtime activities are analyzed over time in Table 2. Nearly 90% of children required more than 30 minutes to fall asleep three or more times a week at at least one age level in the preschool period. Boys and girls were equally likely to have delays in falling asleep. Interruptions of sleep are analyzed in Table 3. No sex or age differences in nighttime awakening were found. Nearly two thirds of the children regularly experienced nightmares up to once every 2 weeks at some point in the preschool period. Nightmares were significantly more likely in older children.

These findings accord with those of other studies examining aspects of sleep and bedtime behavior from a quantitative perspective. Striking similarity is found in studies of children living at different times and in widely disparate geographic areas and social circumstances, suggesting that age-specific patterns of sleep and bedtime behaviors may have a neurophysiologic basis, with maturation occurring in the

TABLE 2.—SELECTED BEDTIME ACTIVITIES IN PRESCHOOL-AGED CHILDREN

	Year 1 N (%)	Year 2 N (%)	Year 3 N (%)	Year 4 N (%)	Year 5 N (%)	Ever N (%)	Cochran Q	df	P
Bedtime routine >30 min	7 (6)	13 (12)	26 (24)	53 (49)	36 (33)	72 (66)	73.02	4	<.001
Falls asleep with light on	8 (7)	14 (13)	22 (20)	33 (30)	25 (23)	52 (47)	24.54	4	<.001
Requests treasured object	20 (18)	50 (46)	54 (50)	46 (42)	22 (20)	83 (76)	154.48	4	<.001
1 or more "curtain calls"/night	15 (14)	28 (26)	46 (42)	53 (49)	55 (50)	82 (75)	75.46	4	<.001
Requires >30 min to fall asleep	28 (26)	47 (43)	67 (61)	75 (69)	72 (66)	96 (88)	70.52	4	<.001

(Courtesy of Beltramini, A. U., and Hertzig, M. E.: Pediatrics 71:153–157, February 1983. Copyright American Academy of Pediatrics 1983.)

TABLE 3.—INTERRUPTIONS OF SLEEP IN PRESCHOOL-AGED CHILDREN

	Year 1 N (%)	Year 2 N (%)	Year 3 N (%)	Year 4 N (%)	Year 5 N (%)	Ever N (%)	Cochran Q	df	P
Night awakening at least once/wk	62 (57)	62 (57)	72 (66)	71 (65)	66 (61)	104 (95)	4.29	4	NS
Awakens 1 or more times every night	32 (29)	30 (28)	36 (33)	32 (29)	21 (19)	76 (70)	3.57	4	NS
Nightmares at least once every 2 wk	5 (5)	10 (9)	31 (28)	42 (39)	41 (38)	68 (62)	67.71	4	<.001

(Courtesy of Beltramini, A. U., and Hertzig, M. E.: Pediatrics 71:153–157, February 1983. Copyright American Academy of Pediatrics 1983.)

preschool period. If a child functions well in other areas of life, the parents can be assured that age-stage-typical behaviors surrounding bedtime are not serious. They should be encouraged to set limits appropriate to the needs of both the child and the family.

► [These are the kinds of facts that every parent will recognize. Parents always are reassured when they exchange anecdotes with their friends and learn they have common bedtime problems. If you are still awake and want to read more about sleep in children, see the 1983 YEAR BOOK, pages 422–424. If not, good night.—F.A.O.] ◄

16–8 **Issues of Concern to Mothers of New Babies.** Awareness by clinicians of a mother's concerns regarding her infant relates significantly to outcomes of well-child care. Although the literature reports the birth of a baby to be a time of stress for parents, their day-to-day experience with the baby in the early months is an understudied area. Karen F. Pridham, Marc F. Hansen, Mary E. Bradley, and Susan M. Heighway (Univ. of Wisconsin—Madison) analyzed daily logs kept by 62 mothers of newborns, including 38 primaparas and 24 multiparas aged 17–43, who had an average of 3 years of education beyond high school. Logs were begun as soon as possible after the baby's birth and continued until the baby was 91 days old. They were analyzed, tabulating 7 major categories of issues regarding concerns about the child, 10 possible sources of help or advice in dealing with issues, and 7 categories of reported stressors or support.

For 5 categories (development, baby care, parenting, stressful events, and illness), the number of issues identified varied significantly with time ($P = .03$; Table 1). Issues regarding illness dropped in frequency significantly across months. Although the total number of issues dropped over the 3 months from 3,787 in the first month to 2,901 in the third, the proportion of concerns within each category remained more nearly constant. The percentage of all issues identified for which help was sought dropped from 35% and 22% in the first

TABLE 1.—MEAN FREQUENCY (AND STANDARD DEVIATION) OF ISSUES PER SUBJECT BY CATEGORY AND TIME IN 62 MOTHER-INFANT PAIRS

Category of Issue	First Month (0-30 days)	Second Month (31-60 days)	Third Month (61-91 days)
Development	7.5 (8.9)	9.6 (9.3)	8.8 (8.7)*
Temperament	2.5 (2.6)	2.2 (2.5)	3.0 (4.2)
Baby care	20.6 (13.4)	13.4 (11.9)	13.1 (13.2)†
Parenting	3.4 (3.9)	1.7 (2.6)	1.6 (2.6)†
Stressful events	5.4 (4.4)	4.0 (4.1)	3.8 (3.9)‡
Illness	19.8 (14.4)	13.7 (9.5)	9.9 (7.7)†
Behavior	5.6 (4.5)	4.4 (4.2)	4.6 (4.6)
Days with no issues	2.0 (3.2)	3.1 (4.5)	3.3 (8.7)

Frequencies are corrected for number of days the log was completed for each time period.

*$P = .03$.

†$P = .00$.

‡$P = .01$.

(Courtesy of Pridham, K. F., et al.: J. Fam. Pract. 14:1079–1085, June 1982.)

(16–8) J. Fam. Pract. 14:1079–1085, June 1982.

TABLE 2.—PERCENTAGE OF SOURCES OF HELP USED FOR ALL ISSUES REPORTED BY MOTHERS IN 62 MOTHER-INFANT PAIRS

	Time Period			
Source of Help	Weeks 1-2	Weeks 3-4	Second Month	Third Month
Self, no help	56	70	81	84
Self, books, other literature	8	8	5	4
Husband or partner	7	3	3	4
Grandparent	4	3	1	1
Other relative	2	1	1	0.3
Friend or neighbor	2	1	2	1
Family physician	8	6	4	3
Nurse clinician	5	4	1	2
Other clinicians	8	1	1	1
Other	0.5	1	0.4	0.3
Total issues	n = 1,905	n = 1,882	n = 3,148	n = 2,901
Proportion of all issues identified for which external help was sought	.35	.22	.13	.12

(Courtesy of Pridham, K. F., et al.: J. Fam. Pract. 14:1079–1085, June 1982.)

and second 2-week periods, respectively, to 13% and 12% in the second and third months, respectively (Table 2). Stressors and supports within each category are summarized in Table 3. Mothers reported their own feelings or status to be a stressor far more often than a support. Multiparas and primiparas did not differ significantly in the total number of issues reported, having a mean of 156 and 150 issues, respectively. Only in the category of parenting did multiparas identify significantly more issues than primaparas ($P = .04$). On the average, primiparas sought help about 1.5 times as frequently as multiparas. By the third month, primiparous mothers sought help for about 1 of 5 issues, whereas multiparas sought it for 1 out of 8. Clinicians were not contacted often and usually at times that would be

TABLE 3.—FREQUENCY (PERCENTAGE) OF REPORTED STRESSORS AND SUPPORTS IN 62 MOTHER-INFANT PAIRS

	Reported Stressors	Reported Supports
Source	No. (%)	No. (%)
Self	683 (15.4)	122 (3.1)
Responsibilities	1,241 (27.9)	279 (7.1)
Resources	276 (6.2)	1,533 (38.8)
Activities, plans, events	596 (13.4)	1,148 (29.1)
Behaviors	741 (16.7)	532 (13.5)
Conditions	853 (19.2)	316 (8.0)
Other events	54 (1.2)	17 (0.4)
Total	4,443 (100.0)	3,947 (100.0)

(Courtesy of Pridham, K. F., et al.: J. Fam. Pract. 14:1079–1085, June 1982.)

convenient to the clinicians. Results show that mothers have more concerns than come to attention of the clinicians.

▶ [This list of topic areas should prove useful to young doctors in organizing their discussions for well-child visits. For the older pediatrician, this list of topics should provide a convenient outline for what to include in the book you always have planned to write about well-child care for parents.—F.A.O.] ◀

16–9 **Maternal Employment: The Child's Perspective.** Maternal employment is an increasingly important factor in child development because of the increasing number of mothers working outside the home. Rosemary Trimberger and Michael J. MacLean hypothesized that more favorable child attitudes would result if the child had more knowledge about his or her mother's employment and felt positively affected by it. Fifty-one children aged 9 to 12 years participated in a questionnaire study dealing with attitudes toward maternal employment. The 29 girls and 22 boys were from intact working- and middle-class families in a large Canadian city. The mothers worked outside the home at least 6 hours a day.

Boys had less knowledge about their mothers' employment than did girls. Knowledge increased with the time of maternal employment. Boys perceived themselves as more positively affected by their mothers' employment than did girls. Children who stayed alone after school did not feel more negatively affected than those who were not alone. The most significant variable in the child's perception of the mother's interest in him or her was knowledge of the mother's employment. Children who perceived their mothers as interested in them were likely to miss the mothers while they were at work. Supervision arrangements were significantly related to attitudes toward maternal employment.

Social-psychologic research could examine communication patterns between mother and child with respect to maternal employment. More knowledge is needed about the sharing of information about maternal employment and the realities of not being home before the child returns from school. The interaction between the mother's feelings toward her work and what is communicated to the child about work also should be examined. The father's attitudes toward the mother's work role also may be important.

▶ [The "latch-key child" is a fact of our present society. How we handle it will have implications for years to come. One simple observation from this study of middle-class families is that the mother always should take the time to explain to the child the nature of her work and why she is doing it. Fathers should take heed as well.—F.A.O.] ◀

(16–9) J. Marriage Fam. 44:469–475, May 1982.

17. Adolescent Medicine

17–1 **Dysuria in Adolescent Girls: Urinary Tract Infection or Vaginitis?** Efstratios Demetriou, S. Jean Emans, and Robert P. Masland, Jr. (Harvard Med. School) studied data on 53 girls, aged 12–21 years, to identify causes of dysuria and to ascertain whether patient reports of internal or external dysuria might be useful in identification of bacterial urinary tract infection (UTI) or vaginitis. Specific inquiries were made about location and duration of pain, fever, vaginal discharge, vulvar lesions, antibiotic use, sexual experience, and contraception, as well as about previous UTI or renal infection. Physical examination included inspection of genitalia and pelvic examination in the 42 sexually experienced patients and in the 7 virginal patients whose introitus permitted introduction of a small speculum without discomfort. Vaginal secretions were sampled in the other 4 patients using moist swabs. Urinalysis, endocervical culture for *Neisseria gonorrhoeae*, vaginal culture for *Candida*, and microscopic examination of vaginal secretions were performed. Six patients in whom initial evaluation showed no cause for dysuria had subsequent urethral and

DIAGNOSES ASSOCIATED WITH DYSURIA

	No.	%
Vaginitis	22	41
Candida	(10)	19
Trichomonas	(8)	15
Candida and *Trichomonas*	(2)	4
Nonspecific	(2)	4
Bacterial urinary tract infection (UTI)	9	17
Bacterial UTI and vaginitis*	9	17
Other	13	25
Genital herpes	(2)	4
Gonococcal infection	(1)	2
Chlamydial infection	(1)	2
Gonococcal and chlamydial infection	(1)	2
Skene's gland abscess	(1)	2
Nonspecific vulvitis	(2)	4
Traumatic urethritis and *Candida* vaginitis	(1)	2
Acute urethral syndrome of unclear etiology	(4)	8

*Includes 1 case with positive endocervical culture for *Neisseria gonorrhoeae*.

(Courtesy of Demetriou, E., et al.: Pediatrics 70:299–301, August 1982. Copyright American Academy of Pediatrics 1982.)

(17–1) Pediatrics 70:299–301, August 1982.

cervical cultures and serum antibodies taken for *Chlamydia trachomatis*.

Results are shown in the table. Vaginitis alone was found in 22 patients (41%), UTI alone in 9 (17%), both UTI and vaginitis in 9 (17%), acute urethral syndrome of uncertain origin in 4 (8%), nonspecific vulvitis in 2 (4%), and herpes simplex infection in 2 (4%). One patient each had gonococcal and chlamydial infections alone; 1 had both infections, 1 had an abscess of Skene's gland, and 1 had traumatic urethritis with candidal vaginitis. Among the 11 virginal patients, 9 showed vaginitis or vulvitis. Among the 15 patients who had no vaginal discharge or irritation, 8 showed some form of vaginitis. Of 9 patients who localized the dysuria internally, 5 had UTI or acute urethral syndrome, 2 had UTI with vaginitis, and 2 had vaginitis alone. Significant bacteriuria was found in only 18 (34%) patients. In a comparable control group of 52 patients seen for routine gynecologic examinations, 8 had vaginitis and none had dysuria.

In the adolescents in this study, vaginitis alone was more than twice as likely as bacterial UTI to cause dysuria. Results were comparable with those for adult women. Pyuria was associated with vaginal infection alone, as well as with UTI.

► [It should come as no surprise that once you assume responsibility for the care of adolescents, you must become proficient in adolescent gynecology. Nothing is easy in this age group. You must disconnect your ingrained association of dysuria with infection of the urinary tract because, as this study shows, vaginitis is much more likely to be the cause of dysuria than is a bacterial infection of the urinary tract. Vaginitis also produces pyuria and diminishes the value of this simple screening procedure. In the study presented here, the authors did not research for *Chlamydia trachomatis* routinely, but this agent is responsible for as many as 25% of all cases of cervicitis, salpingitis and urethritis in adolescent girls (see Fraser, J. J., et al.: *Pediatrics* 71:333, 1983; and 1983 YEAR BOOK, pp. 427–429). Once you begin to investigate the gynecologic complaints of the adolescent girl, particularly those that are sexually active, you should be prepared to culture for gonorrhea, *C. trachomatis*, and *Gardnerella*, examine wet smears for *trichomonas* and *Candida*, and obtain a Papanicolaou smear while you are there. If you don't have the laboratory backup for the culture of *Chlamydia*, and your other diagnostic procedures fail to uncover a pathogen to explain the dysuria-pyuria, Stamm and associates (*N. Engl. J. Med.* 303:409, 1980) have proposed empiric treatment with doxycycline, 100 mg twice daily for 10 days. For more on vaginitis, in the premenarchal girl, see Chapter 7, "The Genitourinary Tract."—F.A.O.] ◄

17–2 **Epidemiologic Study of Young Women With Dysmenorrhea.** A questionnaire and follow-up letters were sent to one fourth of the 19-year-old women of the city of Göteborg, Sweden, by Björn Andersch to investigate the prevalence and severity of dysmenorrhea. The material comprised 656 women and 90.9% answered the inquiry.

Prevalence of dysmenorrhea in the study group was 72.4%, and 90 respondents (15.4%) limited their daily activity because of dysmenorrhea. Prevalence and severity of dysmenorrhea were significantly reduced ($P < .01$) among oral contraceptive users compared to users of intrauterine contraceptive devices (IUDs) or nonusers of IUDs or oral contraceptives. Women with early menarche suffered more from dysmenorrhea than women with late menarche. Severity of dysmen-

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(17–2) Am. J. Obstet. Gynecol. 144:655–660, Nov. 15, 1982.

orrhea increased with longer duration of menstruation as well as with increased menstrual flow. Prevalence and severity of dysmenorrhea in parous women was significantly reduced ($P < .01$) compared with women who had never been pregnant or had had legal (50.5%) or spontaneous abortions. The altered neuromuscular activity in the uterus after term pregnancy may explain the disappearance or reduction of menstrual pain after childbirth, for there was no appreciable difference in prevalence and severity of dysmenorrhea between nulliparous women and women where pregnancy had terminated with abortion. Heredity seems to play an important part as respondents correlated their condition with dysmenorrhea in their mothers or in sisters. A negative correlation existed between cigarette smoking and frequency and severity of dysmenorrhea; depression of the autonomic ganglia and the neuromuscular junction by nicotine may explain this finding.

Analgesics or antispasmodics or both were used regularly by 38.2% during menstruation, and 71 of 89 oral contraceptive users also regularly consumed analgesics or antispasmodics as treatment for dysmenorrhea. A total of 50.9% of respondents reported absence from work or school because of dysmenorrhea, and 7.9% were absent during every menstruation.

Improved understanding of the pathophysiology of dysmenorrhea may result in more effective treatment regimens than described here, thus reducing the social and medical consequences of dysmenorrhea.

▶ [Now that you see the data that document the magnitude of the problem, please go on to the following article.—F.A.O.] ◀

17–3 **Zomepirac Sodium in Treatment of Primary Dysmenorrhea Syndromes.** It has been suggested that excessive stimulation of the uterus by prostaglandins may be a cause of uterine cramping in dysmenorrhea. Penny Wise Budoff (Woodbury, N.Y.) compared zomepirac sodium with placebo in patients with monthly dysmenorrhea bad enough to require a prescription analgesic. Other symptoms of dysmenorrhea syndrome were usually present also. A 6-month, double-blind, multiple-crossover study was carried out. A dose of 100 mg of zomepirac or placebo was taken at the first sign of menstrual pain and repeated every 4 hours as needed to a maximum of six doses a day for up to 5 days during each menstrual period.

Changes in associated symptoms are shown in Table 1. The 47 patients who completed 2 months in the study had a mean age of 27 years. Zomepirac reduced the primary symptoms more than did placebo (Fig 17–1). Severity of the primary symptoms during the study is given in Table 2, and changes in abdominal cramping are indicated in Table 3. Curtailment of normal activities was less with zomepirac treatment than with placebo (Fig 17–2). Use of supplemental analgesic was greater when placebo was used. Patients' global evaluations significantly favored zomepirac over placebo (Fig 17–3). No unusual or unexpected side effects occurred. Most side effects were gastroin-

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(17–3) N. Engl. J. Med. 307:714–719, Sept. 16, 1982.

TABLE 1.—Severity of Associated Symptoms During the Study

Symptom (Patients Affected)	Overall Mean Score *		P Value
	Zomepirac	Placebo	
Performance			
Improved (22)	0.38 †	0.18	0.05
Worsened (44)	0.31 †	0.60	<0.001
Eating habits			
Increased eating (19)	0.34	0.36	0.73
Decreased eating (30)	0.30 †	0.47	0.01
Skin changes			
Acne or oily skin (26)	0.41	0.49	0.30
Other (9)	0.23	0.30	0.44
Constipation (24)	0.36	0.26 ‡	0.09
Diarrhea (32)	0.22 †	0.44	<0.001
Hot sensations (24)	0.22 †	0.47	0.003
Cold sensations (26)	0.26 †	0.40	0.05
Body temperature			
Increase (12)	0.17	0.33	0.15
Decrease (9)	0.22	0.40	0.17
Fainting (10)	0.11	0.06	0.51

*Scale: 0 = No and 1 = Yes. Except for "improved performance," mean score nearer 0 indicates better treatment.

†Significantly different from value for placebo.

‡Marginally different from value for zomepirac.

(Courtesy of Budoff, P. W.: N. Engl. J. Med. 307:714–719, Sept. 16, 1982.)

TABLE 2.—Severity of Primary Symptoms During the Study

Symptom (Patients Affected)	Overall Mean Score *		P Value †	Difference (Mean ±S.D.)
	Zomepirac	Placebo		
Abdominal cramping (47)	1.01	2.00	<0.001	+0.99±0.77
Backache (43)	0.69	1.24	<0.001	+0.55±0.84
Weakness (40)	0.63	1.04	<0.001	+0.41±0.64
Headache (39)	0.53	0.86	0.004	+0.33±0.67
Nausea (36)	0.40	0.80	0.001	+0.40±0.68
Leg pain (35)	0.46	0.93	<0.001	+0.47±0.75
Insomnia (33)	0.30	0.42	0.21	+0.12±0.53
Dizziness (31)	0.34	0.60	0.03	+0.26±0.66
Vomiting (18)	0.07	0.53	0.009	+0.46±0.67
Fatigue/lethargy (41)	0.94	1.20	0.007	+0.26±0.60
Anxiety/irritability (40)	0.71	1.11	<0.001	+0.40±0.63
Swelling (38)	0.89	1.21	0.002	+0.32±0.59
Depression (35)	0.58	0.89	0.003	+0.31±0.57

*Scale: 3 = severe, 2 = moderate, 1 = mild, and 0 = none.

†By paired t test on between-treatment comparisons. Zomepirac was better than placebo for all symptoms.

(Courtesy of Budoff, P. W.: N. Engl. J. Med. 307:714–719, Sept. 16, 1982.)

TABLE 3.—REDUCTION IN SEVERITY OF ABDOMINAL CRAMPING IN PATIENTS WITH MODERATE AND SEVERE BASELINE SYMPTOMS

BASE-LINE SEVERITY SCORE	PATIENTS AFFECTED	ZOMEPIRAC TREATMENT		PLACEBO TREATMENT	
		OVERALL SEVERITY SCORE	DIFFERENCE FROM BASE LINE	OVERALL SEVERITY SCORE	DIFFERENCE FROM BASE LINE
		mean ±S.D.	%	*mean ±S.D.*	%
2.0 (moderate)	15	0.76±0.62	62	1.53±0.77	24
3.0 (severe)	32	1.12±0.61	63	2.22±0.60	26

(Courtesy of Budoff, P. W.: N. Engl. J. Med. 307:714–719, Sept. 16, 1982.)

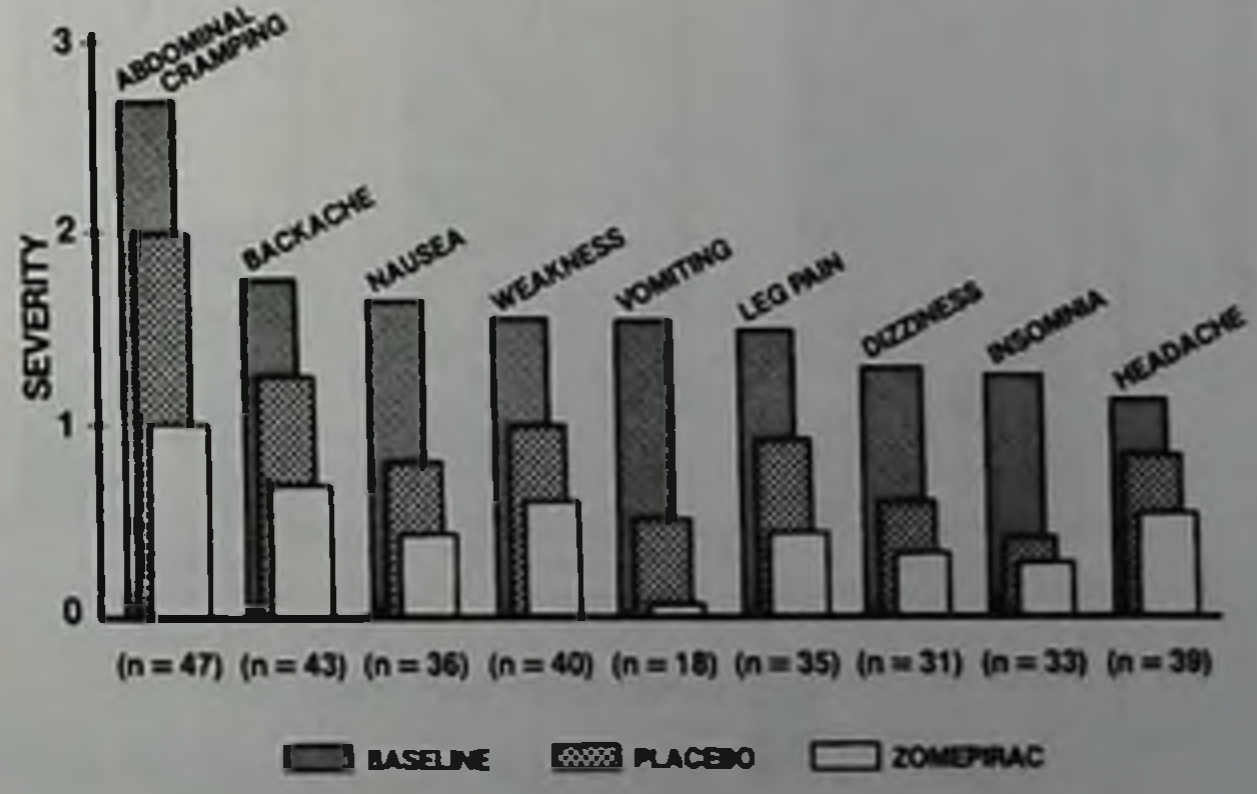
testinal. There were no clinically significant laboratory changes during the study.

Zomepirac provided excellent relief from symptoms of dysmenorrhea in this study. Zomepirac, a prostaglandin synthetase inhibitor, relieves pain without the need for a narcotic, and tolerance to the drug does not develop. Gastrointestinal side effects generally have been mild and transient. Zomepirac sodium should be considered for the treatment of primary dysmenorrhea syndrome.

▶ ["Dr. Iris Litt, Associate Professor of Pediatrics, Stanford University Medical Center, who informs me that she was never herself a teenager, kindly provided the following comments:

This study is a carefully designed double-blind crossover evaluation of an antiprostaglandin (zomepirac) and placebo in a small group of females with dysmenorrhea. The author is to be commended for accomplishing it in the setting of private practice, a largely untapped resource. It would have been helpful to have information about selection of subjects to know how many eligible subjects refused participation and how their characteristics may have differed from those who agreed. Use of a standardized test of menstrual distress (e.g., the Moos Menstrual Distress Questionnaire [Moos, R. A.: *Psychosom. Med.* 30:853–867, 1968]) would have provided data to allow for comparison of this population to others and, hence, enhanced its generalizability. That instrument is helpful, in addition, because of inclusion of a control

Fig 17–1.—Reduction in mean severity of nine primary symptoms. These symptoms were evaluated for severity at baseline and daily during treatment. Zomepirac provided significantly more relief from all nine symptoms than did placebo ($P < .05$). Scale: 3 = severe, 2 = moderate, 1 = mild, and 0 = none. (Courtesy of Budoff, P. W.: N. Engl. J. Med. 307:714–719, Sept. 16, 1982.)



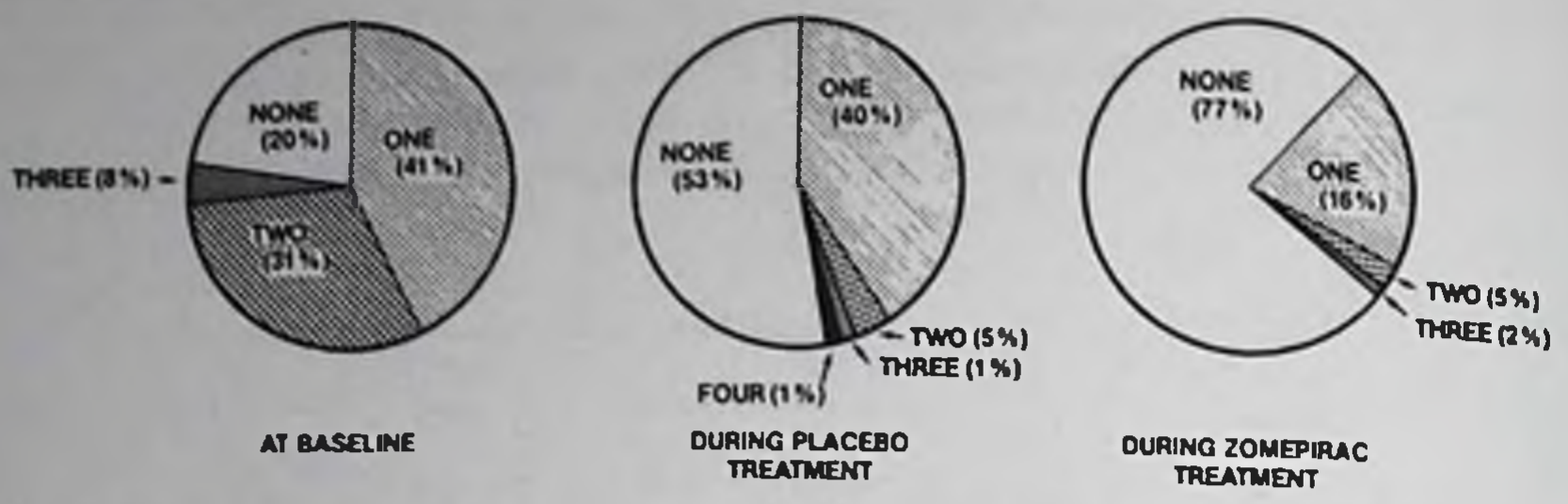
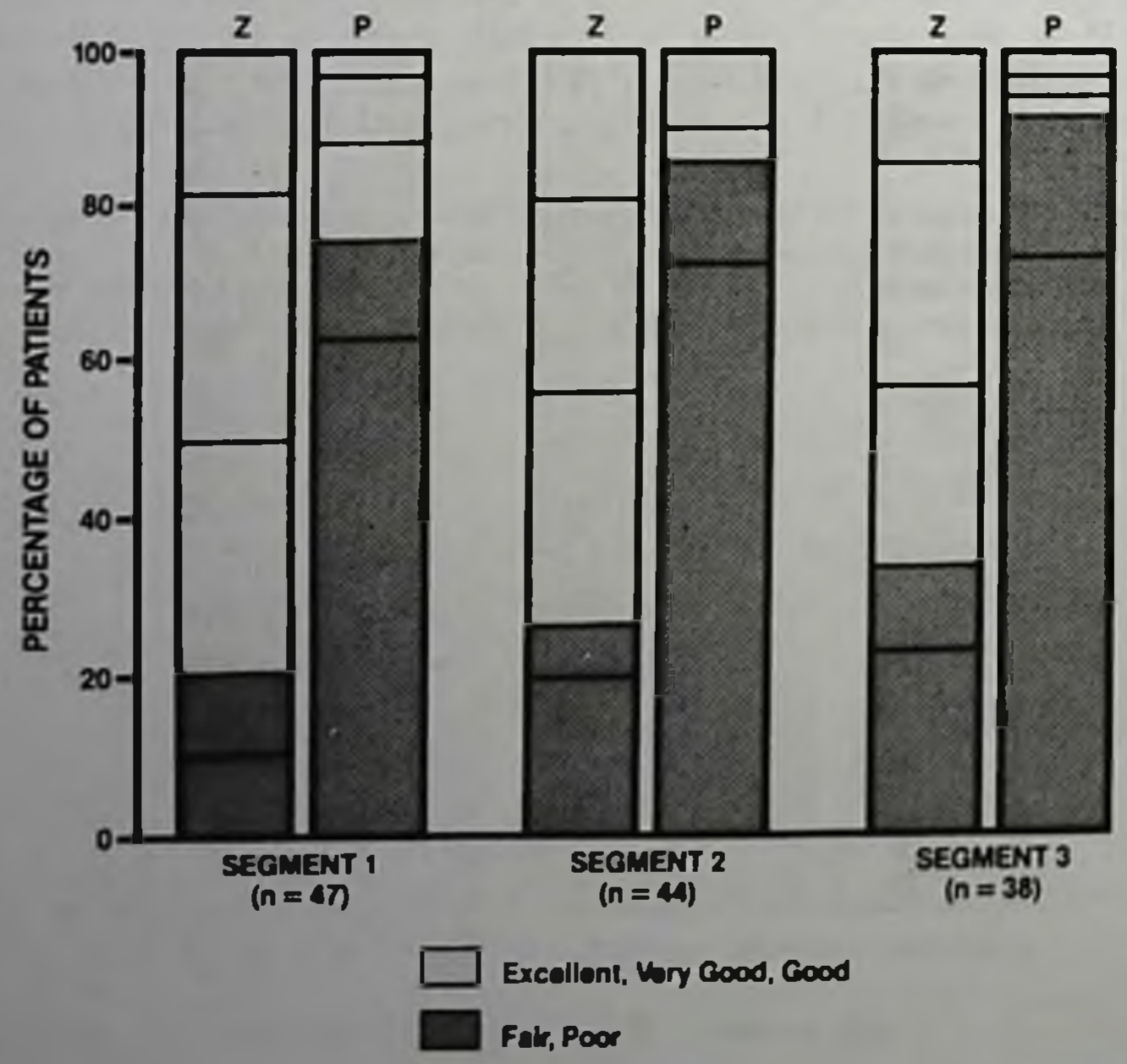


Fig 17–2.—Number of days per month on which normal activities were curtailed because of symptoms of dysmenorrhea (percentage of patients). Eighty percent of patients reported at baseline that their normal activities were curtailed at least 1 day per month. This proportion was 23% during zomepirac treatment and 47% during placebo treatment. (Courtesy of Budoff, P. W.: N. Engl. J. Med. 307:714–719, Sept. 16, 1982.)

scale. For us pediatricians, it would be useful to know how many adolescents were actually enrolled and what the success rate and side effects might have been in this younger age group. The data to support the statement of lack of serious side effects and clinically significant changes in laboratory values (e.g., were stool guiacs performed?) are not included. The conclusion that tolerance doesn't develop is not justified from this short study. These limitations notwithstanding, the study clearly demonstrates superiority of zomepirac over placebo. This is not surprising, as a number of previous studies have shown similar findings of efficacy of prostaglandin inhibitors in dysmenorrhea (Alvin, P. E., and Litt, I. F.: *Pediatrics* 70:516, 1982). Prostaglandins E_2 and $F_2\alpha$ appear to be elevated in those experiencing dysmenorrhea, and their levels are effectively reduced by those agents that prevent their production (acetylsalicylic acid. [Klein, J. R., et al.: *J. Pediatr.* 98:987–990, 1981]) or destroy those produced (zomepirac, sodium naproxen). Choice of a specific prostaglandin inhibitor should be based on rapidity of onset of action, half-life, efficacy, and risks associated with use. A comparison of some of these factors for the commonly prescribed antiprostaglan-

Fig 17–3.—Patients' global evaluations, according to segment. *Z*, zomepirac; *P*, placebo. Zomepirac was evaluated as significantly better than placebo ($P < .001$). Horizontal lines denote excellent, very good, and good in open area of each bar and fair and poor in stippled area of each bar. (Courtesy of Budoff, P. W.: N. Engl. J. Med. 307:714–719, Sept. 16, 1982.)



COMPARISON OF ANTIPROSTAGLANDINS

AGENT GENERIC/BRAND NAME	PLASMA PEAK (HRS)	PLASMA HALF-LIFE (HRS)	RECOMMENDED DAILY DOSE
Fenamates			
Mefanamic acid (Ponstel)	2	6	250–500 mg × 4
Ibuprofen (Motrin)	1–3	3	400 mg × 4 or × 6
Naproxen (Naprosyn)	2–4	13	250 mg × 3 or × 4
Naproxen sodium (Anaprox)	0.5–2	13	275 mg × 4
Aspirin	2	6	600 mg × 4–6
Zomepirac (Zomex)	0.5–2	6	100 mg × 4–6

(Modified from Alvin P., and Litt, I. F.: Pediatrics 70:516, 1982. Copyright American Academy of Pediatrics 1982.)

dins is found in the table. The recent removal of zomepirac from the market due to serious and occasionally fatal presumed hypersensitivity reactions should prompt caution in prescribing not only that specific agent, but the others as well. The cyclooxygenase block caused by antiprostaglandins may potentiate the production of leukotrienes and, hence, may worsen or precipitate asthma. Because oral contraceptives—by preventing ovulation—lower endogenous progesterone levels and by decreasing the amount of endometrial proliferation, decrease prostaglandin production, they also can prevent dysmenorrhea. Those agents should be considered as an alternative to prostaglandin inhibitors, particularly in the sexually active adolescent."] ◀

17–4 **Testicular Volumes of Adolescents** are discussed by William A. Daniel, Jr., Ronald A. Feinstein, Patricia Howard-Peebles, and Wayne D. Baxley. During physical examinations at an ambulatory facility, boys aged 12–19 years (221 black, 127 white) were assigned sex maturity ratings according to the Tanner classification (1962). Separate ratings for genitalia and pubic hair growth and mean values

TESTICULAR VOLUMES IN 348 ADOLESCENTS

*Sex maturity rating**	*Volume (cm³)*	*Left testis*	*Right testis*
1	Mean	4.76	Mean 5.20
	SD	2.76	SD 3.86
2	Mean	6.4	Mean 7.08
	SD	3.16	SD 3.89
3	Mean	14.58	Mean 14.77
	SD	6.54	SD 6.1
4	Mean	19.8	Mean 20.45
	SD	6.17	SD 6.79
5	Mean	28.31	Mean 30.25
	SD	8.52	SD 9.64

*Mean of genital and pubic hair ratinga.

(Courtesy of Daniel, W. A., Jr., et al.: J. Pediatr. 101:1010–1012, December 1982.)

(17–4) J. Pediatr. 101:1010–1012, December 1982.

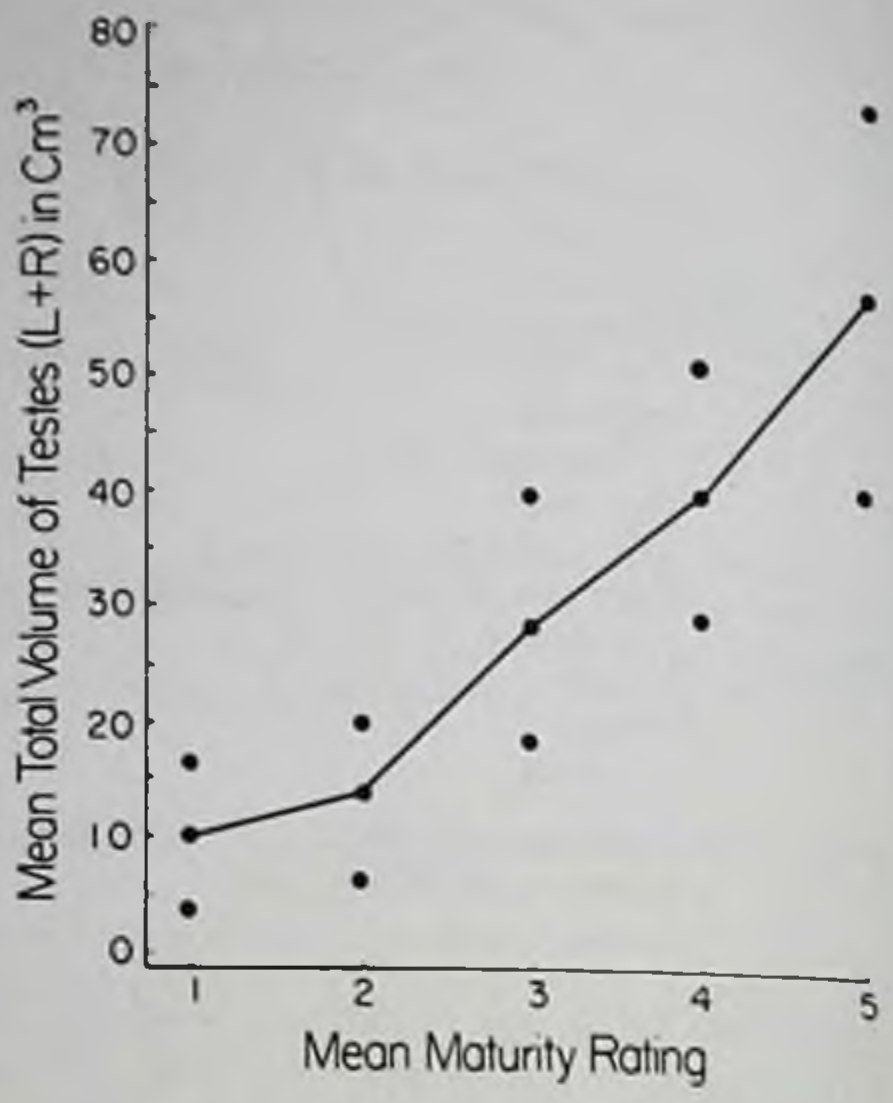


Fig 17–4.—Mean combined testicular volume related to mean sex maturity rating. Dots above and below line indicate 1 SD above and below mean. (Courtesy of Daniel, William A., Jr., et al.: J. Pediatr. 101:1010–1012, December 1982.)

of the combined ratings were recorded. To determine testicular volume, the testis was regarded as an ellipsoid (volume = $\pi/6 \times L \times W^2$ [in cc]).

Testicular volume (table) was more closely correlated with ratings for pubic hair, for genital stage of maturity, and for mean values of the two together than with height, weight, age, race, or any combination thereof. There was no significant difference in testicular volumes between black and white adolescent boys. Testicular volumes of students with less than average intellectual ability and of juvenile offenders fit within the normal range. The mean and 1 standard deviation of combined testicular volumes of right and left testes of the subject sample increased at each mean sex maturity rating (Fig 17–4).

The findings show that concordance of testicular size and volume is highest with sex maturity ratings. Although correlation with maturity ratings for genital stage is slightly greater than that for pubic hair ratings or the mean value of genital plus pubic hair ratings, there is no significant statistical value in using a separate rating.

The fragile X chromosome is a new cytogenetic marker associated with one form of X-linked mental retardation (Turner and Opitz, 1980); macro-orchidism has been reported in most cases. Early diagnosis is valuable, and identification of the syndrome signifies the need for testing and for counseling of possible female carriers. If the syndrome is suspected in an adolescent boy, testicular volumes can be calculated and compared with values for different stages of sexual maturity.

▶ [For "handy use," the table and Figure 17–4 have been reduced to wallet size.—F.A.O.] ◀

17–5 **Factors Associated With Compliance to Oral Contraceptive Use in an Adolescent Population.** Adolescents often do not use con-

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(17–5) J. Adolesc. Health Care 3:120–123, September 1982.

traception effectively. P. W. Scher, S. J. Emans, and E. M. Grace (Harvard Med. School) examined factors in oral contraceptive compliance in 101 subjects aged 13–19 years who selected oral contraception as the first method of prescribed birth control at least 3 months before the study. About half were patients in a comprehensive adolescent unit, and the rest were from an adolescent gynecology clinic. Structured interviews were carried out. The mean age at the time of interview was 18.2 years. About two thirds of the subjects were black.

The mean time since oral contraception had been prescribed was 26.3 months. The subjects tended to recall their initial visit in great detail. Sixty-two percent were classified as compliant. Thirty-four of these patients had been on the pill continuously from the time of the initial visit, for a mean of 18.7 months. Whites appeared to be slightly more compliant than blacks. Active parental involvement

FACTORS RELATED TO CONTRACEPTIVE COMPLIANCE

		Compliant (%)	χ^2 *P* Value
Parent made appointment for visit			
Yes	(15%)	87	4.09
No	(85%)	58	<0.05
Parent accompanied patient to clinic			
Yes	(31%)	81	5.30
No	(69%)	54	<0.05
Parent knew about contraceptives			
Yes	(70%)	65	NS*
No	(30%)	57	
Satisfaction with clinic			
Yes	(87%)	68	7.99
No	(13%)	23	<0.01
Physician considered helpful			
Yes	(80%)	69	6.59
No	(20%)	35	<0.05
Satisfaction with pill as method of contraception			
Yes	(64%)	72	6.53
No	(36%)	44	<0.05
Side effects on pill			
Yes	(76%)	55	7.12
No	(24%)	88	<0.01
Career goals: college bound			
Yes	(35%)	80	6.00
No	(65%)	53	<0.05
Age at oral contraceptive prescription			
13–14	(18%)	72	3.25
15–16	(48%)	53	<0.07
17–19	(34%)	71	
Abortion before oral contraception			
Yes	(27%)	54	NS
No	(73%)	66	

*NS, not significant.

(Courtesy of Scher, P. W., et al.: J. Adolesc. Health Care 3:120–123, September 1982.)

with the initial contraceptive visit was an important factor in compliance (table). The person selecting the type of contraception was not a significant factor. Misgivings about medical sequelae did not significantly influence contraceptive use. Patients who did not have side effects, however, did better. In addition, compliance followed satisfaction with use of the pill as a contraceptive method. Compliant patients who stopped using the pill did so chiefly because of no further need, while noncompliant patients cited side effects and inconvenience as being of primary concern.

Health care providers must reassure adolescent patients about such concerns as weight gain in the course of contraceptive counseling. Written instructions in pill-taking should be provided. Further studies are needed to learn ways of reaching the many adolescents who are not using effective contraception, do not use available health care facilities, or do not have ready access to health care.

► [Andrea Marks, Assistant Professor of Pediatrics, Cornell University Medical College, and Chief, Division of Adolescent Medicine, North Shore University Hospital, and one of our favorite commentators, writes:

"No method of contraception is problem free or always convenient. Compliance with any contraceptive method requires a cognitive and psychological acceptance of one's fertility potential coupled with a firm determination to prevent a pregnancy. In both of these respects, many (but not all!) adolescents are characteristically unaware, uncertain, or ambivalent. Furthermore, the frequency of their sexual activity is often erratic, the timing unpredictable, and the enjoyment derived and comfort felt may be quite marginal.

"Certain findings of this study point to the abivalence many adolescents feel toward their own sexuality, use of birth control, and/or preventing pregnancy. Involvement of a supportive parent and trust in the clinic or physician were factors associated with better compliance, perhaps indicating the importance of adult approval and support of contraception. Better compliance among college-bound and older patients may have resulted from their greater determination to prevent a pregnancy, or an actual wish (perhaps not always fully conscious) among the non-college-bound middle adolescent to become pregnant. In fact, nearly half the noncompliers did become pregnant. Certainly, the reasons given for stopping the pill (e.g., minor medical side effects, 'inconvenient,' and 'ran out') seem a bit like weak excuses compared with the potential consequences of this act.

"The pill generally is touted as the most appropriate and reliable contraceptive for teenagers—the intrauterine contraceptive device exposing the young person to the risk of pelvic infection and possible infertility; the diaphragm requiring too much motivation and planning for most adolescents to use effectively. My colleagues and I are presently studying the relative compliance with and effectiveness of the pill versus the diaphragm in a population of adolescents. It is our hypothesis that the diaphragm is too often overlooked as a reasonable alternative to the pill. Despite its obvious drawbacks, the diaphragm causes virtually no medical side effects, is adaptable to the oftentimes on-again, off-again sexual activity of many teens, and doesn't 'run out.'"] ◄

17–6 **Teenage Mothering, Admission to Hospital, and Accidents During the First Five Years.** Disadvantages for children of teenage mothers continue after birth. Much of the adverse effect associated with low maternal age may be a result of illegitimacy, low socioeconomic status, poor housing and social environment, low educational attainment, lack of support, and inexperience. B. Taylor, J. Wadsworth, and N. R. Butler (Univ. of Bristol) compared health outcomes

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(17–6) Arch. Dis. Child. 58:6–11, January 1983.

in 1,031 singleton children of teenage mothers and 10,950 children of older mothers in the Child Health and Education Study, an ongoing longitudinal cohort study of children born in Great Britain in 1970. A wide range of social, family, and health data was obtained at age 5 years by interviewing the mother at home.

The teenage group was more likely to be socially disadvantaged, to live in a poor urban environment, to have subsequent children, and to be without the natural father when the children were aged 5 years. Hospital admissions were more frequent in the teenage group (Table 1). The relationship held for gastroenteritis but not for lower respiratory tract illness. Accident rates were also higher in children of teenage mothers (Table 2). Types of accident are related to maternal

TABLE 1.—PERCENTAGE OF CHILDREN ADMITTED TO THE HOSTPIAL AT LEAST ONCE DURING THEIR FIRST FIVE YEARS, BY MATERNAL AGE

	Age of mother (years)						
	<18	*18–19*	*20–24*	*25–29*	*30–34*	*≥ 35*	*All ages*
Total number of children	263	768	4368	3805	1837	940	11981
Ever admitted (%)	28·5	29·9	26·4	23·7	23·7	21·2	25·0
After an accident (%)	10·3	8·3	6·5	5·1	4·8	3·9	5·8
Gastroenteritis (%)	4·6	4·3	2·2	2·5	2·7	2·4	2·6
Lower respiratory illness (%)	2·7	4·6	3·7	3·4	2·6	2·3	3·4

(Courtesy of Taylor, B., et al.: Arch. Dis. Child. 58:6–11, January 1983.)

TABLE 2.—PERCENTAGE OF CHILDREN HAVING ANY ACCIDENT, AND PLACE OF ACCIDENT, BY MATERNAL AGE

	Age of mother (years)						
	<18	*18–19*	*20–24*	*25–29*	*30–34*	*≥35*	*All ages*
Total number of children	263	768	4368	3805	1837	940	11981
At least one accident (%)	57·4	49·7	46·0	42·1	40·0	36·6	43·6
2 or more (%)	17·5	16·4	13·6	11·5	10·2	8·4	12·2
Place of accident							
Home (%)	43·0	37·8	35·5	31·8	29·5	24·9	32·9
Outdoors (%)	11·0	9·6	7·2	6·5	6·8	6·4	7·1
Road traffic (%)	2·3	2·3	2·3	1·6	2·0	2·0	2·0
Nursery school (%)	1·9	1·7	1·4	1·7	1·5	1·5	1·6

(Courtesy of Taylor, B., et al.: Arch. Dis. Child. 58:6–11, January 1983.)

TABLE 3.—PERCENTAGE OF CHILDREN FOR EACH TYPE OF ACCIDENT, BY MATERNAL AGE

	Age of mother (years)						
	<18	*18–19*	*20–24*	*25–29*	*30–34*	*≥35*	*All ages*
Total number of children	263	768	4368	3805	1837	940	11981
Poisoning (%)	8·1	9·0	5·4	4·4	3·0	2·4	4·8
Burn (%)	11·4	8·9	6·2	4·9	4·9	5·7	5·8
Superficial injury or laceration (%)	22·8	19·0	17·8	16·6	15·5	13·3	16·9
Head injury (%)	19·4	17·3	17·4	16·2	14·8	12·6	16·3
Fracture or dislocation (%)	9·1	7·4	7·8	5·7	6·6	6·2	6·8
Miscellaneous (%)	5·3	4·8	4·6	4·8	4·2	3·5	4·6

(Courtesy of Taylor, B., et al.: Arch. Dis. Child. 58:6–11, January 1983.)

age in Table 3. All types of accident were likelier in association with teenage mothering, but the differences were significant only for poisoning, burn injury, and superficial injuries of lacerations (Table 4). Factors increasing the risk of two or more accidents in children included a larger family, a teenage mother, a poor urban neighborhood, male sex, and frequent household moves.

Low maternal age, though often a marker for adverse socioeconomic circumstances, is in itself a health hazard for children. Various intervention programs have been instituted in the United States, where the problem is even more important than in Great Britain. Infant outcome is likely to be related closely to the personal develop-

TABLE 4.—TEENAGE (YOUNGER THAN AGE 20) COMPARED WITH OLDER MOTHERING

	Percentage of children		*Significance*
	Teenage mothers	*Older mothers*	
Hospital admissions			
At least once	29·6	24·6	P<0·001
Accidents	8·8	5·5	P<0·001
Gastroenteritis	4·4	2·4	P<0·001
Lower respiratory illness	4·1	3·3	NS
Number of accidents			
At least one	51·7	42·8	P<0·001
2 or more	16·6	12·5	P<0·001
Place of accident			
Home	39·1	32·3	P<0·001
Outdoor	10·0	6·8	P<0·001
Road traffic	2·3	2·0	NS
Nursery school	1·7	1·6	NS
Type of accident			
Poisoning	8·7	4·4	P<0·001
Burn	10·3	5·5	P<0·001
Superficial injuries or lacerations	20·0	16·6	P<0·01
Head injury	17·8	16·1	NS
Fracture or dislocation	7·9	6·7	NS
Miscellaneous	4·9	4·5	NS

(Courtesy of Taylor, B., et al.: Arch. Dis. Child. 58:6–11, January 1983.)

ment of the mother. Programs of prenatal and postnatal social, medical, and educational support for developing parenting skills appear to be necessary to overcome the health difficulties faced by children of young mothers.

▶ [These depressing findings only serve to document what most of us already know. For those who wish to know more about this problem, I would strongly recommend reading the excellent review by Arthur B. Elster, Elizabeth R. McAnarney, and Michael E. Lamb, "Parental Behavior of Adolescent Mothers" (*Pediatrics* 71:494, 1983). This review and the work of Anne Willoughby and associates (*Pediatr. Res.* 17:92A) suggest that adolescent and adult mothers interact differently with their children, and the parenting scores of adolescent mothers are substantially lower than that of older mothers of equal education. The long-term consequences for society may be enormous—Dr. Sol Gordon, from Syracuse University, states that one half of prison inmates in the United States were born to teenage mothers. For a view of the adolescent father, an article by A. B. Elster (*J. Calif. Perinat. Assoc.* 2:44, 1982).—F.A.O.] ◀

17–7 **Comparisons Between Inner-City and Private School Adolescents' Perceptions of Health Problems.** Deborah Klein Walker, Alan W. Cross, Peter W. Heyman, Holly Ruch-Ross, Paul Benson, and John W. G. Tuthill administered a youth health survey questionnaire to 247 students at an inner-city ghetto high school and 404 at a private boarding school. The inner-city sample constituted about 58% of the total school enrollment, whereas the private school sample represented 42% of school enrollment. All but 3% of the former group were from minority populations, whereas 88% of the private school sample were whites.

The private school subjects generally had higher expectations for topics to be included at a health clinic (table). They expressed signifi-

(17–7) J. Adolesc. Health Care 3:82–90, September 1982.

cantly more concern than the urban students for two thirds of topics (Fig 17–5). Sex-related issues were of more concern to the private school youth, and they wanted more help with birth control and with depression-sadness. The inner-city youth had more health concerns

COMPARISON OF PRIVATE AND URBAN HIGH SCHOOL STUDENTS' SELECTION OF TOPICS FOR ADOLESCENT HEALTH CLINIC

	Private school (1978) (n = 404)		Urban school (1978) (n = 247)		Galveston (1976) (n = 3,255)	
Topic for health clinic*	Rank	%	Rank	%	Rank	%
Drugs§	(1)	86.6	(1)	57.5	(1)	66.8
Sex education§	(5)	76.7	(2)	56.7	(2)	58.0
Venereal disease§	(3)	80.9	(4)	42.5	(3)	57.3
Birth control§	(2)	85.1	(5)	41.3	(4)	52.5
Alcohol§	(4)	79.2	(3)	49.8	(5)	50.0
Parent relations§	(6)	55.7	(6)	38.1	(6)	41.4
Child abuse	(11)	40.2	(10.5)	30.0	(7)	40.0
Legal advice‡	(8)	52.0	(7)	36.8	(8)	36.6
Suicide prevention§	(7)	52.2	(8.5)	32.4	(9)	31.0
Adult relations†	(10)	40.8	(10.5)	30.0	(10)	28.8
Peer relations†	(9)	44.8	(8.5)	32.4	(11)	25.8

*Listed in order of importance in Parcel, et al.: Pediatrics 60:157–164, 1977.
†Significant private school-urban school difference $P < .05$.
‡Significant private school-urban school difference $P < .01$.
§Significant private school-urban school difference $P < .001$.
(Courtesy of Walker, D. K., et al: J. Adolesc. Health Care 3:82–90, September 1982.)

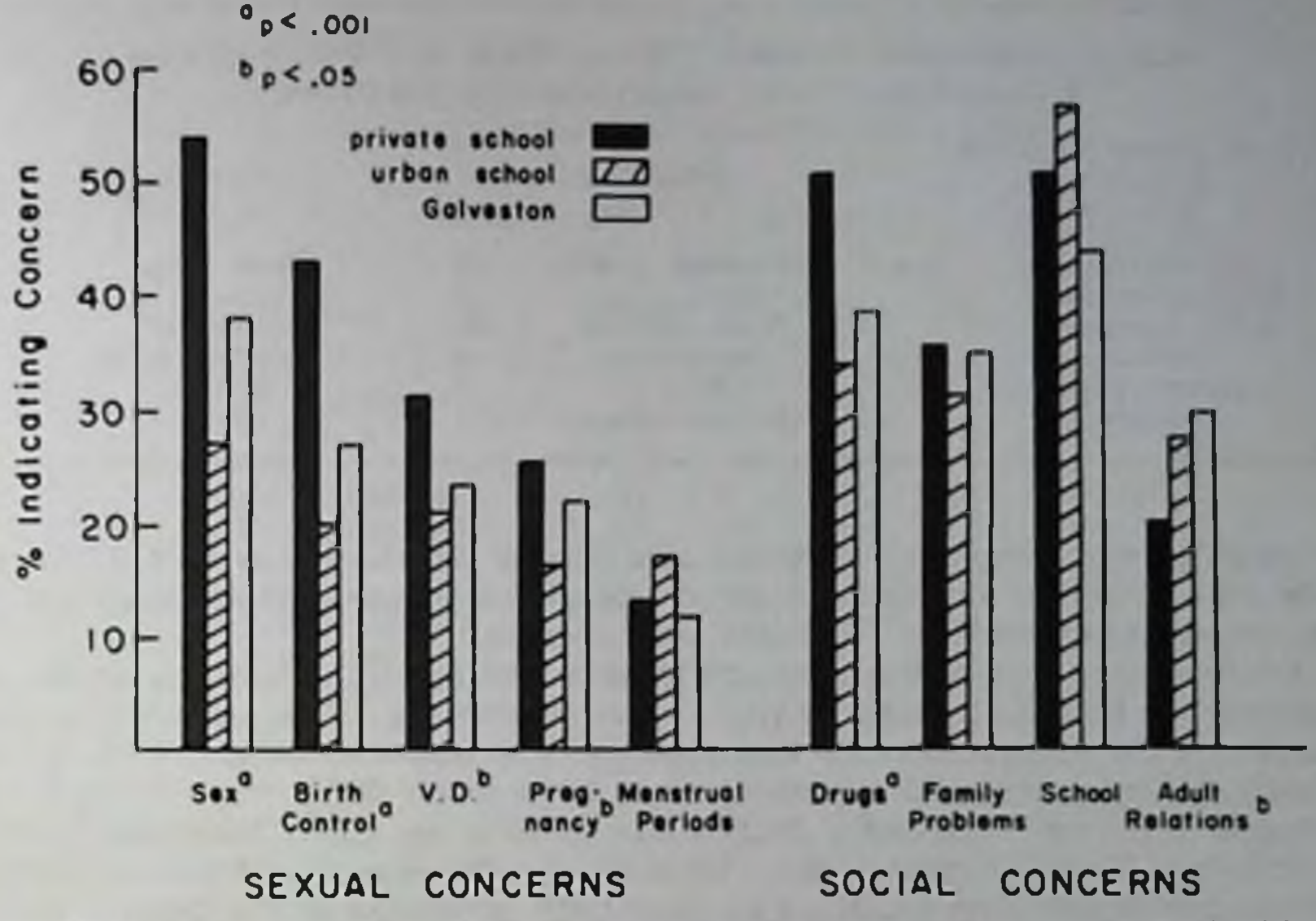

Fig 17–5.—Percentage of private school and urban high school students indicating health concerns, 1978. (Courtesy of Walker, D. K., et al.: J. Adolesc. Health Care 3:82–90, September 1982.)

and indicated a wish for more help with such physical problems as toothaches, headaches, and stomachaches, as well as with social problems such as racial discrimination and parental relations. Most adolescents in both groups perceived large gaps in their health education. About half of all subjects reported sometimes thinking about their health, and fewer than 15% reported hardly ever or never doing so. Over 80% of all subjects considered their health to be very good or pretty good, and only just over 1% as poor.

Adolescents' health concerns are not limited to the popularized issues of sex and drugs. Their perceptions of health status can be used in assessing their service needs. Data on service-use patterns are best interpreted in a local context. Effective adolescent services may be best delivered using a multidisciplinary approach in which traditional medical services are combined with counseling, education, social support, and advocacy efforts.

▶ [Michael I. Cohen, Professor and Chairman, Department of Pediatrics, Albert Einstein College of Medicine, New York, provides us with the following insightful comments:

"Just as morbidity and mortality data for newborns, infants, children, and adults vary among different populations of the same age, it is not surprising to find that over the past 2 decades differing health problems also have been reported among various groups of teenagers. The 40 million Americans in their second decade of live constitute a very heterogenous population. It would be a grievous error to think all age-related populations have some intragroup health problem variation while adolescents represent the singular exception.

"Beyond the obvious intragroup variance among adolescents frequently based on ethnic origin and socioeconomic status, differences also can be appreciated within the same group depending on the health setting in which the patient is seen. The table represents such data derived from three different ambulatory components of our adolescent medicine program at the Einstein/Montefiore complex that demonstrate this latter point. The data represent the percentage of teenagers found to have

HEALTH PROBLEMS (%) OF MINORITY-GROUP URBAN ADOLESCENTS OF LOW SOCIOECONOMIC STATUS BASED ON HEALTH SITE STUDIED

HOSPITAL-BASED AMBULATORY CARE SERVICE N = 18,914		GROUP HOME N = 350		HIGH SCHOOL N = 1250	
Venereal disease	12	Dermatologic problems	80	Dental caries	35
Contraceptive issues	11	Dental caries	55	Infection	7
Health maintenance	9	Vision problems	29	Elevated BP	6
Infection	7	Periodontitis	20	Abnormal urinalysis	5
Dermatologic problems	6	Anemia	5	Murmur	4
Pregnancy	6	Abnormal urinalysis	4	Hernia	2

the recorded problems after physician assessment. Approximately 80% of the patients were black and hispanic surnamed and of low socioeconomic status, yet the problems changed based on the health site surveyed.

"A further extension of the approach to assess intragroup differences among adolescents has been suggested by Walker and co-workers. These authors, however, approached the problem from the less often traveled patient's perspective by utilizing a health survey instrument. A seminal piece of research using this technique with teenagers was first presented a decade ago by Brunswick and Josephson (*Am. J. Public Health* [Suppl.], October 1972). While the results were of considerable interest, and complementary data subsequently have been generated by the National Health Survey, relatively few clinical investigators have made the effort to refine and extend this technique. Walker et al. are to be commended for selecting this not often used patient-mediated approach for studying the issue of intragroup variance among adolescents.

"Perhaps the most important implication of this study is that it points up the value of incorporating teenagers' perceptions of their health needs with knowledge of presumed deficits based on health provider assessments. Too often, health program design is predicated on only the latter. By coupling these two approaches, a more comprehensive program of services for young people should emerge."] ◄

17–8 **Prospective Study of Delinquency in 110 Adolescent Boys With Attention Deficit Disorder and 88 Normal Adolescent Boys.** James H. Satterfield, Christiane M. Hoppe, and Anne M. Schell (California) studied official arrests from childhood through adolescence in 110 boys diagnosed as suffering from attention deficit disorder (ADD) in childhood (Table 1) and in 88 normal control adolescent boys.

Rates of single and multiple serious offenses and of institutionalization (Table 2) for delinquency were significantly higher for ADD subjects. The ADD preceded (in most cases by many years) the serious delinquent behavior.

The poor outcome for drug-treated ADD children in this study is consistent with other studies. The findings suggest a strong relationship between childhood ADD and later arrests for delinquent behavior. The strong relationship between juvenile delinquency and adult arrest suggests that a sizable number of ADD delinquents will become adult offenders. A recently developed multimodality treatment program for ADD children may offer new hope for aborting antisocial behavior and preventing later delinquency and criminality (Satterfield, et al., 1979 and 1981).

► [The authors of this study raise a provocative issue regarding drug treatment of

(17–8) Am. J. Psychiatry 139:795–798, June 1982.

TABLE 1.—SCORES OF 102 ADOLESCENT BOYS WITH ATTENTION DEFICIT DISORDER (ADD) AND 69 NORMAL ADOLESCENT BOYS ON SATTERFIELD TEACHER RATING SCALE*

	Group Score				
	ADD		Controls		
Scale Item	Mean	SD	Mean	SD	t†
Fidgets	2.6	0.7	0.6	0.6	18.9
Easily distracted	2.5	0.7	0.8	0.8	14.4
Restless	2.5	0.7	0.7	0.7	16.5
Talks a lot	2.4	0.8	0.8	0.8	12.9
Bothers children	2.3	0.7	0.5	0.6	17.0
Can't concentrate	2.3	0.8	0.4	0.7	15.5
Demands much attention	2.3	0.9	0.3	0.6	17.1
Disrupts the class	2.3	0.8	0.4	0.6	16.6
Doesn't finish assignments	2.2	0.9	0.5	0.8	12.6
Leaves projects unfinished	2.2	1.0	0.4	0.6	14.3
Says things without thinking	2.2	0.9	0.4	0.5	16.8
Clowns around	2.1	0.9	0.5	0.7	13.1
Doesn't follow directions	2.1	0.9	0.5	0.7	13.6
Hard to discipline	2.0	1.0	0.1	0.4	16.8
Acts silly	1.9	1.1	0.4	0.6	11.2
Does everything in a hurry	1.9	1.1	0.6	0.7	9.5
Fights	1.9	1.1	0.2	0.5	13.0
Doesn't do homework	1.8	1.1	0.3	0.6	10.2
Easily frustrated	1.8	1.1	0.4	0.7	10.6
Doesn't take responsibility	1.7	1.0	0.3	0.5	11.5
Easily upset	1.7	1.0	0.4	0.7	10.2
Unpopular with peers	1.7	1.1	0.1	0.4	13.5
Irritable, quick tempered	1.6	1.1	0.2	0.5	10.6
Uncooperative and resistant	1.6	1.0	0.1	0.3	13.3
Lacks leadership	1.5	1.1	0.5	0.8	6.8
Daydreams	1.4	1.0	0.6	0.8	5.2
Not interested in school	1.4	1.1	0.2	0.6	8.5
Falls apart under stress	1.3	1.0	0.3	0.5	8.3
Feels disliked	1.3	1.1	0.1	0.4	13.5
Lies to get out of trouble	1.2	1.1	0.1	0.2	10.4
Feels like a failure in school	1.0	1.1	0.1	0.4	7.3
Rude or sassy	1.0	1.0	0.1	0.3	8.5
Steals	0.8	1.0	0.1	0.2	7.1
Fearful	0.7	0.8	0.5	0.6	2.3
Overly serious or sad	0.6	0.9	0.4	0.7	2.1
Shy	0.5	0.9	0.7	0.9	0.7

*0 = not at all; 1 = just a little; 2 = pretty much; 3 = very much.

†The ADD group scored significantly higher on all scale items except "shy" ($P < .05$ on "fearful" and "overly serious or sad," $P < .001$ on all other items).

(Courtesy of Satterfield, J. H., et al.: Am. J. Psychiatry 139:795–798, June 1982.)

the child with attention deficit disorder (ADD). They state, "An important question for physicians to consider is whether stimulant medication alone results in more harm than benefit to the child and his family, since it may convince the parents that the child is receiving adequate treatment and divert attention from the need for treatment aimed at other associated disabilities such as poor peer relationships, poor self-image, antisocial behavior, and learning disabilities." For a rosier view of the long-term

TABLE 2.—INSTITUTIONAL PATTERNS FOR 110 ADOLESCENT BOYS WITH ATTENTION DEFICIT DISORDER (ADD) AND 88 CONTROL ADOLESCENT BOYS

	ADD Group		Controls	
Institution	N	%	N	%
Juvenile hall	22	20	1	1
Probation camp	12	11	0	
Residential group home	9	8	0	
Prison or jail	2	2	0	
Psychiatric hospital	8	7	0	
Total	27*	25	1	1

*Other numbers total more than 27 because some subjects had been in more than 1 type of institution. Six had been in 1 type of institution, 17 in 2 types, 3 in 3 types, and 1 in 4 types.

(Courtesy of Satterfield, J. H., et al.: Am. J. Psychiatry 139:795–798, June 1982.)

follow-up of children with this problem see the 1980 YEAR BOOK (pp. 341–343). By the way, it may be wise to soft-pedal the term "ADD" for this disturbance for a while—it is too easy for the parents to confuse it with AIDS. You will end up with the whole family being hyperactive if this confusion occurs.—F.A.O.] ◀

17–9 **Bulimia in the Adolescent.** Bulimia, a recently acknowledged psychiatric diagnosis, is characterized by binge-eating episodes followed by sleep, vomiting, abdominal pain, or use of laxatives or diuretics (Table 1). Although the onset of bulimic behavior appears to occur in the teenage years, most patients with the syndrome are first seen for treatment after age 20. David B. Herzog (Harvard Med. School) reports clinical and demographic data from the first 8 bulimic adolescents (all women) seen at an outpatient eating disorders unit. The criteria used to diagnose primary affective illness and alcoholism in first-order family members are shown in Table 2. Demographic data for 51 female patients seen at the same unit are shown in Table 3.

The syndrome of bulimia should be distinguished from the symptom of binging and purging. Many anorectic patients exhibit bulimia

TABLE 1.—*DMS-III* DIAGNOSTIC CRITERIA FOR BULIMIA

Recurrent episodes of binge eating
At least three of the following:
- Consumption of high-caloric, easily ingested food during a binge
- Termination of binge by abdominal pain, sleep, or self-induced vomiting
- Inconspicuous eating during binge
- Repeated attempts to lose weight by fasting or use of laxatives or diuretics
- Frequent weight fluctuations of greater than 4.5 kg
- Awareness of abnormal eating pattern and fear of not being able to stop eating voluntarily

Depressed mood after binge
Not due to anorexia nervosa or any physical disorder

(Courtesy of Herzog, D. B.: Am. J. Dis. Child. 136:985–989, November 1982; copyright 1982, American Medical Association.)

(17–9) Am. J. Dis. Child. 136:985–989, November 1982.

TABLE 2.—FAMILY HISTORY-RESEARCH DIAGNOSTIC CRITERIA*

Depressive disorder
Evidence of a dysphoric mood change to either of the following:
- Depressive mood
- Other dysphoric mood (eg, anxious, irritable, or worried state)

At least one of the following:
- Electroconvulsive therapy or known antidepressant medication
- Hospitalization
- Suicidal behavior
- Treatment for either depressive or other dysphoric mood
- Gross impairment in work, housework, or school, or social withdrawal
- Four of the following associated symptoms:
  - Loss of interest
  - Appetite or weight change
  - Sleep change
  - Loss of energy
  - Psychomotor agitation or retardation
  - Guilt or self-reproach
  - Impaired concentration

Not accounted for by a chronic physical condition
Minimum duration of two weeks
Not due to schizoaffective disorder

Alcoholism
Drinking problem not limited to isolated incidents
At least one alcohol-related problem in the following areas:
- Legal problem (eg, public intoxication, disorderly conduct, traffic violations)
- Health problem (eg, cirrhosis, delirium tremens, blackouts)
- Marital or family problems
- Impairment in work, housework, or school
- Treatment for alcoholism or attendance at Alcoholics Anonymous
- Social problems, fights, loss of friends

*Developed to enable researchers to diagnose psychiatric illnesses in relatives of study subjects when direct examination of relatives is impossible. If the informant is among relatives about whom information is desired, he or she is asked about himself or herself as well.

(Courtesy of Herzog, D. B.: Am. J. Dis. Child. 136:985–989, November 1982; copyright 1982, American Medical Association.)

as a prominent symptom, and it is included as an associated feature in the diagnostic criteria for anorexia nervosa (Table 4). The bulimic patient tends to be preoccupied with eating and its control, but the anorectic patient is primarily obsessed with weight. The bulimic is of average or slightly above average weight and menstruates. The anorectic tends to be brought for treatment, but the bulimic is distressed by her symptoms and tends to seek help.

The associated preoccupation with food and binging preparation frequently interfere with relationships, activities, and sometimes school performance. A relationship between bulimia and depressive illness (Table 5) may exist. Bulimia is expensive, and some bulimics reported stealing food. Parents reported an inability to keep sufficient food in the home for family or guests. Most of the sample exhibited an outgoing nature on mental status examination. Physical complications included hypokalemia and alopecia. There are reports of parotid enlargement and acute gastric dilatation; the surreptitious vomiter can be diagnosed by erosion of dental enamel.

The frequently chronic course and physical consequences make di-

TABLE 3.—DEMOGRAPHIC DATA ON FEMALE BULIMIC PATIENTS SEEN AT EATING DISORDERS UNIT, MASSACHUSETTS GENERAL HOSPITAL, JULY-OCTOBER 1981.

	No. (%) of Patients		No. (%) of Patients
Race			
White	51 (100)	Age at onset, yr	
Religion*		Range	11-40
Catholic	12 (48)	Mean	18.4
Jewish	10 (40)	Median	19
Protestant	3 (12)	Family history	
Family income*		Alcoholism and primary affective illness	7 (14)
>$45,000	9 (30)	Primary affective illness	10 (20)
$22,000-$45,000	9 (30)	Alcoholism	11 (22)
$14,000-$22,000	7 (23)	Obesity	14 (27)
$8,500-$14,000	2 (7)	Parent with chronic illness	21 (41)
<$8,500	3 (10)		
Age, yr			
Range	14-43		
Mean	24.6		
Median	23		

*Percentages refer only to patients who completed religion and family income questions.
(Courtesy of Herzog, D. B.: Am. J. Dis. Child. 136:985–989, November 1982; copyright 1982, American Medical Association.)

TABLE 4.–*DMS-III* DIAGNOSTIC CRITERIA FOR ANOREXIA NERVOSA

Refusal to maintain minimal normal body weight
Weight loss of at least 25% of original body weight
Disturbance of body image
Intense fear of becoming obese
No known physical illness that would account for the weight loss

(Courtesy of Herzog, D. B.: Am. J. Dis. Child. 136:985–989, November 1982; copyright 1982, American Medical Association.)

TABLE 5.—*DSM-III* DIAGNOSTIC CRITERIA FOR DEPRESSION

Must be present:
Dysphoric mood
At least four must be present:
Poor appetite or weight loss, or increased appetite or weight gain
Sleeping difficulty or sleeping too much
Loss of energy
Psychomotor agitation or retardation
Loss of interest or pleasure in usual activities
Diminished ability to concentrate
Feeling of self-reproach or excessive guilt
Recurrent thoughts of death or suicide

(Courtesy of Herzog, D. B.: Am. J. Dis. Child. 136:985–989, November 1982; copyright 1982, American Medical Association.)

agnosis and early intervention necessary. Treatment should be individualized. Group therapy and antidepressant drugs are often beneficial.

17–10 **Social Placement of Adolescents: Sex Role Influences on Family Decisions Regarding the Careers of Youth.** Contempo-

(17–10) J. Marriage Fam. 44:647–658, August 1982.

rary families influence the placement and social status of their offspring by providing various levels of support for career advancement. Gary W. Peterson, Boyd C. Rollins, Darwin L. Thomas, and L. Kay Heaps sought to determine whether families tend to make decisions providing differential support of the career goals of male and female offspring. A total of 183 families were studied in a simulation game designed for families to plan the career goals of adolescent children. Ninety-six families had both a male and a female adolescent. The daughter was older in 47 families and the son in 49. The other families had either 2 male or 2 female adolescents. A modification of the Simulation of Career Patterns game was used.

The results are given in Tables 1 to 3. Family decisions appeared to favor the career goals of adolescent boys over those of girls 4:1. This difference remained significant after analyses for the effects of ordinal position, religious preference of the parents and religiosity, education of the father, father's income, mother's employment status, and whether the daughter desired an occupational or a home-making career. Daughters appeared to be about equally divided in choosing an occupational or a home-making career. Fathers preferred a domestic goal for their daughters more than the adolescent girls chose it for themselves. Fewer of the families with more-educated mothers deferred the objectives of daughters in favor of those of their sons.

Social placement decisions by families in this study strongly favored the career advancement of adolescent boys over that of girls. The findings are consistent with other work indicating that sex role divisions within families remain traditional. The pervasive and persistent nature of traditional sex role expectations is evident, although

TABLE 1.—ADOLESCENTS COMPENSATED FOR PREVIOUS DEFERRAL OF CAREER IN CROSS-SEX FAMILIES*

	Males		Females		Total	
Family Decision	*N*	%	*N*	%	*N*	%
Received compensation	18	95%	36	51%	54	60%
Did not receive compensation	1	5%	35	49%	36	40%
Total	19	100%	71	100%	90	100%

*χ^2 = 12.11; 1 *df*; $P < .001$; Cramer's contingency coefficient = .37; N = 90.

(Courtesy of Peterson, G. W., et al.: J. Marriage Fam. 44:647–658, August 1982.)

TABLE 2.—ADOLESCENTS RECEIVING CAREER PREFERENCE CONTROLLING FOR OCCUPATIONAL VS. DOMESTIC GOALS*

	Adolescent Receiving Preference					
	Males		Females		Total	
Goal	*N*	%	*N*	%	*N*	%
Female with occupational career	35	74%	12	26%	47	51%
Female with homemaking career	39	85%	7	15%	46	49%
Total	74	80%	19	20%	93	100%

*χ^2 = 1.55, 1 *df*, ns.

(Courtesy of Peterson, G. W., et al.: J. Marriage Fam. 44:647–658, August 1982.)

TABLE 3.—Comparison of Male vs. Female Adolescent Career Attainment in Cross-Sex Families*

Outcome	Males N	Males %	Females N	Females %
Attained goal	64	69%	40	43%
Did not attain goal	29	31%	53	57%
Total	93	100%	93	100%

*$\chi^2 = 12.56$; 1 *df*; $P < .001$; Cramer's contingency coefficient = .26.

(Courtesy of Peterson, G. W., et al.: J. Marriage Fam. 44:647–658, August 1982.)

there are impending challenges to this means of structuring relations.

► [Is it reassuring or discouraging to learn that "traditional beliefs" still remain with us? Have you seen the apron that reads, " 'Working Mothers' is Redundant"?—F.A.O.] ◄

18. Therapeutics and Toxicology

18–1 **Acetaminophen Poisoning in Infancy.** Acetaminophen is widely used in children of all ages to relieve fever and pain. Severe hepatotoxicity from overdose is common in adolescents and adults, but infants have a relatively low degree of liver damage. John W. Greene, Lisa Craft, and Fayez Ghishan (Nashville, Tenn.) report data on 2 very young infants in whom significant hepatotoxicity with hypoglycemia and coma developed after long-term acetaminophen administration. Although neither infant was reported to have received a potentially toxic dose, toxic drug levels were present in both of them.

A female infant, aged 7 weeks, was seen with extreme lethargy and poor peripheral perfusion after having received 0.3 ml of acetaminophen drops every 4–5 hours for 6–8 days. Severe hypoglycemia and elevated liver enzymes were found. The plasma acetaminophen level was 10.7 mg/L about 54 hours after the last known dose. The infant did well after being stabilized on glucose. A male infant aged 6 weeks had similar findings after having received both acetaminophen drops and Tylenol. The blood drug level was 119 mg/L. Acetylcysteine and glucose therapy was followed by rapid improvement and complete recovery.

Acetaminophen is a safe antipyretic-analgesic for use by children when given in appropriate doses. The present infants, however, reportedly received amounts not usually associated with toxicity. Dosage miscalculation and inadvertent overdosage are possible explanations. Both infants initially had hypothermia, an altered neurologic status, and laboratory evidence of significant hepatotoxicity. Neurologic status and liver function subsequently improved rapidly, suggesting a transient process. Acetaminophen overdosage should be considered in infants and children presenting with acute hepatotoxicity. Further consumer education efforts may be needed. Up to 300 preparations contain acetaminophen, each with a different brand name, and most of the names do not indicate that acetaminophen is included.

▶ [The clinical appearance and course of these infants were similar to those in previous reports of acetaminophen overdosage in young children (Piperno, E., et al.: *Pediatrics* 62[Suppl.]:880, 1978; and Rumack, R. H., et al.: ibid., pp. 898). Hypothermia, alterations in neurologic status, and laboratory evidence of hepatic dysfunction are the clues. This combination of findings mimics Reye's syndrome, metabolic liver disease, or sepsis.

You no doubt are aware that the formulation for Tylenol Elixir has been changed. The formulation is now 160 mg/5 ml instead of the previous 120 mg/5 ml. The half-time for plasma elimination is about 1.7 hours in the older child, but may be considerably longer in the neonate.

Parents should be made aware that Tempra and Tylenol are both acetaminophen

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(18–1) Am. J. Dis. Child. 137:386–387, April 1983.

preparations. In 1 of the 2 patients described above, both products had been given, one for irritability and the other for fever. It would seem prudent to avoid acetaminophen in young infants. They will get plenty of opportunities to take it later.

For a scholarly exposition on both aspirin and acetaminophen, take a look at "Efficacy, Disposition, and Pharmacodynamics of Aspirin, Acetaminophen, and Choline Salicylate in Young Febrile Children," by J. T. Wilson et al. (*Ther. Drug Monit.* 4:147, 1982).—F.A.O.] ◄

18–2 **Acetaminophen and Aspirin: Prescription, Use, and Accidental Ingestion Among Children.** Allen A. Mitchell, Frederick H. Lovejoy, Jr., Dennis Slone, and Samuel Shapiro (Boston) report on the Pediatric Drug Surveillance Program designed to identify and characterize both known and previously unsuspected adverse drug reactions among hospitalized children. Among 3,587 hospitalized children monitored between 1974 and 1979, infants aged 12 months or younger made up half of the population, whereas children aged 15 years or older made up 8%. The most common discharge diagnoses were respiratory infection (15%), prematurity (11%), cancer (10%), otitis media (7%), convulsions (7%), respiratory distress syndrome (6%) and asthma (6%).

Acetaminophen was prescribed for 1,158 (32%) of the study population, making it the fourth most commonly prescribed drug; aspirin was prescribed for 120 (3%) patients, and ranked 60th. Fever was the most frequent indication for prescription of each drug, followed by pain. Arthritis accounted for 11% of aspirin use. Prescriptions for each drug were minimal among newborns, peaked among children aged 1–5, and then declined.

Acetaminophen and aspirin were each used by 23% of the patients during the 3 months prior to admission. Fever accounted for 68% of acetaminophen use and for 59% of aspirin use (Table 1).

Included in the present report are data from the Massachusetts Poison Information Center that responds to acute overdose emergencies

TABLE 1.—INDICATIONS FOR PREADMISSION USE OF ACETAMINOPHEN AND ASPIRIN AMONG 3,487 HOSPITALIZED CHILDREN*

Indication	No. (%) Using Acetaminophen	No. (%) Using Aspirin
Fever	545 (68)	478 (59)
Headache, pain, arthritis	236 (30)	311 (39)
Other	16 (2)	17 (2)
Total	**797 (100)**	**806 (100)**

*Excludes 100 children with unknown medication histories.

(Courtesy of Mitchell, A. A., et al.: Am. J. Dis. Child. 136:976–979, November 1982; copyright 1982, American Medical Association.)

TABLE 2.—PREADMISSION USE OF ACETAMINOPHEN AND ASPIRIN FOR FEVER AND PAIN AMONG 3,487 HOSPITALIZED CHILDREN,* BY AGE

	Age					
	≤30 Days	1-11 mo	1-5 yr	6-10 yr	11-15 yr	16+ yr
Fever						
Acetaminophen	0.4†	25	29	12	9	6
Aspirin	0.4	16	33	5	5	0
Pain						
Acetaminophen	0	0.4	5	14	22	16
Aspirin	0	0.7	7	21	27	30

*Excludes 100 patients with unknown medication histories.

†Expressed as percent of patients of a given age who used the drug for the indication given. Percentages are to one decimal place for values less than 1.0. Denominators by increasing age categories are 852, 909, 765, 337, 349, 275.

(Courtesy of Mitchell, A. A., et al.: Am. J. Dis. Child. 136:976–979, November 1982; copyright 1982, American Medical Association.)

TABLE 3.—CALLS TO MASSACHUSETTS POISON INFORMATION CENTER FOR ALL INGESTIONS AND FOR INGESTIONS OF ACETAMINOPHEN AND ASPIRIN FROM 1976 TO 1978

	No. (%) of Calls		
	1976-1977	1977-1978	Increase
All calls	18,205	24,487	6,282(34)
Aspirin	558	761	203(36)
Acetaminophen	216	403	187(87)

(Courtesy of Mitchell, A. A., et al.: Am. J. Dis. Child. 136:976–979, November 1982; copyright 1982, American Medical Association.)

throughout that state. Aspirin and acetaminophen were the first and third most frequently ingested drugs, respectively. In the 1976–1977 period, 774 calls concerning exposure to either acetaminophen or aspirin were received; the comparable period in 1977–1978 showed 1,164 calls (Table 2). Reported ingestions for both drugs were most frequent among children younger than age 6 years.

The study confirmed the increased use of acetaminophen in the pediatric population between 1975 and 1977. This may be due to availability of this drug in liquid form (in contrast to aspirin) that is simpler to administer to children. With wider availability also came more frequent accidental ingestion (Table 3). The decline in the 1978–1979 period in the use of both aspirin and acetaminophen may be due to the concerns about the risks of aspirin therapy coupled with the more recent concerns about hepatotoxic effects of acetaminophen in overdose.

18–3 **Relative Severity of Acute Versus Chronic Salicylate Poisoning in Children: Clinical Comparison.** Aspirin remains one of the leading causes of drug-related poisoning in children. The more severe cases may be associated with chronic aspirin administration. Pierre

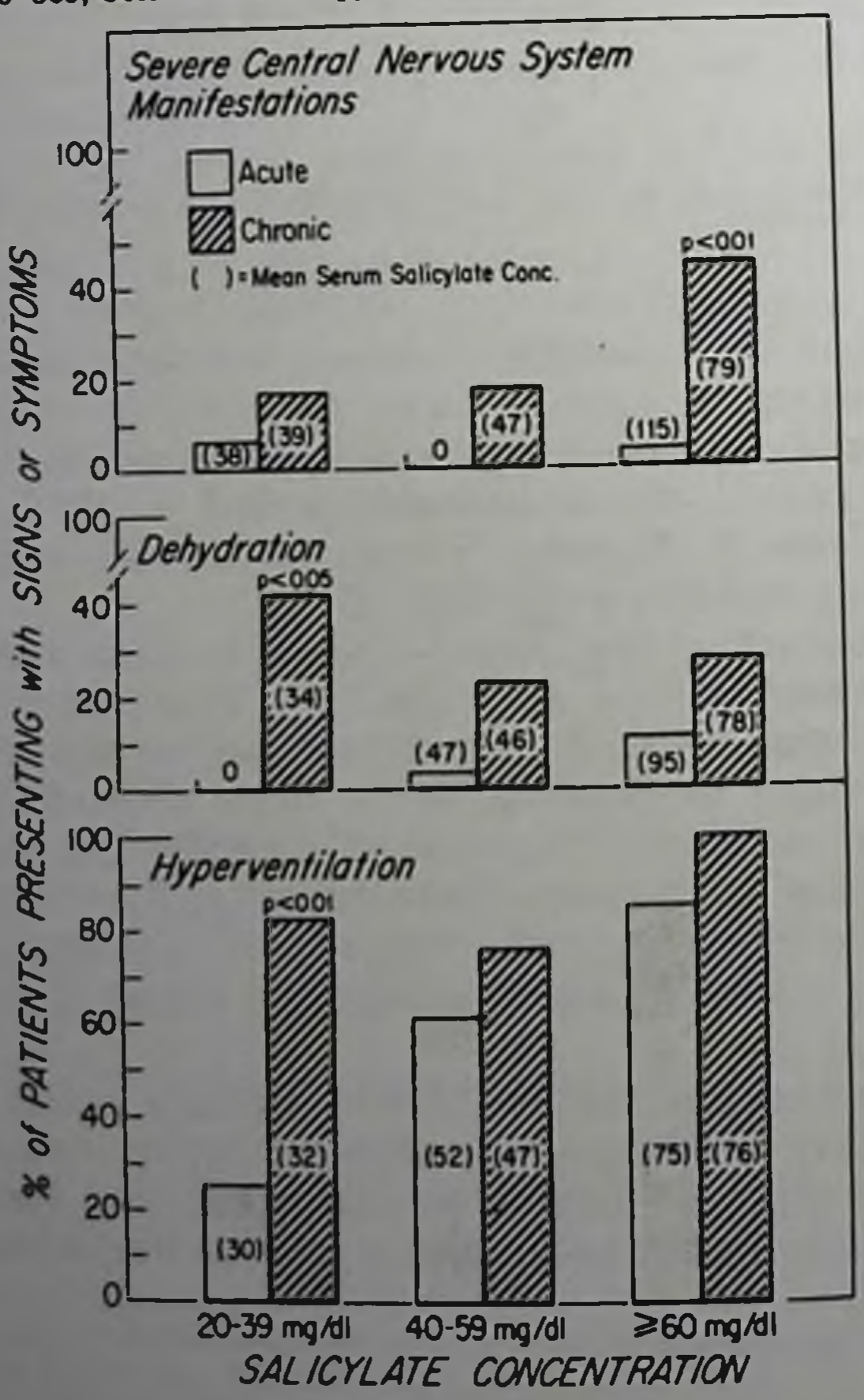
(18–3) Pediatrics 70:566–569, October 1982.

TABLE 1.—FREQUENCY OF FIVE MAJOR CLINICAL SIGNS OR SYMPTOMS IN ACUTE AND CHRONIC GROUPS

Signs or Symptoms	Acute Group (N = 65)		Chronic Group (N = 47)		*P* Value
	No.	%	No.	%	
Hyperventilation	41	63	43	91	<.01
Nausea and/or vomiting	39	60	22	47	NS
Dehydration	3	5	14	30	<.001
Mild CNS manifestations (lethargy/disorientation)	19	29	15	32	NS
Severe CNS manifestations (coma and/or seizures)	2	3	13	28	<.001

(Courtesy of Gaudreault, P., et al.: Pediatrics 70:566–569, October 1982. Copyright American Academy of Pediatrics 1982.)

Fig 18–1.—Frequency of three major clinical signs or symptoms in acute and chronic poisoning groups at three serum salicylate concentration ranges. Numbers in parentheses represent mean concentrations. Only statistically significant *P* values are indicated. (Courtesy of Gaudreault, P., et al.: Pediatrics 70:566–569, October 1982. Copyright American Academy of Pediatrics 1982.)



Gaudreault, Anthony R. Temple, and Frederick H. Lovejoy, Jr. reviewed 65 acute and 47 chronic cases of salicylate poisoning in children seen in 1967–1978. The criterion was an initial salicylate concentration of 20 mg/dl or above. Chronic cases involved repeated administration of therapeutic or excessive doses of salicylate for medical disease over more than 12 hours. The most common indications for treatment were viral upper respiratory tract infection and gastroenteritis. One fourth of acute cases were suicide gestures or attempts.

Acute accidental patients had a mean age of 2½ years, whereas chronic patients had a mean age of 3½ years. The frequency of major clinical features in the two groups is given in Table 1. Little difference was found when patients whose illness might confound the results were excluded. Hyperventilation, dehydration, and severe CNS signs tended to occur more often in chronic cases (Fig 18–1). Severe

TABLE 2.—SEVERITY OF SALICYLATE POISONING BASED ON COMBINATION OF SIGNS AND SYMPTOMS IN ACUTE AND CHRONIC GROUPS

Degree of Severity	Acute Group (N = 65)*		Chronic Group (N = 47)		Mean Serum Salicylate Concentration (mg/100 ml)	
	No.	%	No.	%	Acute Group	Chronic Group
Mild	34	68	16	32	56	53
Moderate	21	54	18	46	56	47
Severe	2	13	13	87	76	65

*Eight patients in the acute group were asymptomatic.

(Courtesy of Gaudreault, P., et al.: Pediatrics 70:566–569, October 1982. Copyright American Academy of Pediatrics 1982.)

TABLE 3.—FREQUENCY OF FIVE MAJOR CLINICAL SIGNS OR SYMPTOMS IN PATIENTS WITH OR WITHOUT ACIDOSIS

Signs or Symptoms	No Acidosis (N = 42)		Acidosis (N = 20)		*P* Value
	No.	%	No.	%	
Hyperventilation	28	67	17	85	NS
Nausea and/or vomiting	24	57	12	60	NS
Dehydration	2	5	7	35	<.01
Mild CNS manifestations (lethargy/disorientation)	14	33	5	25	NS
Severe CNS manifestations (coma and/or seizures)	3	7	6	30	<.05

(Courtesy of Gaudreault, P., et al.: Pediatrics 70:566–569, October 1982. Copyright American Academy of Pediatrics 1982.)

salicylate poisoning was more frequent in the chronic group (Table 2). Acidosis appeared to contribute to increased toxicity in the chronic group (Table 3). The prothrombin time was prolonged in 6 of 13 acute, and in 8 of 10 chronic patients. Only 1 of 11 acute patients had a serum glutamic oxaloacetic transaminase elevation, compared with 9 of 13 chronic patients without juvenile rheumatoid arthritis or Reye's syndrome.

Chronic salicylate poisoning tends to be more severe than acute poisoning. Patients must be warned of the potential risks of chronic salicylate administration. Chronic salicylate poisoning is nearly as frequent as acute poisoning in a hospital population. Decreased oral intake, dehydration, and acidosis all can increase the risk of toxicity.

▶ [Dr. Alan K. Done, Professor of Pediatrics and Pharmacology, Wayne State University, provided us with the following comment:

"With safety packaging, limitations on doses provided by packages of flavored-aspirin preparations, etc., acute accidental ingestions have, comparatively speaking, almost disappeared as causes of severe morbidity or mortality from salicylate poisoning, so we are now seeing a disproportionate number of chronic cases. Not only are these more severe, as demonstrated so nicely by the authors, but they are far more difficult to treat, and since the salicylate level doesn't help—unless, of course, it is very high—evaluation must be based almost entirely on clinical manifestations such as those described in this study.

The mean ages of 3½ and 2½ years, respectively, for the chronic and the acute poisoning groups give a somewhat distorted notion because the chronic group included a smattering of cases at upper age levels. The patients with a chronic case are characteristically younger, as well as sicker, and in this study they were almost a year younger in median age. In more recent years (the study covered the period 1967–1978), the trend undoubtedly has been for more of these babies to receive acetaminophen preparations instead, since they can be given as flavored liquids. Whether this will prove to be the blessing we earlier had thought remains to be seen, now that the same kind of saturation kinetics as obtained with salicylate have been found for acetaminophen in sick youngsters.

Along these lines, it has long been claimed, with little or no evidence to back it up, that saturation kinetics allow aspirin to accumulate to toxic levels even if recommended therapeutic doses are not exceeded. Unfortunately, the present study does not address this question directly. It is of interest, however, that the alleged chronic doses, always taken (if not literally) with a grain of salt, were 32–230 mg/kg/day, with a median of 119. With the present dose recommendation being about 60 mg/kg/day, this would suggest that with most of these patients, parents admitted giving overdoses."] ◀

18–4 **Evaluation of Regional and Nonregional Poison Centers.** Dennis F. Thompson, Harold L. Trammel, Nancy J. Robertson, and J. Routt Reigart attempted to determine whether regional poison centers manage a particular poisoning situation better than nonregional centers. A case involving salicylate ingestion by a child aged 3 years was presented twice, once at daytime and once at night, to each of 15 regional and 15 nonregional poison centers. The questions deemed necessary for an appropriate history are listed in Table 1.

The regional centers consistently obtained more historical information than the nonregional centers and were more proficient in obtaining necessary information. Both types of center collected inadequate information on symptoms. The results are shown in Figure 18–2. Treatment was recommended in 93% of the calls to regional cen-

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(18–4) N. Engl. J. Med. 308:191–194, Jan. 27, 1983.

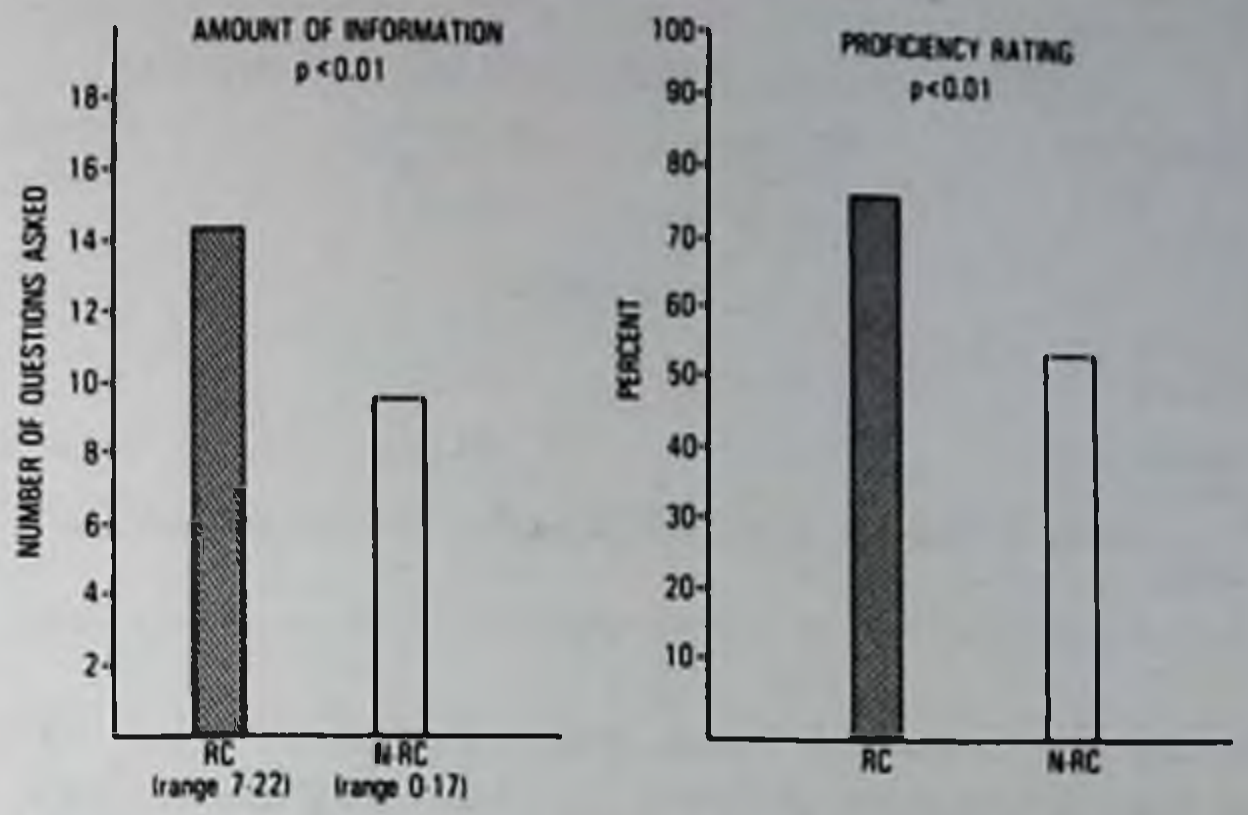

Fig 18–2.—Comparison of history obtained by regional poison centers *(RC)* and by nonregional poison centers *(N-RC)*. (Courtesy of Thompson, D. F., et al.: N. Engl. J. Med. 308:191–194, Jan. 27, 1983.)

ters but in only 67% of calls to nonregional centers (Table 2). The risk of obtaining incorrect treatment information from a nonregional center was 9 times greater than that from a regional center (Table 3). Follow-up procedures were instituted more often in calls to regional centers. Both types of center obtained less historical information from nighttime than from daytime calls, and indications of follow-up were less frequent at night than during the day.

Regional poison centers appear to provide better and more consis-

TABLE 1.—NECESSARY QUESTIONS AS DETERMINED BY DELPHI TECHNIQUE

1. Has someone ingested the product?
2. How long has it been since ingestion?
3. How old is the patient?
4. How much does the patient weigh?
5. How many tablets were ingested?
6. What is the patient's or caller's telephone number?
7. Does the patient have any symptoms?
8. Do you have syrup of ipecac?

(Courtesy of Thompson, D. F., et al.: N. Engl. J. Med. 308:191–194, Jan. 27, 1983.)

TABLE 2.—TREATMENT RECOMMENDATIONS

RECOMMENDATION	REGIONAL POISON CENTERS	NONREGIONAL POISON CENTERS
	no. of calls (%)	
Treatment	28 (93.3)	20 (66.7)
No treatment	2 (6.7)	4 (13.3)
No decision	0 (0)	6 (20)

(Courtesy of Thompson, D. F., et al.: N. Engl. J. Med. 308:191–194, Jan. 27, 1983.)

TABLE 3.—OVERALL MANAGEMENT OF THE POISONING

MANAGEMENT	REGIONAL POISON CENTERS	NONREGIONAL POISON CENTERS	RELATIVE RISK
	no. of calls (%)		
Correct	28 (93.3)	12 (40)	
Incorrect	2 (6.7)	18 (60)	18/2 = 9

(Courtesy of Thompson, D. F., et al.: N. Engl. J. Med. 308:191–194, Jan. 27, 1983.)

tent poisoning information than nonregional centers. The findings support the regionalization process in poisoning care. Both the health care community and the public can be expected to benefit from continued regionalization of this service.

18–5 **National Estimates of Blood Lead Levels: United States, 1976–1980: Association With Selected Demographic and Socioeconomic Factors.** Kathryn R. Mahaffey, Joseph L. Annest, Jean Roberts, and Robert S. Murphy reviewed data from the second National Health and Nutrition Examination Survey. A total of 27,801 persons from 64 sampling areas were selected as being representative of the US civilian population aged 6 months through 74 years.

Mean blood lead concentrations by race and age are shown in Figure 18–3. A total of 22% of subjects had blood lead concentrations less than 10 μg/dl, whereas 1.9% had values of 30 μg/dl or above. Concentrations were elevated in 4% of children aged 6 months through 5 years. The prevalences of elevated values were 12.2% in black children and 2% in white children. Higher blood lead concentrations were found in blacks among both children and adults, among

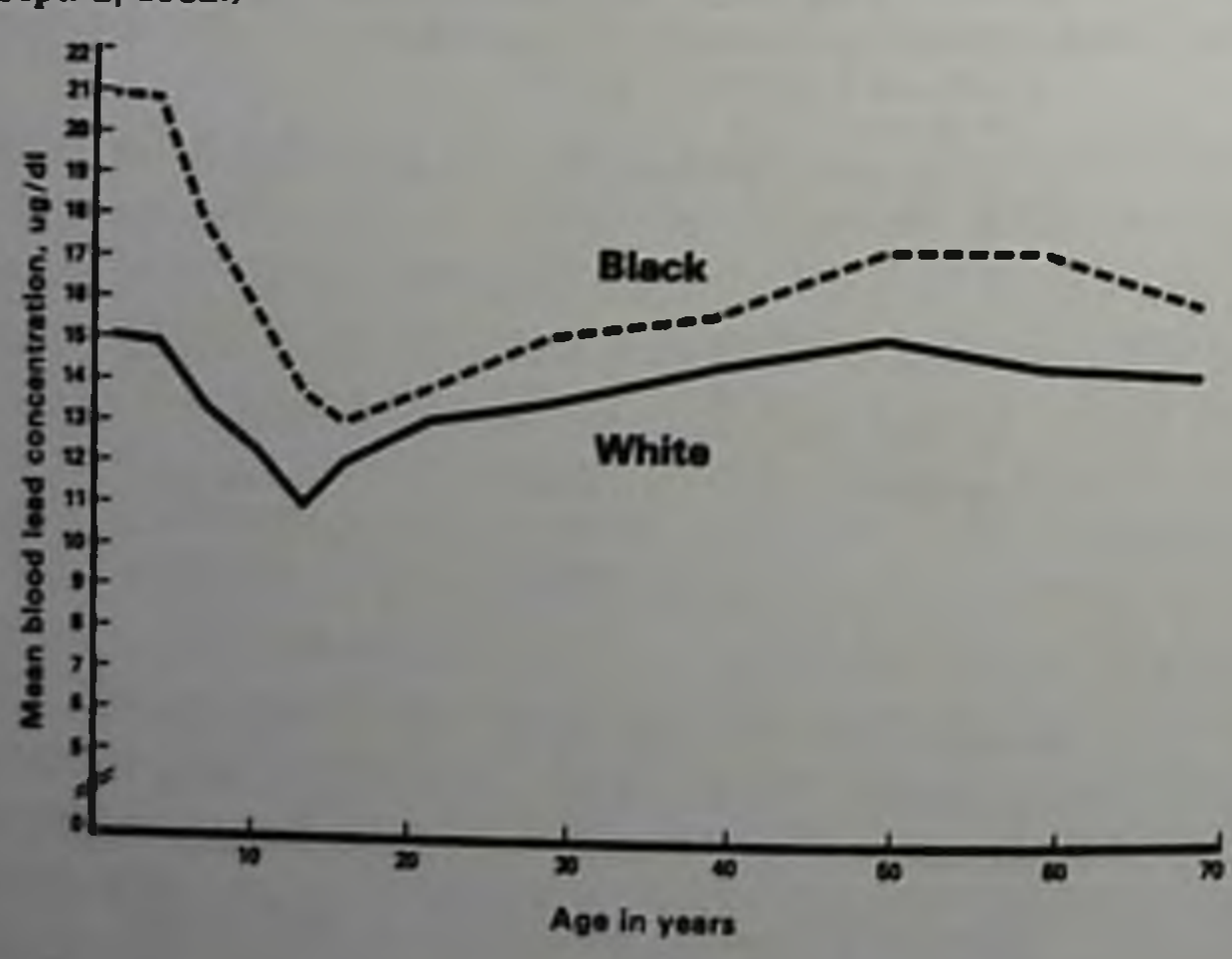

Fig 18–3.—Blood lead concentrations by race and age in the United States according to second National Health and Nutrition Examination Survey, 1976 to 1980. To convert blood lead values to micromoles per liter, multiply by 0.04826. (Courtesy of Mahaffey, K. R., et al.: N. Engl. J. Med. 307:573–579, Sept. 2, 1982.)

(18–5) N. Engl. J. Med. 307:573–579, Sept. 2, 1982.

TABLE 1.—Blood Lead Concentrations by Race and Age in the United States, 1976 to 1980

Race and Age	Estimated Population	No. of Persons Examined †	Mean Blood Lead Level ‡	Median Blood Lead Level	Blood Lead Level (μg/dl)						
					<10	10–19	20–29	30–39	40–49	50–59	60–69
	thousands*		μg/dl		% distribution						
White											
6 mo–2 yr	6186	589	15.0±0.56	14.0	16.1	64.1	17.3	2.2	0.0	0.2	0.0
3–5 yr	7455	1287	14.9±0.41	14.0	13.6	69.1	15.4	1.6	0.1	0.0	0.0
Black											
6 mo–2 yr	1164	141	20.9±0.96	19.0	0.3	50.2	34.2	13.0	1.4	0.5	0.4
3–5 yr	1421	278	20.8±0.55	20.0	3.8	42.5	43.3	8.5	1.4	0.5	0.0

*Estimated population at midpoint of second National Health and Nutrition Examination Survey, Mar. 1, 1978.
†With lead determinations from blood specimens obtained by venipuncture.
‡Means ± SEM. To convert blood lead values to micromoles per liter, multiply by 0.04826.
(Courtesy of Mahaffey, K. R., et al.: N. Engl. J. Med. 307:573–579, Sept. 2, 1982.)

young children in urban and rural areas, and among members of low- to higher-income families (Tables 1 and 2). Young children from families with incomes less than $6,000, both white and black, had a higher prevalence of elevated lead concentrations than those from households with higher incomes.

TABLE 2.—Blood Lead Concentrations in Children Aged 6 Months Through 5 Years by Annual Family Income and Degree of Urbanization of Place of Residence in the United States, 1976 to 1980

Demographic Variable	All Races *			White			Black			Prevalence of Blood Lead Levels >30 μg/dl ‡		
	Estimated Population †	No. of Persons Examined	Blood Lead ‡	Estimated Population †	No. of Persons Examined	Blood Lead ‡	Estimated Population †	No. of Persons Examined	Blood Lead ‡	All Races *	White	Black §
	thousands *		*μg/dl*	*thousands* *		*μg/dl*	*thousands*		*μg/dl*	*% of persons examined*		
Annual family income ¶												
<$6,000	2465	448	20.0±0.6	1408	256	18.1±0.6	917	176	22.9±0.9	10.9±1.4	5.9±1.3	18.5±3.6
$6,000–14,999	7534	1083	16.2±0.5	6252	887	15.3±0.5	1037	163	20.7±0.6	4.2±0.7	2.2±0.5	12.1±1.9
>$15,000	6428	774	14.1±0.4	5707	690	13.7±0.4	502	60	17.2±0.8	1.2±0.4	0.7±0.3	2.8±1.2
Degree of urbanization												
Urban ≥1,000,000 persons ‖	4344	544	18.0±0.5	3112	358	16.6±0.6	1093	172	22.2±0.8	7.2±0.7	4.0±0.7	15.2±1.5
Central cities	1822	286	20.0±0.7	885	133	17.4±0.8	855	143	23.1±1.3	11.6±1.9	4.5±1.9	18.6±2.8
Non-central cities	2519	257	16.5±0.6	2223	224	16.2±0.6	238	29	19.2±0.7	3.7±0.8	3.8±0.8	3.3±1.4 **
Urban <1,000,000 persons	6891	944	16.5±0.7	5297	699	15.4±0.7	1246	205	20.3±0.8	3.5±0.6	1.6±0.4	10.2±2.4
Rural	5627	884	13.9±0.6	5233	819	13.5±0.6	245	42	18.3±2.6	2.1±0.9	1.2±0.5	10.3±5.3 **

*Includes data for races not shown separately.

†Estimated at midpoint of second National Health and Nutrition Examination Survey, Mar. 1, 1978.

‡Means ± SEM. To convert blood lead values to micromoles per liter, multiply by 0.04826.

§One child (black boy with family income less than $6,000, living in rural area, with blood lead conc. of 76 μg/dl) was excluded. This exclusion had negligible effect on national estimates shown here.

¶All values shown for this variable reflect exclusion (from analysis and tests for significance) of children in households that declined to report their income.

‖A child not specified as living in either central or noncentral city was included in calculation of values shown for this entry, but was excluded from calculation of values shown for central and noncentral cities.

**Fewer than 50 persons in sample cell.

(Courtesy of Mahaffey, K. R., et al.: N. Engl. J. Med. 307:573–579, Sept. 2, 1982.)

Racial differences in blood concentrations may reflect differences in lead exposure, absorption, or both. Estimates of the prevalence of elevated blood lead concentrations in the general population are useful in a variety of health assessment and planning programs. Large numbers of persons with elevated blood lead concentrations are unde-

tected, particularly among preschool black children from low-income households.

▶ [Dr. Herbert L. Needleman, Associate Professor of Psychiatry and Pediatrics, University of Pittsburgh, provided the following comment:

"Many myths surround the problem of lead poisoning, and they die hard. Two badly wounded by this careful epidemiologic study are, first, that lead exposure affects only minority children in the inner city, and second, that with the banning of lead from newly processed household paint, the disease has become rare. Cases of lead encephalopathy have become relatively hard to find, but lesser forms of toxicity are disturbingly common. Mahaffey and her colleagues show here that 4% of American children of all races and stations of life have elevated blood lead concentrations. It is also clear that being poor or black carries an increased risk of bearing an elevated lead burden. Poor white children have 9 times the incidence of overexposure than their more fortunate peers, and poor blacks have an incidence 3 times greater than poor whites. Lead is associated with, and multiplies, the many assaults on central nervous system development that accompany being poor.

"Household paint has, since 1975, contained less than 0.06% lead. But many homes have paint over 50 years old on their walls. Automobile emissions continue to be an important source. Lead in gasoline has been shown to contribute as much as 25% to an individual's body burden (Faschetti et al.: *Status Report*, CEC Joint Research Center 1983). As sales of alkyl lead have decreased, blood lead levels have dropped in close correlation (Rabinowitz and Needleman: *Lancet* 1:63, Jan. 8, 1983). The second National Health and Nutrition Examination Survey indicates that 600,000 children in the United States younger than age 5 years have hazardous amounts of lead in their bodies. A number of recent reports (Needleman et al.: *N. Engl. J. Med.* 300:689, 1979; Yule et al.: *Dev. Med. Child. Neurol.* 23:567, 1982; and Winneke et al. *Int. Arch. Occup. Environ. Health* 51:169, 1982) have shown psychological deficits due to low-level exposure to the metal. Whether small amounts of lead are injurious to children's brains no longer deserves prolonged and debilitating debate. The technical means to make this man-made disease almost as rare as smallpox are currently available. It is only a matter of translating that knowledge into action."

For those of you interested in reading more by Doctor Needleman about this subject, see "The Epidemiology of Low-Level Lead Exposure in Childhood," by H. L. Needleman and D. C. Bellinger (*J. Am. Acad. Child Psychiatry* 20:496, 1981).—F.A.O.] ◀

18–6 **Prolonged Seizures Associated With the Use of Viscous Lidocaine.** Peter Rothstein, Jeffrey Dornbusch, and Bennett A. Shaywitz (Yale Univ.) report 2 cases of prolonged seizures after the prescribed use of 2% viscous lidocaine in children.

Girl, 3½ years, with inspiratory stridor from croup, was given 2 doses of about 300 mg of lidocaine each at a 4-hour interval, and had a tonic-clonic seizure 10 minutes after the second dose. Phenobarbital and phenytoin were administered. The child awoke about 10 hours after the seizure and had normal neurologic findings. An EEG obtained 5 weeks later showed one episode of spike-and-wave activity.

Boy, 15 months, was given 0.5 teaspoon of 2% viscous lidocaine 4–5 times daily for nearly a week for upper respiratory tract infection. A generalized seizure occurred, and seizures recurred despite diazepam administration. The concentration of lidocaine in venous blood taken 2 hours after the last dose of lidocaine was 4.9 μg/ml; cerebrospinal fluid obtained at the same time contained 2.6 μg/ml.

Viscous lidocaine is absorbed from the mucosa of the mouth, pharynx, and esophagus, as well as from the gut. Central nervous system toxicity has been reported with blood lidocaine levels of 5–10 μg/ml, and may occur with lower levels when the monoethylglycinexylidide

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(18–6) J. Pediatr. 101:461–463, September 1982.

concentration is elevated. The first of the present patients was given the recommended adult dose, and the second received repeated doses of about 6 mg/kg of body weight. The total single dose of viscous lidocaine in children probably should not exceed 5 mg/kg. It should be used only for direct application to an oropharyngeal lesion and should not be given as a drink. Infants should not receive the drug. Pharyngitis and croup are not indications for its use. Aspiration is a possible side effect from anesthesia of the entire oropharynx. Seizures induced by local anesthetic should be treated with diazepam or an ultrashort-acting barbiturate such as thiopental. To avoid hypoxemia, seizures should be terminated even if apnea ensues.

▶ [R. I. Sakai and J. E. Lattin (*Am. J. Dis. Child.* 134:323, 1980) have previously reported another example of seizures associated with the use of viscous lidocaine. Be careful. The author's recommendation that dosing not exceed 5 mg/kg seems reasonable—remember that a single tablespoon of lidocaine HCl contains 300 mg, which is enough for the mythical 60-kg man. I guess it is time to return to the use of popsicles or topical antihistamine preparations to reduce discomfort in children with severe gingivostomatitis.—F.A.O.] ◀

18–7 **Gasping Syndrome and Benzyl Alcohol Poisoning.** Benzyl alcohol is commonly used as an antibacterial agent in a variety of formulations intended for intravenous administration. Juan Gershanik, Betty Boecler, Harry Ensley, Sharon McCloskey, and William George (New Orleans) report that 10 premature infants developed clinical syndromes characterized by deterioration of multiple organ systems and eventual death believed to be the result of benzyl alcohol poisoning.

All infants originally presented with respiratory distress requiring mechanical ventilation and umbilical arterial catheterization for frequent blood gas analysis. They received multiple injections of heparinized bacteriostatic sodium chloride for flushing the catheters and medications reconstituted with bacteriostatic water, both containing 0.9% benzyl alcohol. The infants then followed a typical course: gradual neurologic deterioration (hypoactivity, hypotonia, depression of the sensorium, apnea, seizure activity, coma), severe metabolic acidosis, striking onset of gasping respiration, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, and cardiovascular collapse. Extensive workup and postmortem findings failed to reveal any recognized cause. Eight infants had EEGs that showed very low voltage and severely abnormal electrical activity.

Infants with the gasping syndrome received average daily quantities of benzyl alcohol, in the form of bacteriostatic sodium chloride and bacteriostatic water, of 99–234 mg/kg of body weight before onset of gasping (table). A matched control group (8 infants who received solutions containing benzyl alcohol as a preservative but did not have the gasping syndrome) received average daily quantities of benzyl alcohol of 27–99 mg/kg over the same period. In comparing the time to onset of gasping in selected infants with gasping syndrome with daily dosages of 0.9% benzyl alcohol, a significant correlation coefficient of

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(18–7) N. Engl. J. Med. 307:1384–1388, Nov. 25, 1982.

INTAKE OF BENZYL ALCOHOL, AGE AT ONSET OF GASPING, AND AGE AT DEATH

INFANTS WITH GASPING SYNDROME			AGE AT ONSET OF GASPING (DAYS)	AGE AT DEATH (DAYS)	MATCHED CONTROL INFANTS		
CASE NO.	AVERAGE DAILY INTAKE OF 0.9% BENZYL ALCOHOL BEFORE ONSET OF GASPING				CONTROL NO.	AVERAGE DAILY INTAKE OF 0.9% BENZYL ALCOHOL OVER SAME PERIOD AS MATCHED INFANT WITH GASPING SYNDROME	
	ml/kg/day	*mg of benzyl alcohol/kg/day*				*ml/kg/day*	*mg of benzyl alcohol/kg/day*
1 †	16	144	16	22	§	§	§
2 †	26	234	2	19	§	§	§
3 ‡	14	126	28	31	3	4	36
4	18	162	9	11	4	6	54
5	17	153	19	23	5	3	27
6	23	207	5	12	6	10	90
7	19	171	3	6	7	11	99
8 †	15	135	9	23	8	5	45
9 †	12	108	7	14	9	8	72
10 †	11	99	13	46	10	4	36
Means	17	153	11	21		6	54

†Both blood and urine specimens were available.
‡Only blood specimen was available.
§No suitable matched control was available.
(Courtesy of Ensley, H., et al.: N. Engl. J. Med. 307:1384–1388, Nov. 25, 1982.)

–0.83 was determined, suggesting a definite relation between intake of benzyl alcohol and time to onset of gasping.

Blood from 6 infants with gasping syndrome showed benzyl alcohol levels of 0.610–1.378 mmole/L. Urine samples from 5 infants with gasping syndrome contained significantly higher levels of benzoic and hippuric acid (breakdown products of benzyl alcohol) than samples of infants not exposed to benzyl alcohol preparations.

Since discontinuing use of bacteriostatic sodium chloride and bacteriostatic water, no further cases of gasping syndrome have been seen; there has been no increase in incidence of sepsis or meningitis. The experience suggests that the addition of benzyl alcohol to preparations given to infants must be reassessed.

► [W. J. Brown and associates have described 10 additional examples of the "gasping syndrome" in Portland, Oregon (*Lancet* 1:1250, 1982). All 10 of these fatalities occurred in infants weighing less than 1,250 gm. All of the infants had at least one centrally placed catheter that was flushed periodically with bacteriostatic saline containing benzyl alcohol (9 mg/ml). Before the onset of obvious symptoms, the infants had developed an initially unexplained progressive metabolic acidosis. In retrospect, the acidosis was a result of accumulation of benzoic and hippuric acid in the blood and caused the "anion gap" acidosis.—F.A.O.] ◄

18–8 **Pharmacologic Interactions Among Chloramphenicol, Phenytoin, and Phenobarbital** were studied by Keith Krasinski, Helen Kusmiesz, and John D. Nelson (Univ. of Texas, Dallas) to delin-

(18–8) Pediatr. Infect. Dis. 1:232–235, July 1982.

SERUM PHARMACOKINETIC MEASUREMENTS OF BIOACTIVE CHLORAMPHENICOL IN 29 PATIENTS

	Serum Concentration (μg/ml)		Serum Half-life (hours)	AUC[a] (μg × hours/ml)	VD (ml/kg)
	Peak	Trough			
Chloramphenicol only ($n = 17$)					
Mean	25.3	13.4	3.6	93.9	1592
Range	10.4–50	<2–18	0.5–12.8	102–178	306–4997
SD	8.7	6.0	2.8	41.1	1245
SE	2.11	1.47	0.7	11.3	3716
Chloramphenicol and phenobarbital ($n = 6$)					
Mean	16.6	7.5	3.3	53.3	2364
Range	10.2–22	2.3–9.4	2.2–6.4	30–109	1418–3136
SD	5.2	3.4	1.5	30.3	647
SE	2.3	1.38	0.64	12.4	264
Chloramphenicol and phenytoin ($n = 6$)					
Mean	41.7	26.5	4.1	108.3	1475
Range	28–57	8.5–36.5	2.1–5.5	50–167	803–2877
SD	10.15	9.0	1.50	42.9	725
SE	4.14	3.7	0.6	17.5	296

[a]AUC indicates area under time-concentration curve; VD indicates volume of distribution.
(Courtesy of Krasinski, K., et al.: Pediatr. Infect. Dis. 1:232–235, July 1982.)

eate the extent of alterations in the pharmacokinetics of chloramphenicol in patients who are also receiving anticonvulsant drugs. Phenytoin may inhibit chloramphenicol metabolism, whereas phenobarbital, by induction of hepatic microsomal enzymes, may accelerate the conjugation of chloramphenicol.

Bioactive chloramphenicol was measured in the serums of 34 infants and children receiving intravenous chloramphenicol succinate (25 mg/kg/dose) as treatment for meningitis, pneumonia, brain abcess, or Rocky Mountain spotted fever. The agar well diffusion method of Bannatyne and Cheung (1979) was used to gauge chloramphenicol levels. Subtherapeutic levels were defined as peak serum concentrations of less than 10 μg/ml. Potentially toxic levels were defined as peak serum concentrations greater than 25 μg/ml.

Peak and trough serum concentrations as well as apparent serum half-life, area-under-the-time-concentration curve, and apparent volume of distribution determined for 29 patients are shown in the table. In 17 children receiving chloramphenicol succinate alone, mean peak and trough serum concentrations of chloramphenicol were 25.3 and 13.4 μg/ml, respectively. Concurrent administration of chloramphenicol succinate and phenobarbital in 6 patients resulted in reduced peak and trough concentrations of chloramphenicol of 16.6 and 7.5 μg/ml, respectively ($P < .05$). Concurrent administration of chloramphenicol succinate and phenytoin in 6 patients resulted in an elevated mean peak serum concentration of chloramphenicol of 41.7 μg/ml ($P < .05$). Five other patients treated with phenytoin had indeterminate serum chloramphenicol half-life values with chloramphenicol concentrations of 29–90 μg/ml. Potentially toxic chloramphenicol concentrations occurred in 9 of 17 controls, in none of 6 patients who had received phenobarbital ($P = .001$), and in 11 of 11 patients who had received phenytoin ($P = .008$). Patients receiving combined chloramphenicol succinate and anticonvulsant therapy require monitoring of serum concentrations of the drugs and adjustments in the amount of chloramphenicol succinate given.

▶ [These reported interactions of chloramphenicol with phenytoin and phenobarbital are not new, but deserve retelling in view of the resurgence in the use of chloramphenicol. Some of these drug interactions were reviewed in the 1983 YEAR BOOK (pp. 438–440). Patients receiving both phenytoin and chloramphenicol may have toxic levels of both drugs. In contrast, the simultaneous use of phenobarbital and chloramphenicol may result in subtherapeutic levels of the antibiotic.

Patients with renal or hepatic dysfunction or patients with vascular instability may rapidly become overdosed with chloramphenicol. R. T. Brown (*J. Adolesc. Health Care* 3:53, 1982) describes a 16-year-old girl with Rocky Mountain spotted fever who developed the "gray syndrome" as a result of chloramphenicol toxicity. For those who have had the good fortune never to have encountered this syndrome, first described in infants but now reported in older children (Graft, A. W., et al.: *Arch. Dis. Child.* 49:235, 1974) and adults (Thompson, W. L., et al.: *JAMA* 234:149, 1975), it consists of peripheral vascular insufficiency, metabolic acidosis, and encephalopathy. Monitor drug levels in patients with hepatic dysfunction, renal dysfunction, and in shocklike states. Monitor drug levels in patients receiving chloramphenicol in early infancy and when the drug is given in combination with other agents for which interactions have not been determined.

On the brighter side, chloramphenicol was reported to produce a response in a child with chronic neutropenia. H. A. Pearson and E. A. Adams termed this "A Clinical Paradox" (*Pediatr. Res.* 17:240A, 1983), and rightfully so. On three separate occa-

sions, this 15-year-old with chronic neutropenia displayed a rise in the neutrophil count 8 to 10 days after receiving the drug for the treatment of pyoderma. The patient, at the time of the report, had received chloramphenicol therapy for 6 months, maintained a normal white blood cell count, and been free of previous infections. Swords do cut both ways.—F.A.O.] ◀

19. Miscellaneous

19–1 **Detection of Clubbing—Schamroth's Sign: Closing the Window and Opening the Angle.** Clubbing is an important clinical sign because it is associated with chronic pulmonary conditions and congenital cyanotic heart disease. Schamroth (1976) noticed that by placing together the dorsal surfaces of the terminal phalanges of similar fingers, assessment of occult clubbing was facilitated. Richard M. Lampe and Arnold Kagan (Baylor College of Medicine) report that this sign is also useful in pediatric patients.

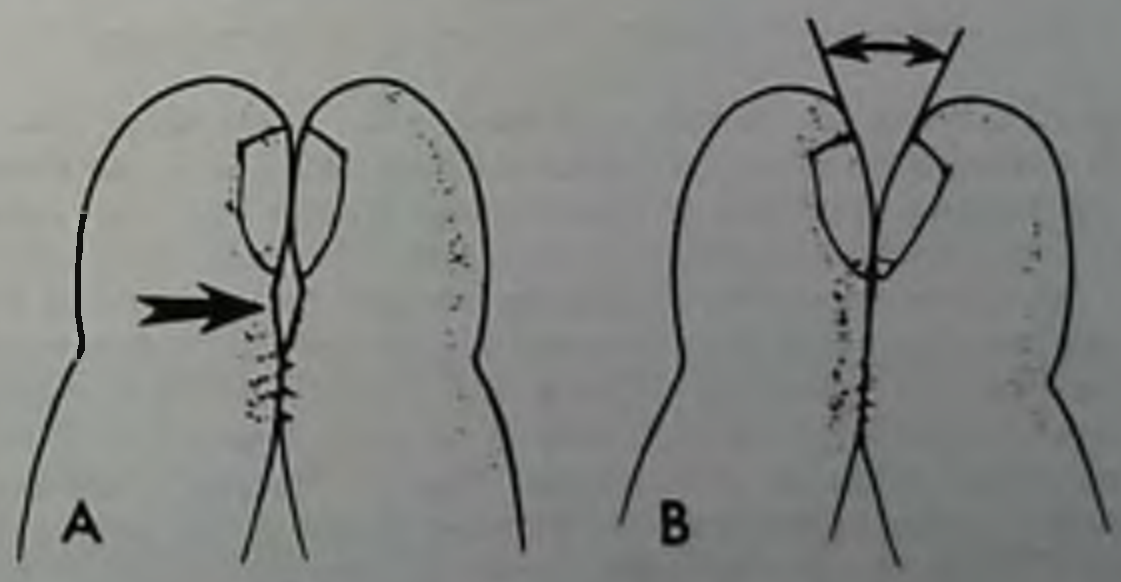
A boy, aged 4 years, with repeated pulmonary infections, a persistent left lower lobe infiltrate, and a diagnosis of bronchiectasis showed both loss of the normal diamond-shaped window at the base of the nailbed and a prominent distal angle between the ends of the nail (Fig 19–1).

Schamroth noticed that obliteration of the window was one of the earliest signs of clubbing associated with a case of endocarditis, and that the window reappeared 2 months after the infection had been controlled, whereas the prominent distal angle was still present 8 months after control of the endocarditis. The frequency, duration, and reversibility of the window and angle signs in children are unknown.

▶ [Shamrocks to Schamroth! This is a clever little test that, quite frankly, I have never heard about. Schamroth first published his observation in the *South African Medical Journal* in 1976 (50:297). "Closing the window" is an easy sign to elicit and is certainly more useful than playing "This little piggy went to market" with a patient's toes.—F.A.O.] ◀

19–2 **Diagnostic Index for Down's Syndrome.** A. P. Rex and M. Preus (McGill Univ., Montreal) ranked 24 characters (table) according to discriminative efficiency and relative frequency in patients with and without trisomy 21 (Down's syndrome). The percentage discrimina-

Fig 19–1.—Normal patient (A) and clubbed patient (B), illustrating loss of window *(single arrow)* and prominent distal angle *(double arrow)*. (Courtesy of Lampe, R. M., and Kagan, A.: Clin. Pediatr. (Phila.) 22:125, February 1983.)



(19–1) Clin. Pediatr. (Phila.) 22:125, February 1983.
(19–2) J. Pediatr. 100:903–906, June 1982.

CHARACTERS RANKED ACCORDING TO THEIR DISCRIMINATIVE EFFICIENCY AND POWER

	Sample size	
	Down	*Non-Down*
1. Hallucal pattern	301	298
2. Digit 2 pattern	662	607
3. Height of palmar triradius	300	291
4. Ear length	139	21
5. Wide-spaced 1st toe	150	66
6. Internipple distance	46	20
7. Brushfield spots	165	71
8. Excess neck fat pad	104	52
9. Digit 5 pattern	660	607
10. Fifth digit crease	305	104
11. Flat occiput	104	59
12. Head circumference	85	49
13. Tone	129	66
14. Digit 3 pattern	662	607
15. Interdigital 3 pattern	298	286
16. Thenar pattern	592	586
17. Digit 4 pattern	660	607
18. Flat face	111	63
19. Fissure slant	150	66
20. Palm width/length	50	26
21. Fontanelle size	64	39
22. Height	87	34
23. Palmar crease	299	100
24. Digit 1 pattern	657	607

(Courtesy of Rex, A. P., and Preus, M.: J. Pediatr. 100:903–906, June 1982.)

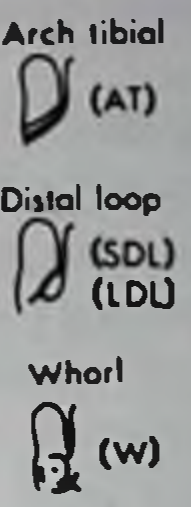
tion between subjects with Down's syndrome and those who did not have it reached a plateau at 8 phenotypic findings (Fig 19–2), which were used to develop an effective diagnostic index for this syndrome. The 8 features in the index include 3 dermatoglyphic traits (hallucal

Fig 19–2.—Diagnostic index for Down's syndrome. A 5× magnifying lens with light (or an otoscope) is needed for observation of dermal patterns (characters 1 to 3) and Brushfield spots; short rule calibrated in centimeters is needed to measure ear length; and tape measure is needed to measure internipple distance and chest circumference. Instructions: (1) Hallucal area—covers tibial area of ball of foot. Dermal ridges are counted along straight line connecting triradius to pattern core. However, estimation of small or large can usually be made without counting ridges. SDL = small distal loop (less than 21 ridges); LDL = large distal loop (equal to or greater than 21 ridges). (2) Digits 2 (forefinger)—if dermal pattern on both is an ulnar loop, circle "UU." If one forefinger (right or left) has whorl and other an arch, circle "WA." (3) Palmar triradius—mark position of highest palmar triradius and measure distance between it and distal wrist crease (h = height). Measure palm length (l) from crease to proximal crease at base of digit 3; "h" is then expressed as ratio of 1 (h/l). It is often clear without measurement that h is greater than or less than 0.40. (4) Internipple distance (character 6)—measure with tape from center of nipples at rest and express as ratio of chest circumference. Scoring: Circle one score in each of the eight groups. The eight scores

Circle one score in each of the 8 groups:

1. Hallucal area of the foot:

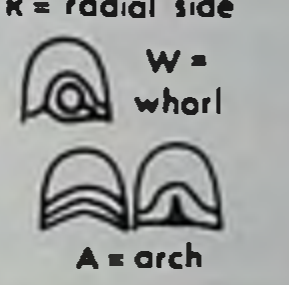
AT bil.	+2.17
AT uni.	+1.58
SDL bil. (<21 ridges)	+0.50
SDL/LDL	−0.19
SDL/W or other*	−0.58
LDL bil. (≥21 ridges)	−0.70
LDL/W	−1.08
W bil.	−1.50
other* bil. or with LDL or W	−2.11



*(other means any pattern but AT, SDL, LDL or W)

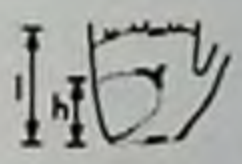
2. Digits 2 (forefinger)

UU	+0.62
UW	−0.26
UA	−0.32
WA	−0.64
WW	−0.82
UR	−0.83
AA	−0.90
WR, RR, RA	−1.66



3. Palmar triradius: h/l ≥ 0.40

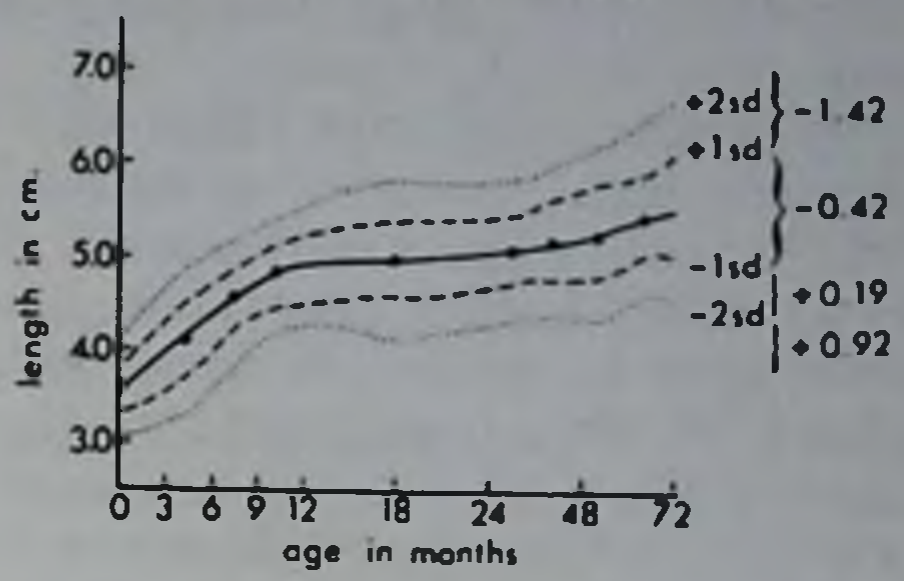
bil.	+0.98
uni.	+0.40
neither	−1.01



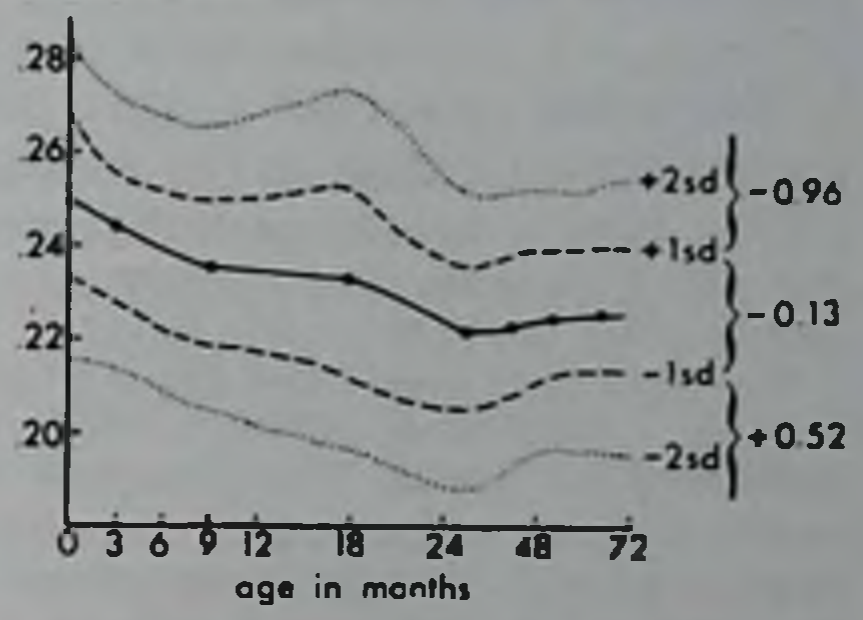
4. Brushfield spots (white speckles of iris, usually in mid and outer third in a concentric ring)

no	−0.31
yes	+0.70

5. Ear length: maximum superior to inferior pinna



6. Internipple distance ÷ chest circumference



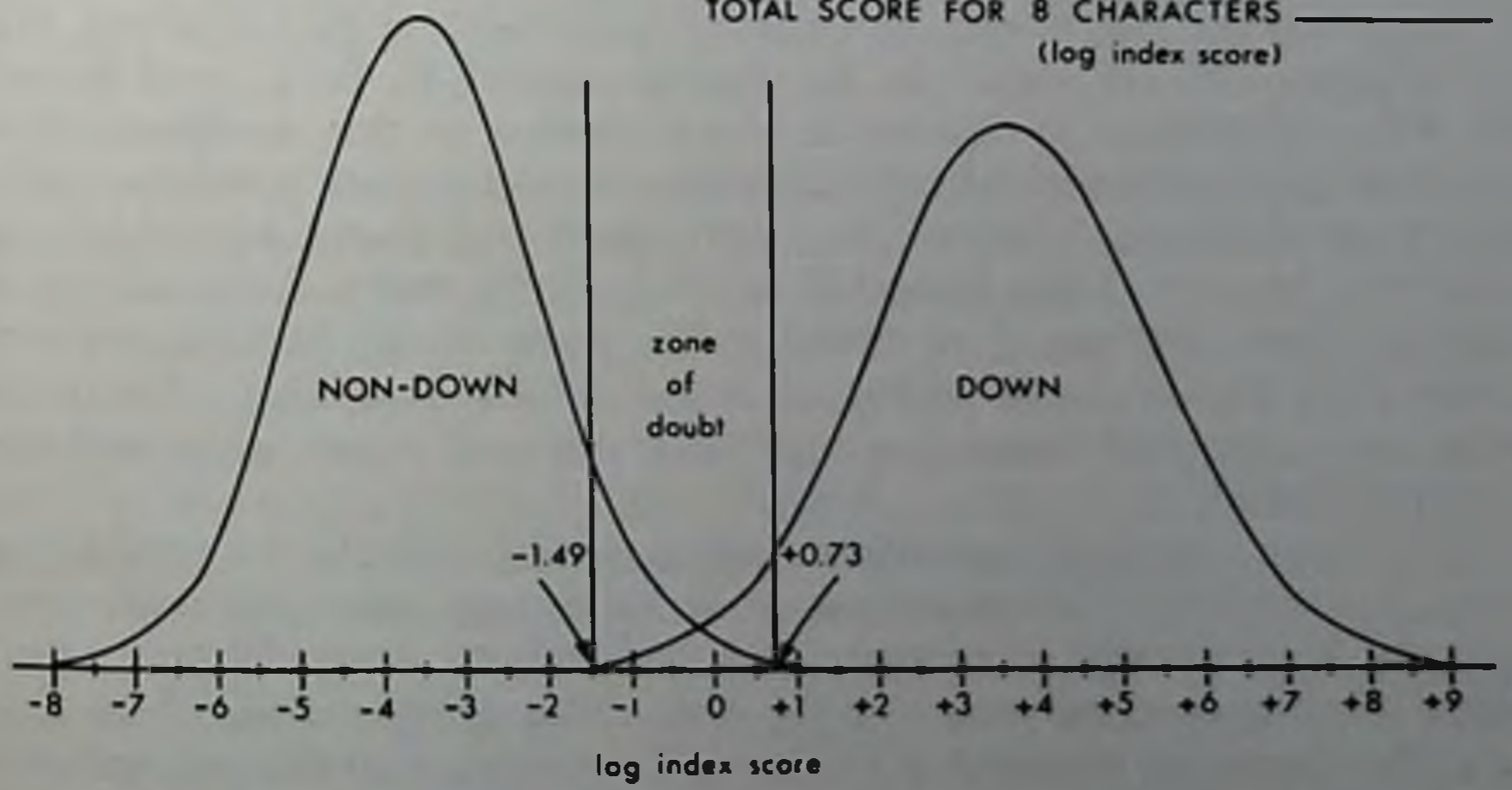
7. Widespace between 1st & 2nd toe:

about the width of the 2nd toe. usually associated with a deep plantar crease	no	−0.40
	yes	+0.79

8. Neck, back skinfold/fat pad:

excess neck skin evident on palpation and inspection	no	−0.35
	yes	+0.66

TOTAL SCORE FOR 8 CHARACTERS _____
(log index score)



are then added to get total score. A total score greater than +0.73 indicates that patient has Down's syndrome; scores in range of −1.49 to +0.73 indicate that definite diagnosis is not possible and karyotype is necessary; and total score lower than −1.49 indicates that suspect does not have the syndrome. (Courtesy of Rex, A. P., and Preus, M.: J. Pediatr. 100:903–906, June 1982.)

and forefinger pattern and height of palmar triradius), 2 measurements of physical traits (ear length and internipple distance), and 3 other clinical findings (Brushfield spots, wide-spaced first toe, and excess skin at back of neck).

It is estimated that about 95% of patients suspected of having Down's syndrome can be categorized as having or not having it with 99.9% confidence. A fast clinical diagnosis on most suspects can be made before karyotyping is complete, allowing parents to be informed soon after birth and, in some instances, to make medical decisions about life-threatening defects. The expense of chromosome studies (unless there are other indications) can be avoided on most patients who do not have the syndrome. Among patients whose score is in the non-Down zone, karyotyping is suggested only in those with more than three minor anomalies and developmental delay. If a karyotype is requested, the index score is of use in the cytogenetics laboratory.

The index presented is simple to use, relatively quick to administer, and can be done in the newborn nursery or pediatrician's office.

► [This is not quite as simple as Schamroth's sign, but is very useful nevertheless. A magnifying glass should be part of your diagnostic equipment in order to read dermatoglyphics (and Fig 19–2 in the text).

We continue to learn more about Down's syndrome. T. P. Cooney and W. M. Thurlbeck (*N. Engl. J. Med.* 307:1171, 1982) reported that these children frequently have pulmonary hypoplasia. This is evidenced by a smaller total number of alveoli and a smaller alveolar surface area. This pulmonary hypoplasia may be responsible for the aggravation of pulmonary hypertension in these children. The tonsilar and adenoidal hypertrophy, the large tongue, and the relatively small posterior oropharynx also contribute to upper airway obstruction with subsequent pulmonary hypertension.

On the subject of Down's syndrome, we were reminded in the past year in a *Special Olympics Bulletin* that as many as 10% of children with Down's syndrome may have atlantoaxial dislocations. This anomaly involving the C1 and C2 cervical vertebrae may increase the risk of serious injury to these children during activities that require hyperextension or radical flexion of the neck. The Special Olympics, Inc., advised that these children not participate in activities such as gymnastics, diving, butterfly stroke in swimming, high jump, or soccer until an x-ray examination of the neck indicated that this anomaly was not present.—F.A.O.] ◄

19–3 **Significance of Fever Following Operations in Children** was investigated by Raymond S. W. Yeung, James R. Buck, and Robert M. Filler (Toronto) to determine the incidence of this symptom, gain a better perspective of its pathogenesis, and formulate a rational plan for its evaluation. Selected for study were 256 children undergoing elective surgery at the Hospital for Sick Children in Toronto. Age of patients ranged from 2 months to 18 years; about 50% of patients were girls. All children operated on except those needing the intensive care unit and those having endoscopy or outpatient procedures were included.

Diagnosis, type of operation, duration of operation, antibiotics, transfusions and the presence of infection on admission were recorded. Body temperature was measured at least every 12 hours for 3 days after operation; criterion for fever was temperature of 38 C or greater. Need for laboratory tests was determined by the physician in charge at the time; evaluations to determine the cause of fever were

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(19–3) J. Pediatr. Surg. 17:347–349, August 1982.

EPISODES OF FEVER

	No. Patients	No. Febrile	≥39°	<39°	% Febrile
General Surgery	58	16	13	3	27.6
Orthopedics	73	31	24	7	42.5
Urology	33	9	7	2	27.3
Plastic Surgery	60	3	2	1	5.0
Neurosurgery	32	14	8	6	43.8
Total	256	73	54	19	28.5

(Courtesy of Yeung, R. S. W., et al.: J. Pediatr. Surg. 17:347–349, August 1982.)

not standardized. Patients were followed for 1 month after surgery to determine any postoperative complications.

Fever developed in 73 children (28.5%). In only 4 (5.5%) did the fever represent a septic process. Physical examination led to proper diagnosis in all. Risk factors that correlated statistically with postoperative fever were operation of longer than 2 hours ($P < .001$), intraoperative transfusion ($P < .001$), preexisting infection ($P < .01$), and the use of preoperative antibiotics ($P < .001$). Anatomical site of operation, age, and sex were not significantly correlated. The type of procedure and incidence of fever are shown in the table.

Many factors other than infection are responsible for postoperative fever. Only a small proportion of children with early postoperative fever undergo significant septic complications. In the assessment of postoperative fever, a protocol that indiscriminately includes laboratory investigations and x-ray films is costly and usually not diagnostic. Laboratory tests are indicated mainly to confirm diagnoses suspected by clinical evaluation.

▶ [The four infections in this study included pneumonia in 2 patients, urinary tract infection in 1, and ventriculoperitoneal shunt infection in 1. In all 4 patients, physical examination first suggested the complication responsible for fever. Laboratory investigations in these postoperative fevers in the absence of positive physical findings failed to uncover any unsuspected septic problems. How's that for cost containment?—F.A.O.] ◀

19–4 **Incidence of Postoperative Pain in Children.** Laurence Mather and Josephine Mackie (Flinders Univ. of South Australia, Bedford Park) determined the incidence of postoperative pain in 170 children at two major teaching hospitals and analyzed the use of analgesic medication. Patients were visited two to four times over 2 or 3 days by a pediatric nurse familiar with the postoperative nursing procedures at the respective hospitals. Pain scores were estimated from a questionnaire modified for recording responses from very young patients. The 101 boys and 69 girls in the study had a mean age of 8 years. At least 90% of patients were premedicated before surgery, most often with a mixture of papaveretum and hyoscine.

Postoperative narcotic or nonnarcotic medications, or both, were ordered for 84% of patients (Table 1). Narcotics alone were infrequently

(19–4) Pain 15:271–282, March 1983.

TABLE 1.—Prescribing Patterns of Primary (More Potent) and Secondary (Less Potent) Medication

Primary medication	Secondary medication												
	None		Pethidine		Paracetamol		Paracetamol and codeine		Aspirin		Codeine		Totals
	n	%	n	%	n	%	n	%	n	%	n	%	n
None	27	16	–	–	–	–	–	–	–	–	–	–	27
Pethidine	15	9	–	–	58	34	3	2	2	1	1	1	79
Papaveretum	7	4	1	1	21	12	5	3	–	–	–	–	34
Paracetamol	27	16	–	–	–	–	–	–	–	–	–	–	27
Paracetamol and codeine	2	1	–	–	–	–	–	–	–	–	–	–	2
Morphine	–	–	–	–	–	–	1	1	–	–	–	–	1
Totals	78		1		79		9		2		1		170

Percent column indicates percentage of patients having that combination ordered.
(Courtesy of Mather, L., and Mackie, J.: Pain 15:271–282, March 1983.)

ordered. In about 40% of cases the primary drugs ordered were not administered; the vast majority were narcotic analgesics (Table 2). Only one fourth of patients were free of pain on the day of surgery, whereas about 40% of patients had moderate or severe pain (Table

TABLE 2.—Cases Where the Primary Drugs Ordered Were Not Given

Drug	Type of surgery														
	Abdominal		Orthopaedic		ENT		Genito-urinary		Plastic		Limb		Other		Total
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n
Pethidine	4	13	4	15	11	25	7	23	5	38	–	–	3	33	34
Papaveretum	4	13	1	7	10	23	3	10	–	–	–	–	2	22	20
Paracetamol	1	3	1	7	3	7	2	7	2	16	1	17	–	–	10
Paracetamol and codeine	–	–	1	7	–	–	–	–	–	–	–	–	–	–	1
Morphine	–	–	1	7	–	–	–	–	–	–	–	–	–	–	1
Totals	9		8		24		12		7		1		5		66

Percent column indicates percentage of patients having that type of procedure.
(Courtesy of Mather, L., and Mackie, J.: Pain 15:271–282, March 1983.)

TABLE 3.—Pain Assessment

Surgery	n	Day*	No pain		Pain assessment						Patients receiving postoperative analgesics		Patients receiving postoperative analgesia with reports of mild or no pain	
					Mild pain		Moderate pain		Severe pain					
			n	%	n	%	n	%	n	%	n	%	n	%
Abdominal	31	1	7	23	8	26	8	26	8	26	25	81	12	48
		2	13	42	4	13	7	23	7	23	25	81	12	48
Orthopaedic	27	1	7	26	8	30	8	30	4	15	21	78	10	48
		2	14	52	5	19	6	22	2	9	21	78	14	67
ENT	44	1	9	20	17	39	14	32	4	9	33	75	19	58
		2	19	43	2	5	12	27	11	25	33	75	14	42
Genito-urinary	30	1	8	27	12	40	8	27	2	7	20	67	12	60
		2	23	77	2	7	3	10	2	7	20	67	16	80
Plastic	13	1	7	54	1	8	3	23	2	15	4	31	2	50
		2	7	54	2	15	2	15	2	15	4	31	4	100
Limb	6	1	1	17	2	33	2	33	1	16	6	100	3	50
		2	4	67	1	16	0	0	1	17	6	100	5	83
Ophthalmic	10	1	5	50	0	0	2	20	3	30	2	20	1	50
		2	2	22	3	33	3	33	1	11	2	20	1	50
Other	9	1	2	22	3	33	3	33	1	11	6	67	2	33
		2	5	55	1	11	3	33	0	0	6	67	4	67
Totals	170	1	43	25	57	34	48	28	22	13	117	69	61	52
	170	2	90	53	17	10	35	21	28	16	117	69	70	60

*1, operative day; 2, first postoperative day.
Percent column indicates percentage of patients in that surgical group; in totals, it represents the percentage of all patients.
(Courtesy of Mather, L., and Mackie, J.: Pain 15:271–282, March 1983.)

TABLE 4.—GLOBAL ASSESSMENT OF TREATMENT PROVIDED

	%
Analgesic effects	
No recorded comment	62
Totally effective	7
Mostly effective	8
Some effects for some of the time	18
Totally ineffective	7
Side effects	
No recorded comment	85
Nausea	2
Dizziness	2
Sleepiness	7
Nausea and dizziness	4

Percent column pertains to percentage of all patients surveyed (total number equals 170).

(Courtesy of Mather, L., and Mackie, J.: Pain 15:271–282, March 1983.)

3). About two thirds of patients had no or only mild pain the day after operation. Patient age was not related to reports of pain on the day of surgery or the first postoperative day. Global assessments of treatment generally indicated some effect for some of the time (Table 4).

Moderate or severe pain was frequently reported by children in the postoperative period in this survey, regardless of treatment. Prescribing patterns were far from uniform, and interpretations of medication orders by nurses often contributed to poor analgesia. Improvement is needed in all aspects of postoperative pain management in children, starting with adequate preparation for surgery.

▶ [Most of the pain medication orders in this study were written "PRN," which often is interpreted by the nursing staff as "as little as possible." Many of the children surveyed became withdrawn, and this was interpreted as coping with the pain. Other children were so frightened by the prospect of a "needle" that they suffered with the pain. Why is it, as reflected by the preceding article by Yeung et al., that we overstudy postoperative fever and undermedicate postoperative pain? "Suffer the little children." As pediatricians, we should learn the principles of appropriate analgesia and make certain our surgical consultants use them. We should begin using the hot line to report these examples of child abuse.—F.A.O.] ◀

19–5 **Pedestrian Traffic in a Pediatric Ward.** The modern pediatric ward is much different from the formally organized ward of 2 decades ago, and an increase in pedestrian traffic may have contributed to the change. Valerie J. Grant (Univ. of Auckland) analyzed the traffic in a six-bed room in a pediatric ward on three separate occasions over a 2-year period. In addition, the number of different persons interacting with a single unaccompanied child was determined, and the responses of the child were analyzed in detail. The number of times people entered the room are shown in Table 1 and the number of different

(19–5) N.Z. Med. J. 96:91–93, Feb. 9, 1983.

TABLE 1.—Number of Times People Entered Six-Bed Pediatric Room

Date	6 am-10 am	10 am-2 pm	2 pm-6 pm	Total
Thursday 8 May 1980	56	193	64	313
Friday 9 May 1980	54	128	146	328
Thursday 7 May 1981	168	131	81	380
Friday 8 May 1981	40	150	84	274
Saturday 9 May 1981	65	156	119	340
			Average number of entrances:	327

(Courtesy of Grant, V. J.: N.Z. Med. J. 96:91–93, Feb. 9, 1983.

individuals entering the room, in Table 2. There were more than 300 entrances by 100 different persons each day. Analysis of interactions with a single patient indicated that the multiple interactions may have constituted a stress. The infant cried for a total of 68 minutes during 12 hours of observation, but for only 6 minutes during the 4 hours his mother was present.

Heavy social demands on an unaccompanied child at a psychologically vulnerable age may add to the stress of hospitalization. The present figures may actually underrepresent the actual situation. Both teaching and an open ward policy for visitors contribute to the number of pediatric patient interactions. An unaccompanied child is constantly looking for his or her mother and seems much more concerned with monitoring all who enter the room. This emphasizes the importance of the mothers of preschool children staying with their children, if at all possible. There is an urgent need for changes in planning pediatric wards. Each mother and child pair requires a separate room so that staff entrances will be reduced to a moderate level

TABLE 2.—Number of Individuals Entering Six-Bed Pediatric Room

Date	6 am-10 am	10 am-2 pm	2 pm-6 pm	Total
Thursday 8 May 1980	30	76	37	143
Friday 9 May 1980	34	37	61	132
Thursday 7 May 1981	30	36	21	87
Friday 8 May 1981	16	34	27	77
Saturday 9 May 1981	22	32	38	92
			Average number of individuals	106

(Courtesy of Grant, V.J.: N.Z. Med. J. 96:91–93, Feb. 9, 1983.)

and so that visits by members of the extended family will be less disruptive to those who prefer fewer visitors. Rooms for infants admitted without parents should be within direct view of the nursing station.

▶ [Can you imagine yourself being sick in bed and having 106 different people coming into your room for a total of 327 visits a day?—F.A.O.] ◀

19–6 **Infantile Water Intoxication After Swimming Lesson.** Symptomatic water intoxication in infants usually follows improper feeding or the administration of tap water enemas. Gerald N. Goldberg, Elmer S. Lightner, Wayne Morgan, and Sid Kemberling (Univ. of Arizona) describe water intoxication in an infant that occurred after a swimming lesson.

Healthy boy, aged 10 months, swallowed much water when "going under" during a 45-minute swimming lesson, but did not choke or exhibit respiratory distress. Two large clear emeses occurred within an hour after the lesson and urine output was increased. The infant became lethargic and experienced two brief seizures followed by momentary apnea. The skin turgor was normal, and the lungs were clear. Funduscopy showed splinter hemorrhages in both optic discs and blurred disc margins bilaterally; the veins were engorged. The infant was given 5% glucose in half-normal saline, diazepam, phenobarbital, and dexamethasone. In addition, mannitol was infused because of suspected cerebral edema. The initial serum sodium concentration was 123 mEq/L, and serum osmolarity was 252 mOsm/kg.

Apnea necessitated intubation and mechanical ventilation. Fluids were restricted, but a generalized seizure occurred some hours after admission. The child was given 66 mEq sodium in the next 18 hours. The serum sodium concentration and osmolarity returned to normal. Over 1 L of urine was passed on the first hospital day. The infant improved rapidly and was extubated within 24 hours. He was discharged on the third day.

This infant ingested an estimated 800 ml of water during the multiple submersions, or nearly 10% of his total body weight. Acutely increased intracranial pressure was evident, presumably due to cerebral edema from the rapid fluid shift. The diagnosis could have been made earlier, rather than near-drowning with seizures caused by cerebral anoxia being suspected, had more attention been paid to the history and the absence of abnormal findings in the lungs. Small volumes of hypertonic saline probably would have precluded the need for anticonvulsants, which may have contributed to respiratory depression and the need for ventilatory assistance.

▶ [These reports are now reaching epidemic proportions. R. M. Kropp and J. F. Schwartz (*J. Pediatr.* 101:947, 1982) described a previously healthy infant who was admitted to the hospital with a 3-hour history of almost continuous seizures. That afternoon, the infant had been taken by her parents into a neighbor's pool on two separate occasions of no more than 20 minutes each over about 4 hours. Approximately 30 minutes after the second "swimming" episode, she vomited and then began having generalized tonic-clonic seizures. Initial laboratory studies disclosed a serum sodium concentration of 118 mEq/L with a serum osmolality of 252 mOsm/L.

H. J. Bennett and associates (*Pediatrics* 72:125, 1983) described an 11-month-old infant who developed irritability, lethargy, and disorientation and then seizures about 30 minutes after a 1-hour swimming lesson. The serum sodium level of the infant at admission was 122 mEq/L.

(19–6) Pediatrics 70:599–600, October 1982.

In each of the 3 reported cases it was assumed that the infants became acutely water intoxicated as a result of consuming large quantities of water from the swimming pool.

Isn't being baptized enough water submersion for most young infants? Who has established that early swimming lessons do, in fact, minimize later fear of water or reduce the risk of drowning? More swimmers drown than nonswimmers, just as more people are accidentally killed by "unloaded" guns than loaded guns.

Infants, unlike horses, can be taken to the water and be made to drink.—F.A.O.] ◀

19–7 **Unusual Injury? Recent Injury in Normal Children and Children With Suspected Nonaccidental Injury.** D. M. Roberton, P. Barbor, and D. Hull (Univ. Hosp., Nottingham, England) examined 400 normal children aged 2 weeks to 11 years brought from a relatively disadvantaged inner city area for routine medical assessments to determine the prevalence and site of recent minor traumatic lesions as well as evidence of more major injury such as burns or fractures.

There was evidence of injury, usually bruising, in 37% overall due to recent minor trauma; injuries were uncommon before age 9 months, with a steady increase to a plateau at age 3 years (60% prevalence by the end of the third year of life). Bruising of the hands, feet, and lower legs was the most frequent type of injury. Head and facial injuries were most common between age 18 months and 3 years (17% of children) but were rare at other ages. Injury to the lumbar region was unusual before age 5 years, but was present (usually bruising) in 14% of school-age children.

In 84 children of similar age where nonaccidental injury was proved or suspected, a different pattern of injury was present; 60% had injuries to the head and face (table), and this increase in prevalence was seen at all ages (Fig 19–3). These children also had more frequent injuries in the lumbar region, particularly before age 5 years.

This study shows the altered pattern and distribution of lesions in children with actual or probable nonaccidental injury and gives some guidelines for comparison at different ages.

INJURY SITE IN CHILDREN, AGED 2 WEEKS TO 11 YEARS, WITH ACCIDENTAL INJURY AND SUSPECTED OR DEFINITE NONACCIDENTAL INJURY (NAI)

Site/type of injury	% with injury: Normal children (n = 400)	Suspected/definite NAI (n = 84)
Head and face	6·5	59·8
Chest	1·5	12·6
Upper back	2·0	11·5
Arms	8·5	38·1
Lumbar region	3·75	21·4
Thigh and buttocks	9·25	41·7
Lower legs	21·5	28·7
Fracture(s)	0	10·3
Burn(s)	0·75	11·3

(Courtesy of Roberton, D.M., et al.: Br. Med. J. 285:1399–1401, Nov. 13, 1982.)

(19–7) Br. Med. J. 285:1399–1401, Nov. 13, 1982.

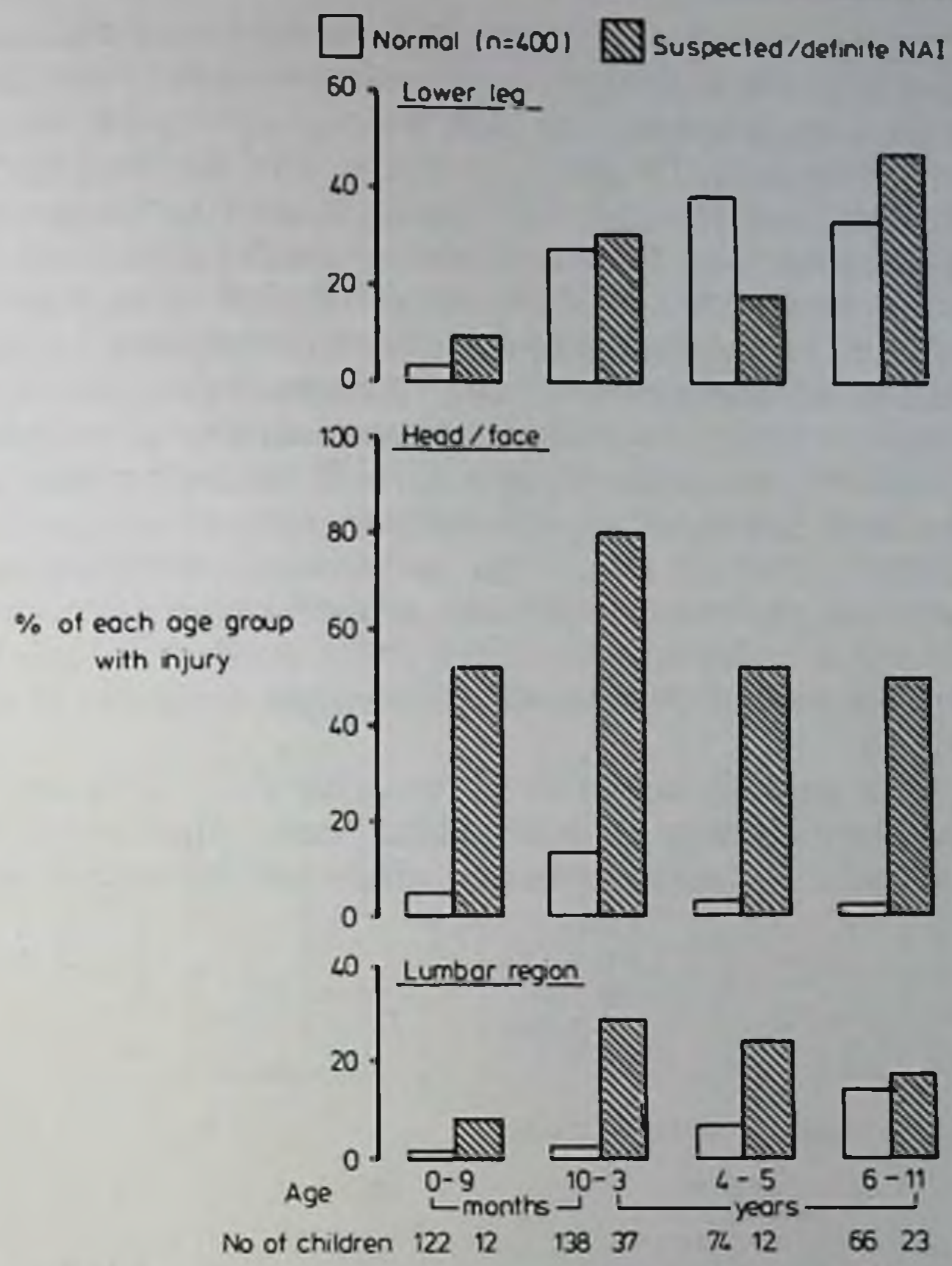

Fig 19–3.—Injury at specified sites with respect to age in 400 normal children and 84 children with suspected or definite nonaccidental injury *(NAI)*. (Courtesy of Roberton, D. M., et al.: Br. Med. J. 285:1399–1401, Nov. 13, 1982.)

▶ [This is a handy little guideline. What is new regarding the establishment of the diagnosis radiologically? A sobering note—D. F. Merten and associates (*Radiology* 146:377, 1983) reviewed the radiologic findings in 563 abused infants and children with respect to radiographic examination of the skeleton. Skeletal trauma was detected in less than one third of all patients and was uncommon beyond age 2 years. Fractures were rarely present without clinical evidence of physical abuse. Bone scanning may be more productive. That is the conclusion reached by J. R. Sty and R. J. Starshak (ibid., p. 369). They compared the radiographic and scintigraphic skeletal surveys of 261 children who were suspected victims of abuse. Radiography was positive in 105 children (40.2%) and produced false negative results in 32; scintigraphy was positive in 120 children and produced false negative results in 2. The authors feel that although radiography traditionally has been used to assess the skeletal injuries of battered children, scintigraphy should be the screening procedure of choice. If the bone scan "lights up," it certainly is illuminating.—F.A.O.] ◀

19–8 **Failure to Thrive: Diagnostic Yield of Hospitalization.** Donald M. Berwick, Janice C. Levy, and Ruth Kleinerman (Boston) reviewed the records of 122 infants aged 1 to 25 months admitted to a teaching hospital with a diagnosis of failure to thrive (FTT) but with no underlying disease apparent at admission.

(19–8) Arch. Dis. Child. 57:347–351, May 1982.

For 34% of these infants there was still no diagnosis after evaluation (Table 1); 32% were thought to have a social or environmental explanation for poor growth; and 31% were given a specific organic or physiologic diagnosis. Of the last group, two-thirds had a functional gastrointestinal disorder (gastroesophageal reflux or nonspecific chronic diarrhea) and one-third had a specific structural disease (Table 2). In 38 children whose FTT was attributed to an organic process, the gastrointestinal tract was the site of the process in 31 (82%). Only 10% of the children were found to have a specific structural disease other than gastrointestinal reflux or chronic diarrhea. This pattern of diagnosis was not statistically different even among children with the most profound growth failure.

Three features noted on admission histories were associated with ultimate diagnosis: medicaid eligibility, growth pattern before admission, and history of vomiting. Children from medicaid-eligible families accounted for 43% of those with a discharge diagnosis of socioenvironmental FTT.

The composite growth curve of those with FTT that was unexplained at discharge (group 1) showed that these infants were following normal growth channels, although displaced downward from the

TABLE 1.—DISCHARGE DIAGNOSES IN 122 PATIENTS

Discharge diagnostic category	*Total children* *No*	*%*
1 Unexplained Unknown (33) Constitutional (8)	41	34
2 Social-environmental Social deprivation (22) Malnutrition (17)	39	32
3A Functional gastrointestinal Oesophageal reflux (16) Chronic diarrhoea (10)	26	21
3B Specific structural	12	10
4 Not failure to thrive	4	3

(Courtesy of Berwick, D. M., et al.: Arch. Dis. Child. 57:347–351, May 1982.)

TABLE 2.—SPECIFIC STRUCTURAL CAUSES OF FAILURE TO THRIVE

Discharge diagnosis	*No of children*
Partial intestinal obstruction Pyloric stenosis (2) Malrotation (1)	3
Urinary tract infection	3
Tuberculosis	1
Neurological Leigh's disease (1) Cerebral palsy (1)	2
Coeliac disease	2
Hypercalcaemia	1

(Courtesy of Berwick, D. M., et al.: Arch. Dis. Child. 57:347–351, May 1982.)

third centile. Children with presumed e
(group 2) were characterized by an aggreg
below the third centile than that of grou
deviating progressively with age from n
with chronic diarrhea or gastroesophageal
most strikingly deviant growth curves in
timate diagnoses suggesting esophageal re
most from birth, with curves of nearly flat s
chronic diarrhea appeared to grow well du
life and then to deviate suddenly and mark
ing was often associated with organic or s
gain during the hospital course was genera
of the discharge diagnosis.

TABLE 3.—Test Abnormalities Useful in Diagnosing Cause of Failure to Thrive

Diagnostic group	*No*	*Cases with positive test*	*Number of positive tests*	*Test types positive*
2 Socioenvironmental	39	1	1	Bone *x*-ray films (1)
3A Gastro-oesophageal reflux or chronic diarrhoea	26	6	6	Upper gastrointestinal series (4) Intestinal biopsy (2)
3B Specific diseases				
Structural bowel disease	3	3	5	Upper gastrointestinal series (2) Barium enema (1) Abdominal *x*-ray film (1) Laparotomy (1)
Coeliac disease	2	2	6	Intestinal biopsy (2) Upper gastrointestinal series (1) Abdominal *x*-ray film (1) Carotene (1) Folate (1)
Urinary tract infection	3	3	8	Urine culture (3) Intravenous pyelogram (2) Voiding cystourethogram (2) Urine analysis (1)
Neurological disease	2	2	5	Skull *x*-ray film (2) Electroencephalogram (1) Electroretinogram (1) Sonar scan (1)
Idiopathic hypercalcaemia	1	1	6	Calcium (3) Electrocardiogram (1) Intravenous pyelogram (1) Bone *x*-ray film (1)
Tuberculosis	1	1	2	Chest *x*-ray film (2)

(Courtesy of Berwick, D. M., et al.: Arch. Dis. Child. 57:347–351, May 1982.)

On average, about 40 laboratory tests and roentgenographic studies were performed per infant. Although many abnormalities were noted, in only 19 (16%) of the 122 cases did an abnormality seen on a test help to diagnose the cause of FTT. In these 19 cases, a total of 39 tests, or 0.8% of all tests done, helped to establish the cause of FTT. Upper gastrointestinal series, intestinal biopsy, and abdominal films accounted for 13 (33%) of these tests. The 39 tests are summarized in Table 3. The value of some tests in ruling out diagnoses was not established.

The results stress the importance of social and environmental factors as basic causes of FTT and suggest that admission to a hospital and laboratory testing is unlikely to lead to a specific organic diagnosis in a child whose FTT is unexplained after careful history and physical examination; in such cases, the pursuit of organic diagnosis should be tempered by increased attention to the nurturant interactions of parents and child. Gastroesophageal reflux was the most common single specific diagnosis in this study. The review suggests that vomiting should serve as a target to guide initial diagnostic study.

► [Dr. Richard Sills, Associate Professor of Pediatrics, State University of New York at Buffalo, provided us with the following comment:

"The evaluation of failure to thrive is commonly mismanaged. Pediatric training and the literature have tended to overemphasize the "more interesting" organic causes of this problem. This often has led us to ignore several vital facts about failure to thrive.

"1. Nonorganic disorders, especially environmental deprivation, are the most common causes of failure to thrive. Therefore, a detailed psychosocial evaluation is an absolutely essential part of the evaluation of this disorder.

"2. When failure to thrive is due to organic disorders, the actual diagnosis is almost always suggested by a thorough history and physical examination. Laboratory studies not indicated by the clinical presentation are rarely, if ever, helpful.

"The study by Berwick et al. corroborates these facts. Several aspects of the study warrant further comment. The usefulness of growth curves that are so readily available must be emphasized. The relatively minor role of laboratory studies is confirmed by the positive contribution of less than 1% of the tests performed. The analysis demonstrating that 24% of the cost of the hospital stay was for laboratory data is thought-provoking. Although various laboratory tests were helpful in 16% of the patients, the study does not note whether the tests were indicated by the clinical evaluation. On the basis of previous studies, I assume that most of them were.

"Hospitalization to observe weight gain has been widely recommended as a means to establish a diagnosis of environmental deprivation. The authors report that such weight gain did not help differentiate organic from nonorganic diagnoses. Considering the tremendous cost of inpatient observation, it is critical to evaluate its usefulness. However, I am not convinced that this type of retrospective chart review can accomplish that. A prospective study is needed to answer this question.

"I certainly agree with the authors' conclusion that an aggressive search for organic disease as the primary cause of failure to thrive is not beneficial. If the etiology of failure to thrive is unknown and organic disorders are not suggested by the clinical evaluation, our efforts must be directed toward environmental problems. Studies like this one are pointing us in the right direction."] ◄

19–9 **Ostensible Versus Actual Reasons for Seeking Pediatric Attention: Another Look at the Parental Ticket of Admission.** It is not uncommon in pediatric practice for parental anxiety to seem excessive relative to the nature of the child's chief complaint. Lee W.

(19–9) Pediatrics 70:870–874, December 1982.

ACTUAL REASON FOR SEEKING PEDIATRIC ATTENTION

	No.
Family history or past history of similar disease	39
Parents thought the worst	30
Parental fear of cancer or leukemia	10
Authority figures causing the visit	10
"Too much" or "too long"	9
Death	8
Travel or moving	7
"Vital" organs	7
Absent parent	5
Total	125

(Courtesy of Bass, L. W., and Cohen, R. L.: Pediatrics 70:870–874, December 1982. Copyright American Academy of Pediatrics 1982.)

Bass and Richard L. Cohen (Univ. of Pittsburgh) reviewed 370 sick-patient visits to one pediatric office over a 3-month period to assess the degree and nature of parental concern. Questioning revealed an actual reason for coming underlying the ostensible reason in one third of cases. The underlying actual reasons are given in the table. A family history or a past history of illness was the most common underlying reason for visiting the office. Thirty parents usually interpreted symptoms to mean the worst. In 8 instances a family member, friend, or another child had died and the parent wished to make sure that a similar life-threatening illness was not present.

An underlying actual reason for coming is present in a significant number of pediatric office visits. Discussion of its relationship with the ostensible reason for coming can lead to better resolution of parental anxiety, eliminate unnecessary prescriptions, and result in satisfaction on the part of the parent. The few extra moments needed to elicit the actual reason for the visit are well worthwhile.

▶ [In 1961, S. Yudkin published a manuscript entitled "Six Children with Coughs: The Second Diagnosis" (*Lancet* 2:7202, 1961), and this paper has become a classic that should be required reading at least once in the lifetime of every pediatrician. This study by Bass and Cohen provides additional data in support of the earlier observations of Yudkin. No patient should leave the office without you being able to answer the question, "Why is this patient coming to see me now?"—F.A.O.] ◀

19–10 **Medical Problems at a Summer Camp.** William Fiedelman, Kathleen Carbon, and Debbie Lewis reviewed the health care services provided over 8 weeks on the boys' side of a "brother-sister" summer camp. A total of 159 upper-middle-class white boys, aged 6 to 15 years, attended camp. Twelve campers had medical conditions of significance before arriving at camp. Another 13 had seasonal or perennial allergies and used an antihistamine; 3 of them were being desensitized. Eleven campers were allergic to penicillin. Nine campers, all aged 14 to 15 years, were admitted to the infirmary for exhaustion. Four others were admitted overnight to prevent weight-

(19–10) N.Y. State J. Med. 83:209–212, February 1983.

												Dispensary	
Week No.	Ankle Sprain	Finger Sprain	Knee Sprain	Wrist Sprain	Other Sprain	Fracture	Abrasion	Laceration	Blister	Splinter	Sunburn	Insect Sting/ Bite	Rash
1	18	3	11	8	9	1	18	13	6	5	16	6	23
2	9	4	8	11	7	0	11	7	1	3	2	3	5
3	8	10	6	4	12	1	16	7	2	3	1	8	1
4	6	2	5	4	1	1	11	4	0	3	0	2	3
5	12	7	4	4	6	2	4	4	1	0	2	1	3
6	9	4	3	6	6	0	8	6	0	1	0	1	2
7	4	5	4	1	2	0	4	1	1	1	3	1	7
8	4	7	0	1	2	0	0	4	1	1	0	2	2
TOTALS	70	42	41	39	45	5	72	46	12	17	24	24	46

(Courtesy of Fiedelman, W., et al.: N.Y. State J. Med. 83:209–212, February 1983.)

bearing, 2 because of nausea and vomiting after eating large amounts of pizza, and 2 for temperatures over 100 F. Dispensary visits are summarized in the table. Trauma constituted a significant proportion of dispensary visits but declined in proportion as the summer progressed.

The camp physician and nurse can sharpen their skills in a variety of areas in the camp setting as well as enjoying time in the country. It can be rewarding to provide health care to children without their parents being present. Anticipation of problems and preplanning can help the staff prepare for what will occur. Lower limb trauma has been most frequent in the first week of camp. A disproportionate number of injuries have occurred after dinner. Otitis increased significantly in the middle of the camp period as swimming skills improved. Rashes were related to the presence of the gypsy moth caterpillar. The frequent complaint of "sore throat" unaccompanied by physical findings may relate to the tendency of campers to shout a lot.

▶ [Do you remember that once popular song, "The Things We Did Last Summer, I'll Remember All Winter Long"? The study by Fiedelman and his summer comrades should bring back pleasant and unpleasant memories for all ex-campers and camp doctors and serve as an accurate preview for all who are contemplating such a job. Be ready to answer the big question: "Can Alex go swimming today?"—F.A.O.] ◀

19–11 **Infant Apnea Syndrome: A Prospective Evaluation of Etiologies.** Using a protocol, Peter Camfield, Carol Camfield, Philip Bagnell, and Elihu Rees (Halifax, N.S.) investigated 28 consecutive infants younger than age 6 months with infant apnea syndrome (IAS), also termed "near-miss" sudden infant death syndrome. In this study, apnea was defined as an episode in which the baby had appeared lifeless to the caretaker and mouth-to-mouth resuscitation had been initiated. Only infants were included whose initial examination did not define a cause.

This in-hospital evaluation included, for all patients: blood counts; blood chemistries; blood gas determination; x-ray films of skull, chest, and barium swallow; lumbar puncture; ECG, echocardiogram, 24-hour Holter cardiac monitor; viral and bacterial cultures of blood,

(19–11) Clin. Pediatr. (Phila.) 21:684–687, November 1982.

VISITS

Tinea Pedis	Pediculosis Capitis	Skin Infection	Eyes	Ears	Throat	Gastroenteritis	Asthma	Upper Respiratory Infection	Headache	Allergy	Miscellaneous	Follow-up	TOTALS
1	1	7	7	9	10	10	5	15	15	1	7	30	255
1	2	1	7	5	7	10	1	13	8	1	7	45	179
9	0	2	6	27	7	10	1	11	10	0	9	65	256
0	0	3	5	20	8	11	1	4	12	2	9	71	188
4	0	0	2	2	8	11	1	7	8	1	10	30	134
0	0	1	1	5	8	8	1	8	14	0	7	10	109
0	8	0	3	1	11	6	1	4	8	0	6	19	101
0	14	1	7	2	8	3	2	17	3	2	2	14	99
15	25	15	38	71	67	69	13	79	78	7	57	304	1321

throat, urine, stool, and cerebrospinal fluid; EEG; and esophageal pH study for gastroesophageal reflux (GER).

A probable cause for IAS was found in 17 infants (table). Patients with GER were treated by positioning at 60 degrees for 1 hour after meals and while sleeping; on repeat pH probe study at 8–9 months, all had improvement or resolution of reflux. Because no patient with encephalitis appeared ill, the diagnosis would not have been discovered without lumbar puncture. Home apnea monitors were used only by 3 patients, all with no diagnosis; only these 3 had repeat apneic episodes. Among those not using monitors, pyloric stenosis later developed in 1, a convulsive disorder in 1, and a sleep disorder characterized by hypersomnolence in 1. There were no deaths during follow-up of 12–24 months.

It is concluded that detailed evaluation of IAS often yields a specific diagnosis. Lumbar puncture, EEG, and esophageal pH studies were the most valuable investigations.

▶ [Dr. John G. Brooks, Director, Pediatric Pulmonary Medicine, University of Rochester School of Medicine and Dentistry, provided us with the following commentary:

"The proposed take-home message from this article is: 'Do an extensive workup of any infant who presents with a history of a frightening apneic episode that was perceived to require mouth-to-mouth resuscitation.' The rationale is that there is a good chance of discovering a diagnosis for which specific (and often effective) ther-

DIAGNOSES IN INFANT APNEA SYNDROME

Diagnosis	Number of Infants
Gastroesophageal reflux	6
Encephalitis	4
Convulsive disorder	3
Periventricular edema	1
Arnold-Chiari malformation	1
Milk allergy	1
Normal periodic breathing	1
No definite diagnosis	11
TOTAL	28

(Courtesy of Camfield, P., et al.: Clin. Pediatr. (Phila.) 21:684–687, November 1982.)

apy or reassuring counseling can be initiated. This conclusion is based on a very small series of 28 patients and, as has been the experience of others, in the majority no cause-and-effect relationship between the specific diagnosis and the apnea was proved. For example, an abnormal EEG, even with recurrent clinical seizures, does not prove that the first episode was a seizure, particularly in the absence of a history of prior seizures. The hypoxia of the first episode may have resulted in a seizure disorder. Only if an infant has recurrent apnea that ceases when specific therapy is initiated (e.g., anticonvulsants or head elevation), can one begin to infer a cause-and-effect relationship.

"The abnormalities of the cerebrospinal fluid consistent with a diagnosis of encephalitis in 4 infants who did not appear particularly ill is most intriguing. Are we justified in reassuring such parents that since we have a specific diagnosis, their infant is not at risk of subsequent apnea? Or, is this infant demonstrating his vulnerability to clinically mild infections? The data to answer these questions are not available, and until they are, I think it is not necessary to perform a lumbar puncture on all infants presenting after a single episode of severe apnea unless there are other findings compatible with meningitis. However, one must distinguish the routine clinical from the research approach to these infants; the researcher must be rigorous, comprehensive, and consistent, while the workup for clinical purposes should be individualized for each patient. The extensive evaluation performed by Camfield et al. is appropriate for research, but only rarely for the routine clinical evaluation.

"Finally, I must urge caution about the conclusion that since only those 3 infants who were given home apnea monitors had repeat episodes, the correct infants were selected for monitoring. Alternative possibilities are that the monitored infants had recurrent false alarms and that those who were not monitored may have had recurrent undetected apneic episodes. It is important that all 25 infants without home monitoring survived.

"These authors have raised significant issues and have begun to provide some important data. With such a difficult and emotionally charged topic, it is essential to exercise great caution to distinguish established fact from hypothesis or bias, and to distinguish research from clinical practices."] ◀

19–12 **Identification of Infants Destined to Die Unexpectedly During Infancy: Evaluation of Predictive Importance of Prolonged Apnea and Disorders of Cardiac Rhythm or Conduction** is presented, in the first report of a multicentered, prospective study into the sudden infant death syndrome (SIDS), by D. P. Southall, J. M. Richards, M. de Swiet, W. A. Arrowsmith, J. E. Cree, P. J. Fleming, A. J. Franklin, R. L.'E. Orme, M. J. Radford, A. J. Wilson, D. C. Shannon, J. R. Alexander, N. J. Brown, and E. A. Shinebourne. The ECG and breathing movement were recorded prospectively for 24 hours in 6,914 full-term and 2,337 preterm or low birth weight infants in the first 6 weeks of life to identify those who would die suddenly in infancy. Forty recordings were obtained in 29 infants who subsequently died of SIDS and 13 in 10 other infants who died suddenly and unexpectedly. Details of the term infants monitored are given in Table 1, in which NA means that no attempt was made to obtain follow-up recordings, and of sudden and unexpected deaths in this group in Table 2. Details of the SIDS cases are given in Table 3, in which small for dates means less than the 10th centile.

None of the 29 SIDS infants had prolonged cessation of breathing movements; the longest apneic pause was 13.2 seconds. One preterm infant had multiple ventricular premature beats of parasystolic ori-

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(19–12) Br. Med. J. 286:1092–1096, Apr. 2, 1983.

TABLE 1.—DETAILS OF FULL-TERM INFANTS UNDERGOING RECORDINGS (JULY 1, 1980, TO JULY 31, 1981)

Centre	Population born	Age at first recording	No of first recordings obtained	No of refusals	No of follow up recordings obtained	No of refusals for follow up recordings
Brighton	2630	<2 weeks	2294	263 (10%)	1462 (64%)	832
		2–4 weeks	60	13	NA	
Doncaster	3506	<2 weeks	3314	77 (3%)	2599 (78%)	715
		2–4 weeks	94	21	NA	
Exeter	1252	1–4 weeks*	69	0 (8%)	65 (94%)	4
		5–7 weeks	1083	100	NA	
Totals	7388		6914 (94%)	474 (6%)	4126 (73%)†	1551

*Before discharge from special care baby unit.
†Proportion of infants assigned for follow-up recordings.
(Courtesy of Southall, D. P., et al.: Br. Med. J. 286:1092–1096, Apr. 2, 1983.)

gin. No infant exhibited ventricular preexcitation. None of 28 evaluable SIDS infants had a prolonged QTc index. No abnormal QT prolongation was found in the SIDS group in comparison with 211 control infants from whom recordings were obtained.

Sudden infant deaths could not be predicted in this study by the presence of prolonged apnea or of cardiac rhythm or conduction disorder on 24-hour recordings obtained in the first 6 weeks. Such disorders may occur just before death in this syndrome. The findings, however, do suggest that the prolonged apnea that sometimes follows a near-miss episode may be the result of the episode rather than its cause. A more detailed study of the heart rate and breathing patterns of SIDS cases and controls is planned in the hope of finding clues predictive of infants at increased risk.

TABLE 2.—Details of Sudden and Unexpected Deaths of Full-Term Infants Notified by Jan. 1, 1983

Centre	No of infants born	No of sudden unexpected infant deaths	No adequately explained	No with indefinite explanation	No (and incidence) of cases of sudden infant death syndrome
Brighton	2630	3			3 (1·11/1000)
Doncaster	3506	13	2: one with undiagnosed congenital heart disease (univentricular heart); one with fractured skull (road traffic accident)	2: one with bronchopneumonia (undetected by parents); one with epileptic convulsion (previous meningitis with residual brain damage)	9 (2·57/1000)
Exeter	1252	5	3: one with undiagnosed congenital heart disease (multiple pulmonary artery stenoses, aortic and pulmonary outflow tract hyperplasia); one with undiagnosed endocardial fibroelastosis; one with asphyxia after inhalation of a foreign body	1: intractable epilepsy of unknown origin, with chickenpox	1 (0·80/1000)
Totals	7388	21	5	3	13* (1·76/1000)

*Eleven (85%) underwent tape recordings (Cases 1 to 11, Table 3).
(Courtesy of Southall, D. P., et al.: Br. Med. J. 286:1092–1096, Apr. 2, 1983.)

TABLE 3.—Summary of Results of Recordings Made in 29 Infants Who Subsequently Died of SIDS

Case No	Birth weight maturity	Age(s) at recording(s) (days)	Age at death (weeks) (and days)	Longest episode of apnoea on each recording (s)	Arrhythmia or pre-excitation
1	Full term; small for dates	5, 47	15 (108)	9·6, 9·6	None
2	Full term	6	34 (237)	8·4	"
3	Full term	2	5 (39)	12·0	"
4	Full term; small for dates	8, 52	21 (148)	7·2, 9·6	"
5	Full term	24, 63	10 (74)	10·8, 8·4	"
6	Full term (twin)	5, 40	23 (159)	9·6, 7·2	"
7	Full term	3	25 (175)	13·2	"
8	Full term	3, 41	16 (112)	8·4, 7·2	"
9	Full term	19, 61	13 (95)	8·4, 7·2	"
10	Full term	40	12 (87)	6·0	"
11	Full term; small for dates	2	65 (457)	12·0	"
12	Preterm (twin)*	8	31 (220)	9·6	"
13	Preterm*	69	13 (93)	9·6	"
14	Preterm*	43	15 (105)	10·8	"
15	Preterm*	25	24 (169)	10·8	"
16	Full term; small for dates*	6	10 (73)	12·0†	"
17	Preterm; small for dates*	2, 48	8 (54)	9·6, 10·8	"
18	Preterm*	44	8 (59)	12·0	Ventricular premature beats 38/h
19	Full term; small for dates*	30	9 (65)	8·4	None
20	Preterm (twin)*	37, 58, 61	29 (203)	10·8, 13·2, 10·8	"
21	Full term; small for dates (twin)*	16	43 (303)	10·8	"
22	Preterm (twin)*	39	9 (61)	13·2	"
23	Preterm*	87	14 (96)	9·6	"
24	Full term; small for dates*	11	3 (27)	13·2	"
25	Preterm; small for dates*	15, 65	41 (285)	12·0, 10·8	"
26	Full term‡	133, 134	21 (150)	No respiratory recording	"
27	Full term; small for dates‡	16	3 (27)	10·8	"
28	Preterm*	144	24 (167)	9·6	"
29	Preterm; small for dates*	38	13 (88)	9·6†	"

*First recording made before discharge from neonatal unit.
†Less than 12 hr of adequate breathing signals.
‡Previous near-miss episode.
(Courtesy of Southall, D. P., et al.: Br. Med. J. 286:1092–1096, Apr. 2, 1983.)

▼ [The conclusions from this prospective study should certainly give pause to those zealots who advocate the use of apnea monitors for a myriad of unsubstantiated indications. For a current overview of apnea and sudden infant death, the commentary by Mary Ellen Avery and Ivan Frantz, III (*N. Engl. J. Med.* 309:107, 1983), is a very useful place to start.

Since they said it so well, I've taken the liberty of quoting their closing passages, which go like this:

"Because of our limited ability to predict which infants are at risk, it is not possible to decide which should be monitored. Monitoring carries little physical risk, but it

does have large costs in terms of both dollars and potential disruption of family life. Adverse effects can be minimized with family support.

"This pessimistic review of the lack of progress in either our understanding or the cause of sudden infant death syndrome or our ability to predict it should not deter investigators from performing other potentially important studies of the control of breathing in infancy. It may be that the concept of sudden death as a syndrome has been misleading. Nonetheless, sudden death occurs in about 2 live-born infants per 1,000. The reason for sudden death may be multiple, and our inability to determine a cause means only that we are asking the wrong questions or using the wrong investigative approaches. The final common event in sudden infant death is the quiet cessation of breathing during sleep. Further study of the factors that regulate sleep and ventilatory control is surely warranted."—F.A.O.] ◀

Review Articles of Interest to the Pediatrician

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