THE YEAR BOOK *of* PEDIATRICS 1974

EDITED BY
SYDNEY S. GELLIS, M.D.

THE YEAR BOOK
of
PEDIATRICS
1974

EDITED BY

SYDNEY S. GELLIS, M.D.

Professor and Chairman, Department of Pediatrics,
Tufts University School of Medicine;
Pediatrician-in-Chief, Tufts-New England Medical Center;
Lecturer on Pediatrics, Boston University
School of Medicine and Harvard Medical School;
Consultant, Boston City Hospital and The Children's Medical Center

---

YEAR BOOK MEDICAL PUBLISHERS

INCORPORATED

35 EAST WACKER DRIVE CHICAGO

THE PRACTICAL MEDICINE YEAR BOOKS

Medicine: DAVID E. ROGERS, M.D.; ROGER M. DES PREZ, M.D.; PAUL HELLER, M.D.; EUGENE BRAUNWALD, M.D.; NORTON J. GREENBERGER, M.D.; PHILIP K. BONDY, M.D.; FRANKLIN H. EPSTEIN, M.D.

Surgery: SEYMOUR I. SCHWARTZ, M.D.; JOHN S. NAJARIAN, M.D.; ERLE E. PEACOCK, JR., M.D.; G. TOM SHIRES, M.D.; WILLIAM SILEN, M.D.; FRANK C. SPENCER, M.D.

Anesthesia: JAMES E. ECKENHOFF, M.D.; EDWARD A. BRUNNER, M.D.; JOHN W. DITZLER, M.D.; H. STEELE HOLLEY, M.D.; HARRY W. LINDE, PH.D.

Drug Therapy: DALE G. FRIEND, M.D.

Obstetrics & Gynecology: J. P. GREENHILL, M.D.

Pediatrics: SYDNEY S. GELLIS, M.D.

Radiology: *Diagnosis*—WALTER M. WHITEHOUSE, M.D.; JOSEPH J. BOOKSTEIN, M.D.; TRYGVE O. GABRIELSEN, M.D.; JOHN F. HOLT, M.D.; WILLIAM MARTEL, M.D.; JOHN R. THORNBURY, M.D. *Therapy*—HOWARD B. LATOURETTE, M.D.; ROBERT T. GUTHRIE, M.D.; A. CURTIS HASS, M.D.

Ophthalmology: WILLIAM F. HUGHES, M.D.

Ear, Nose & Throat: M. STUART STRONG, M.D.; MICHAEL M. PAPARELLA, M.D.

Neurology & Neurosurgery: RUSSELL N. DE JONG, M.D.; OSCAR SUGAR, M.D.

Psychiatry & Applied Mental Health: FRANCIS J. BRACELAND, M.D.; DANIEL X. FREEDMAN, M.D.; ARNOLD J. FRIEDHOFF, M.D.; LAWRENCE C. KOLB, M.D.; REGINALD S. LOURIE, M.D.; JOHN ROMANO, M.D.

Dermatology: FREDERICK D. MALKINSON, M.D.; ROGER W. PEARSON, M.D.

Urology: JOHN T. GRAYHACK, M.D.

Orthopedics & Traumatic Surgery: H. HERMAN YOUNG, M.D.

Plastic & Reconstructive Surgery: KATHRYN L. STEPHENSON, M.D.; REED O. DINGMAN, M.D.; JOHN C. GAISFORD, M.D.; BOYD W. HAINES, JR., M.D.; ROBERT J. HOEHN, M.D.; FREDERICK J. MCCOY, M.D.; GREER RICKETSON, M.D.

Endocrinology: THEODORE B. SCHWARTZ, M.D.; WILL G. RYAN, M.D.; FRANK O. BECKER, M.D.

Pathology & Clinical Pathology: FRANK A. CARONE, M.D.; REX B. CONN, JR., M.D.

Nuclear Medicine: JAMES L. QUINN, III, M.D.

Cancer: RANDOLPH LEE CLARK, M.D.; RUSSELL W. CUMLEY, PH.D.

Cardiovascular Medicine & Surgery: W. PROCTOR HARVEY, M.D.; WALTER M. KIRKENDALL, M.D.; JOHN W. KIRKLIN, M.D.; ALEXANDER S. NADAS, M.D.; OGLESBY PAUL, M.D.; EDMUND H. SONNENBLICK, M.D.; IRVING S. WRIGHT, M.D.

Printed in U.S.A.

Library of Congress Catalog Card Number: CD 38-22

There are twenty YEAR BOOKS in various fields of medicine and one in dentistry. Publication of these annual volumes has been continuous since 1900. The YEAR BOOKS make available in detailed abstract form the working essence of the cream of recent international medicoscientific literature. Selection of the material is made by distinguished editors who critically review each year more than 500,000 articles published in the world's foremost journals.

TABLE OF CONTENTS

The material covered in this volume represents literature reviewed up to May, 1973.

Controlled Trial of Antepartum Glucocorticoid Treatment for Prevention of Respiratory Distress Syndrome in Premature Infants. G. C. Liggins and R. N. Howie[1] (Univ. of Auckland) carried out a double-blind trial of betamethasone therapy in 282 mothers in whom premature delivery threatened or was planned before 37 weeks' gestation, in the hope of reducing the incidence of neonatal respiratory distress syndrome by accelerating functional maturation of the fetal lung. Each patient was given an intramuscular injection of a mixture of 6 mg. betamethasone phosphate and 6 mg. betamethasone acetate or a control of 6 mg. cortisone acetate, the glucocorticoid potency of the latter being about one 70th that of the betamethasone preparation. Unless delivery had already occurred, a second injection of the same material as the first was given 24 hours later. An attempt was made to delay delivery for 48–72 hours from the time of the first injection by inhibiting uterine activity with intravenous infusions of ethanol or salbutamol.

Among 226 infants born to 213 mothers after unplanned premature labor, the fetal death rate was similar in the treatment and control groups (about 3%), but there was a significantly lower perinatal death rate in the treatment group (6.4%) than in the controls (18%). In all babies of unplanned deliveries, the incidence of respiratory distress syndrome in the betamethasone-treated group was only one-third that of the controls (9% vs. 25.8%). In the babies whose mothers had received two injections, the difference in incidence of the disorder was more marked—4.3% in the treatment group and 24% in the controls. In the infants whose mothers had received two injections, the neonatal mortality rate was 3.2% in the treated group and 14.1% in the controls—a significant difference. Hyaline membrane disease was present at autopsy in 5 control infants (6.7% of the 75 liveborn infants) and in none of the 93 betamethasone-treated liveborn infants. Eight of 12 infants of under 30 weeks' gestation who were treated with betamethasone lived 28 days, but none of 8 control infants.

There may be an increased risk of fetal death in pregnancies complicated by severe hypertension-edema-proteinuria syndromes in which the patient was treated with betamethasone, but no other complication of pregnancy, labor, delivery or the puerperium was detected that could have been attributed to steroid medication. There was no added risk of fetal or neonatal infection with betamethasone therapy and no differences between treated and control groups in Apgar scores at birth or in the incidence of hypoglycemia, jaundice or diarrhea.

These results support the hypothesis that in man, as in experimental animals previously studied, glucocorticoid administration to the fetus accelerates lung maturation. The apparent promptness of the effect, even in the most immature fetuses, may in part be due to release of surfactant already stored within the alveolar epithelium. Steroids

---

(1) Pediatrics 50:515–525, October, 1972.

should probably be given to the fetus at least 24 hours before delivery if therapy is to have any noticeable effect on lung function.

► [Although this is a most impressive study that appears to offer the prematurely born infant a greatly increased chance of survival and a much lower risk of respiratory distress, dire warnings have been given by a number of investigators. They point out that we know little or nothing about the effects of steroids transmitted across the placenta on fetal organs other than the lungs. Will enzyme systems in brain and adrenal glands be affected in adverse ways? Will lung development be adversely affected as suggested by some animal studies?

It is difficult to make recommendations. Medicine has grown sufficiently sophisticated to make us cautious in our enthusiasm. We have learned that it may take a long time to recognize untoward effects of medication: witness the development of adenocarcinoma of the vagina in children whose mothers were given stilbestrol during pregnancy so freely in the past. On the other hand, we are faced with the immediate problems of pulmonary hyaline membranes in prematurely born infants; this is a disease that continues to cause many deaths despite increasing sophistication in technics of assisting pulmonary ventilation. For this reason and after weighing known risks against the unknown, it seems appropriate to go the route outlined in this article, with full knowledge that we may be exchanging some risks for others.

Additional work of interest in this field is that reported by Dr. R. Bauer and co-workers (Spring, 1973, Meetings of the Pediatric Societies, San Francisco) in which studies of total blood corticoid levels were measured in mothers and infants and proved to be higher in maternal and infant plasmas when rupture of membranes occurred more than 16 hours before delivery, with little or no respiratory distress occurring under such circumstances. Thus, rupture of membranes more than 16 hours before delivery appears to stress the fetus, raise fetal cortisol levels, stimulate production of lung surfactant and protect the fetus against pulmonary hyaline membranes. We always worry about prolonged rupture of membranes but here there seems to be a real benefit to be gained. C. J. Richardson and co-workers point out that traditionally pregnancies with premature rupture of membranes are terminated by 24 hours of rupture regardless of fetal maturity. Their studies of pregnancies yielding premature infants in which rupture of membranes was present less than 24 hours as compared to those where rupture was present more than 24 hours indicate that there is no difference in maternal morbidity or mortality in the two groups but that the incidence of respiratory distress syndrome and death is much lower in infants with rupture of membranes in excess of 24 hours before delivery than in those with rupture of membranes less than 24 hours. They feel that rupture of membranes over 24 hours before delivery accelerates lung maturation in the fetus by factors as yet undefined.

Additional improvement in survival figures from respiratory distress syndrome appears to result from exchange transfusion as recommended by R. A. deLemos and co-workers at the same meeting. Pointing out that assisted ventilation has reduced mortality but that deaths from intracranial or pulmonary hemorrhage remain a problem, they recommend using the partial thromboplastin time (PTT) as a screening technic in the newborn. In infants with PTT greater than 90 seconds, two volume exchange transfusions with fresh heparinized blood every 12 hours resulted in a striking increase in survival. This appears to be another important advance in the management of the premature infant with or without respiratory distress. J. V. Aranda and A. Y. Sweet find that fast exchange transfusion will produce a marked fall in blood pressure that may be a factor in determining morbidity and mortality from the procedure. Their data strongly support exchange transfusion performed slowly—10 ml. in and out every 3 minutes.

The amount of work being done on the premature infant and his lung problems is encouraging and profitable. It is, however, all patchwork; we need more basic information on organ development and function in the fetus, the causes of prematurity and how to prevent premature birth. When we can achieve this glorious state, we will be able to throw out the assisted ventilation gadgetry and the exchange transfusions.—Ed.] ◄

Pneumopericardium in the Newborn: Complication of Respirator Management. Kunwar R. Singh, F. W. Wiglesworth and Leo Stern[2] (Montreal Children's Hosp.) report 2 cases of tension pneumopericardium in newborns with hyaline membrane disease who were being treated with a mechanical ventilator. One case was recognized clinically and prompt pericardicentesis was successful in saving the patient. The other case was recognized only at autopsy.

Boy, weighing 2,320 Gm., was born by spontaneous delivery at 38 weeks of gestation. At age 8 hours difficulty in respiration, grunting, retraction and cyanosis developed. A chest x-ray was compatible with hyaline membrane disease. On the basis of deteriorating arterial blood gases, the baby was placed in 100% oxygen, without amelioration of his condition. At age 30 hours he was placed in a

(2) Canad. M. A. J. 106:1195–1196, June 10, 1972.

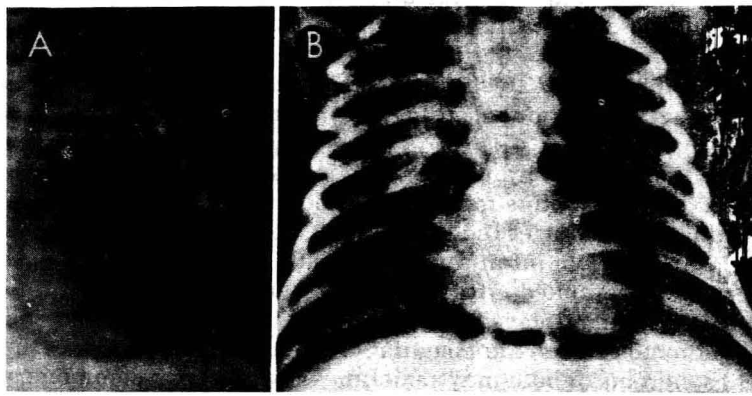

Fig. 1.—Lateral (*A*) and anteroposterior (*B*) views, showing tension pneumopericardium at age 48 hours. (Courtesy of Singh, K. R., *et al.*: Canad. M. A. J. 106:1195–1196, June 10, 1972.)

negative-pressure respirator. Color improved as did arterial blood gases and the infant was more active. At age 48 hours his condition suddenly deteriorated; he became pale and the heart sounds were no longer heard. A chest x-ray showed a large pneumopericardium (Fig. 1). Immediate pericardicentesis by the subxiphoid approach was done, with striking improvement. The infant survived the underlying disease and was successfully weaned from the respirator. At age 5 years he was well.

Case 1 followed use of a negative-pressure respirator and Case 2 followed addition of a constant negative extrathoracic pressure to a positive-pressure respirator, suggesting that the effects of both positive- and negative-pressure respiration are similar in the face of identical pressure gradients.

Immediate chest x-rays are suggested for all newborns whose condition suddenly deteriorates while they are being treated by an artificial lung.

► [With increasing use of assisted ventilation in the newborn, pneumopericardium, once a rare disorder, is being reported much more frequently. A. Löhrer (Schweiz. med. Wchnschr. 102:1248, 1972) reports 3 cases, 2 occurring with respiratory distress syndrome and 1 with hypoplasia of the lungs. He states that air enters the pericardial cavity through rupture of the perivascular pulmonary and mediastinal connective tissue close to the point where the pericardium and pleura are connected. T. H. Shawker *et al.* (Am. J. Roentgenol. 116:514, 1972) report a case in which autopsy revealed no tear in the pericardium. Air was demonstrated in the interstitial vascular sheaths of the lung and apparently dissected through the pericardial reflection around the great vessels. J. A. Gil-Rodriguez *et al.* (Brit. J. Anaesth. 44:1219, 1972) report a case. They recommend continuous drainage of the pericardium because of the risk of sudden cardiac tamponade

This condition must be considered in any infant with respiratory distress and assisted ventilation whose condition suddenly worsens. Pneumopericardium may occur with or without pneumothorax. The presence of the latter should not lessen the care with which the physician views the chest x-ray for presence of air within the pericardium.—Ed.] ◄

Disseminated Intravascular Coagulation in Respiratory Distress Syndrome. Carmi Z. Margolis, Marcello M. Orzalesi and Allen D. Schwartz[3] (Yale Univ.) studied 11 consecutive infants diagnosed as having severe idiopathic respiratory distress syndrome to determine the possible role of disseminated intravascular coagulation (DIC) in this syndrome. There were 8 males and 3 females; 5 infants died.

A decreased platelet count or decreased fibrinogen together with de-

(3) Am. J. Dis. Child. 125:324–326, March, 1973.

creased factors V and VIII indicated DIC. Only 2 infants had definite evidence of disseminated intravascular coagulation. One died at age 1 day. The other had low fibrinogen and factor VIII levels early in the disease; on the 8th day, this infant had definite evidence of coagulation while on a respirator but survived. In both cases, there was a history of abruptio placentae.

Four of the other 9 infants died. Autopsies were performed on 3 and showed extensive hyaline membranes and atelectasis in all and severe intracranial hemorrhages in 2.

Since only 2 of 11 infants with idiopathic respiratory distress syndrome had disseminated intravascular coagulation, it is highly unlikely that the coagulation plays an integral role in pathogenesis of the distress syndrome. Either the coagulation is sometimes triggered by the distress syndrome or both may sometimes result from a common cause.

► [S. Sarraf and co-workers (Spring, 1973, Meetings of the Pediatric Societies, San Francisco) investigated the incidence of disseminated intravascular coagulation (DIC) in the 1st week of life in 26 babies with significant external bleeding. The following causes and incidence were found: DIC 15.3%, vitamin K deficiency 23%, cow's milk colitis 11.6%, trauma 11.6%, infectious and nonspecific colitis 7.7%, thrombocytopenia 7.7%, hemophilia 3.8%, unclassified 7.7% and incompletely studied 11%. They state that although DIC is an important cause of severe neonatal bleeding, bleeding due to vitamin K deficiency remains a significant problem despite the recommendation that vitamin K be given prophylactically at birth. They point out that milk colitis is a definite cause of localized gastrointestinal bleeding that has not been recognized in studies already reported. Their full report will be of interest and should elicit some debate.

At the same meeting R. Miller and C. T. Kisker pointed out that petechiae may occur in neonatal listeriosis and are usually associated with a fatal outcome. They diagnosed DIC in such an infant who was receiving penicillin and gentamicin and noted clinical improvement within 24 hours and disappearance of soluble circulating fibrin 12 hours after heparin therapy was begun. They conclude that a short course of heparin is beneficial when neonatal listeriosis is accompanied by DIC.

The arguments for and against therapy in DIC will continue until well-controlled studies are available. In the interim most clinicians will go on using it. Clearly the most important aspect of therapy is to seek out the underlying cause of the coagulation and properly treat the basic condition. It is quite possible and even likely that in the infant with bleeding due to listeriosis, improvement in intravascular coagulation would have resulted from the antimicrobial therapy for the infection.—Ed.] ◄

Premature Rupture of Membranes and Effects of Prophylactic Antibiotics. Alex H. Habel, George S. Sandor, Nancy K. Conn and W. Morrice McCrae[4] (Edinburgh) compared 100 infants born 24 hours or more after the initial rupture of membranes with 100 infants born within 24 hours of membrane rupture. Samples taken at birth from the eyes, nasopharynx, umbilicus and fetal surface of the placenta of 194 infants showed no evidence of significant bacterial growth. In 6 infants, significant surface bacterial colonization had occurred before or during delivery; 1 of these was in the control series, delivery having been 16½ hours after membrane rupture. Three of the 6 infants received antibiotics (ampicillin and cloxacillin) for 5 days but none of the 6 showed evidence of clinical infection at any time, and in no case did evidence of bacterial colonization persist.

Six neonatal infections were recorded, three in the study infants and three in the controls. Staphylococcus albus was isolated from all six lesions. In contrast, clinical fungal infection (oral and perianal candidiasis) occurred in 12 of 66 (18%) infants receiving antibiotics but in only 3 of 129 (2.3%) not receiving antibiotics. Examination of the day 4

(4) Arch. Dis. Childhood 47:401–404, June, 1972.

specimen cultures revealed a general suppression of growth from all sites in the antibiotic-treated patients along with a notable alteration of the bacterial flora of the feces. Forty-five per cent of the treated infants were unnaturally sterile, having completely negative cultures from all sites, except for fecal yeasts. No yeasts were isolated from the feces of any untreated patient, but from 70% of infants receiving antibiotics. The growth of these antibiotic-resistant yeasts was the sequel of suppression of the normal bowel flora by the broad-spectrum antibiotics used. It is probable that the use of prophylactic antibiotics affected the neonate adversely by encouraging the growth of fungi.

The results of this trial indicate that prophylactic administration of antibiotics to infants delivered after prolonged rupture of the membranes is unnecessary and potentially dangerous.

► [Here is additional evidence against the use of prophylactic antibiotics, which seem to get us into trouble each time they have been proposed. As I view the problem, there seem to be several situations in which prophylactic antimicrobials can be justified: the prevention of streptococcic infection with antibiotics in children who have had rheumatic fever and prophylaxis against subacute bacterial endocarditis in children with congenital or acquired heart disease. It is important to prevent pneumococcic infection in children who have been splenectomized in the first 2 years of life. We do not yet know if penicillin given daily to such children will be effective in prevention of this type of infection, but we are justified in giving prophylaxis. Finally, the preliminary studies that suggest that ampicillin may be of value in prevention of otitis media (see 1973 YEAR BOOK, p. 133) need confirmation before we can be certain that prophylaxis is successful and that we are creating no new problems by its use. There may be other situations in which antimicrobial prophylaxis is indicated but I cannot recall any at the moment. Repeatedly we need to learn that we must avoid antimicrobials unless we know that we are dealing with infection susceptible to antimicrobial therapy and know the organism. We can be excused for treating blindly and without having isolated a specific organism when the patient is at real risk.

When an infant is born after prolonged rupture of membranes the risk of infection may be increased. However, we shall be much less likely to cause harm if appropriate cultures are taken and treatment is begun only when such an infant shows any signs suggestive of invasion by bacteria. Polymorphonuclear leukocytes in the swab of the ear canal, bacteria in the gastric aspirate, infiltration of the cord by leukocytes all suggest that the infant has been exposed to potential infection by bacteria but none of these findings indicates that organisms have invaded the body.

Finally it must be emphasized that we do not really know what is meant by prolonged rupture of membranes. It is commonly considered to be anything over 24 hours before delivery, but this is an arbitrary figure. Perhaps it should be 48. We do know that within 24 hours of membrane rupture the amniotic fluid is colonized by bacteria in over 80% of cases and that if a figure has to be pulled out of a hat, 24 is as good as any. For the advantage to the premature infant of prolonged rupture of membranes, see the editorial comment to the first article in this chapter.

B. Goldberg and co-workers (Spring, 1973, Meetings of the Pediatric Societies, San Francisco) studied 235 infants with rupture of membranes over 12 hours before delivery to identify those at greatest risk from sepsis. A simple evaluation score for some major risk factors was combined with examination of the gastric aspirate. Each infant scored 1 each for prematurity (less than 37 weeks) and maternal fever greater than 100.5 F., and 2 each for membrane rupture greater than 24 hours before delivery and Apgar score of less than 7 at 1 minute. The aspirate was considered positive with more than 5 polymorphonuclear leukocytes per high-power field. Sepsis—clinical signs and a positive blood culture—did not occur in any infant with a negative aspirate (132 infants). Of 103 positive infants 12 (11.7%) had sepsis. If the sepsis score was combined with a positive aspirate, the risk of sepsis increased markedly.

This appears to be a logical approach to the problem of sepsis in the newborn and deserves further investigation.—Ed.] ◄

Umbilical Vessel Catheterization: Indications, Management and Evaluation of the Technic are considered by Martin R. Symansky and Howard A. Fox[5] (Mount Sinai School of Medicine). Of 143 infants who had catheter insertions, only 2 had a catheter in place for longer than 5 days. All were treated with intravenous aqueous sodium penicillin and intramuscular kanamycin therapy for the duration of catheterization plus 48 hours.

(5) J. Pediat. 80:820–826, May, 1972.

Among the 112 patients who received umbilical artery catheters, there were 50 deaths; 48 autopsies were performed. In no instance was a catheter complication considered to be a significant factor in death. At autopsy, 7 babies (15%) had changes that could be attributed to the catheter.

Bacterial cultures from 7 umbilical artery catheter tips were positive (6%). In each case coagulase-negative staphylococci were isolated. None of these infants received antibiotic therapy beyond the usual 48 hours after catheter withdrawal, and none showed clinical evidence of generalized sepsis. The over-all complication rate for umbilical artery catheterization was 17%, whereas the complication rate in the autopsied group was 15%.

The vein was used in 31 patients who received umbilical catheters; in 24 venous catheters were inserted because an arterial catheter could not be passed. Twenty infants died; autopsies were performed on 18. Eleven (61%) of the 18 had thrombi in the umbilical vein, ductus venosus or portal vein. In at least 3 instances these thrombi resulted in significant tissue changes at autopsy: 2 babies had hepatic infarcts, and pulmonary emboli were found in 1 infant with umbilical and portal vein thrombi. The over-all complication rate related to umbilical venous catheter insertion was 35%.

Although potentially serious thrombi were found in 6% of patients autopsied after umbilical artery catheterization, 44% of patients autopsied after umbilical vein catheterization had such thrombi. Thus, except in unavoidable circumstances, the risk of prolonged umbilical vein catheterization, despite its technical ease, outweighs its clinical usefulness in the management of high-risk or acutely ill newborns. Indwelling umbilical artery catheters resting in the descending thoracic aorta represent, with smaller risk, a significant aid in treatment of the low birth weight or acutely ill newborn.

► [The problem of iatrogenic disease as a result of umbilical vessel catheterization is made difficult by the fact that the infants requiring catheters are acutely ill with hypoxia, acidosis and hypovolemia. Thus the procedure and its complications are doubly difficult to evaluate. This is especially true for umbilical vein catheterization inasmuch as most of these babies were extremely ill and catheterization of the umbilical artery had been unsuccessful.

In addition to the acute complications that may be responsible for infant deaths, we are faced with the possibility that long-term sequelae may take place. No follow-up of the surviving infants in the present series is recorded; however Oski *et al.* (1963–1964 YEAR BOOK, p. 218) reported the data on 4 children with portal hypertension who had umbilical vein catheterization in the newborn period. With increasing numbers of infants subjected to such procedures we may expect more cases of portal hypertension resulting from thrombosis of the portal vein.

The practical recommendations given by the authors should help reduce the complications of catheterization. It is also important to stress the need to evaluate carefully the indications for the procedure and to avoid its routine use merely because it provides such an easy means of supplying blood samples.

Dr. Daniel Shannon commented:

"There is an inherent difficulty in evaluating any hospital's experience with umbilical vessel catheterization, i.e., technical virtuosity. Considering the major variables of insertion, infusion composition, sample withdrawal, flushing technic, method of pushing medications, stopcock(s), Millipore filter, intravenous tubing, infusion pump and use of antibiotics, there are at least two ways of performing each of 13 operations and therefore at least 8,192 possible variations on the theme. J. S. Bach couldn't do better. Thus, the results achieved with umbilical artery catheterization can only be applied to the subsequent experience of any given newborn unit, providing they carry out all operations in the same order each time.

"The paper by Symansky and Fox further complicates evaluation since there is as much left to the imagination as there is described. No one would question the American-apple-pie goals stated at the end of the paper. I would, however, question some of the specific comments in the paper.

First, when difficulty is encountered in passing the catheter past the first 3–4 cm., I have found that the various suggestions given by Ketterman and the present authors for using continuous steady pressure or even Xylocaine infusion are seldom helpful. Transient hypoxemia would be the most effective but I am not willing to try it. An umbilical venous catheter, regardless of the position of its tip, should not be considered a substitute for arterial catheterization, even for a short time. Capillary blood gases provide just as much useful information as venous gases and are much safer. An umbilical venous line can be a temporary (less than 24 hours) route for injection of water, electrolyte, colloid or medication. If we are faced with the inability to place an umbilical arterial line we then insert a radial or temporal artery catheter which can be done in most infants of 1,200 Gm. and over. Next, I think that it is not good practice to inject blood that was drawn from the infant in order to flush the catheter. Drawn into a glucose solution, it hemolyzes; drawn into the saline, the baby becomes overloaded with sodium. There's no rationale for the use of routine antibiotics to 'cover the catheter insertion.' The possibility that infusion of hypertonic solutions causes the observed thromboses is raised by these authors. The most hypertonic solution pediatricians use is stock sodium bicarbonate; the 0.88 mM./L. solution has an osmolality of 1,760 mOsm./L. or 6 times that of the infant. If its rate of injection does not exceed 2% of the rate of aortic blood flow, osmolality of aortic blood will not exceed 10% of normal. If cardiac output is not grossly impaired, flow is about 200 ml./kg./minute. Thus, bicarbonate could be given safely at 4 ml./kg./minute. A rate of half that is suggested when cardiac output is impaired.

"Finally, culturing the tip of a catheter withdrawn through a dirty umbilical stump probably has no meaning and shouldn't be used as an index of complications.

"Since most complications can be attributed to injection of organisms, the essence of catheter care is prevention of sepsis. In our unit this means (1) daily change of all stopcocks, Millipore filter and intravenous tubing (2) frequent anointing of the umbilical stump with Betadine ointment (3) maximal duration of usage of 7 days and (4) special technics for drawing samples of blood. Each catheter is connected to three stopcocks in series, each of which is melded to the next with a metal yoke to prevent accidental disconnection. The stopcock closest to the infant is used only for blood sampling; the next is used only for withdrawing initial blood to flush with 1 ml. of maintenance solution to clear blood from the line. The third is used only to monitor arterial blood pressure. The line is constantly flushed by an infusion pump using 10% dextrose containing 1 unit of heparin per ml. of solution and drawn through a Millipore filter with 0.45-μ pores.

"Used in this manner, we have experienced no known serious complications when the catheter was withdrawn within 7 days of insertion. Also, virtuosity wins again."

W. A. Neal *et al.* (Pediatrics 50:6, 1972) investigated the data on 100 consecutive infants admitted to their neonatal intensive care unit. Seventy-nine of the infants had umbilical catheters inserted. Eighty-six per cent of the catheters were placed in an umbilical artery. Approximately one fourth of the infants with umbilical artery catheters were randomly selected to have aortograms at the time of catheter removal. In all but 1 case there was no clinical evidence of thrombus formation. Ninety-five per cent of the infants with aortograms showed distinct arterial thrombus formation. The authors speculate that a higher concentration of heparin in the maintenance solution (200 units per L.) might have lowered the incidence of thrombosis.

Despite these findings, the complications caused by umbilical artery thromboses appear to be relatively rare. W. H. Tooley (ibid., p. 1) states that follow-up of infants from their unit has revealed no signs of vascular insufficiency to the legs.

Obviously there is far less danger in umbilical artery catheterization than in catheterization of the vein. Since the advantages in umbilical artery catheterization for the sick neonate far outweigh the dangers, it will continue to be used all too freely.—Ed.] ◄

Phototherapy and Insensible Water Loss in the Newborn Infant. William Oh and Hanne Karecki[6] (Univ. of California, Los Angeles) performed water balance studies in 12 full-term hyperbilirubinemic newborns receiving phototherapy. The results were compared with those in 14 control and 10 jaundiced infants who did not receive phototherapy. Birth weight, sex and racial distribution were similar for the three groups. Incubator temperature, rectal temperature and relative humidity in all three groups during the study were also comparable.

During the study, the phototherapy infants breathed significantly faster than infants in the other two groups. The phototherapy infants had significantly greater stool water loss and insensible water loss than the controls. The differences in stool water loss and insensible water loss between the phototherapy and nonphototherapy jaundiced infants were also significant.

(6) Am. J. Dis. Child. 124:230–232, August, 1972.

Increased insensible water loss and stool water loss must be taken into account in the calculation of parenteral fluid intake for sick low birth weight infants receiving phototherapy.

► [We are being deluged with articles about phototherapy for jaundiced newborns. This is appropriate for we have much to learn about this new "drug." In this article it is clear that too little attention has been given to such side effects as water loss. At the Spring, 1973, Meetings of the Pediatric Societies, San Francisco, several presentations on phototherapy were of special interest. J. F. Lucey and co-workers reported a 4- to 6-year follow-up of low birth weight infants treated with phototherapy. Fifty-five light-treated infants and 44 controls were found to show no statistical differences in weight, height, head circumference, intelligence, speech, hearing and neurologic function. J. E. Hodgman and co-workers in a 1-year follow-up study of the effect of phototherapy on the subsequent growth of low birth weight infants found that treated infants were significantly smaller than the controls. At 2 years a significantly greater number of treated infants were still below the 10th percentile in all measurements; however, the number with head circumference below 2 S.D. was no longer different from controls.

Most studies of the possible untoward effects of phototherapy involve relatively small groups of infants and it will require larger series before we can be certain of the results. At this point there appears to be no solid evidence that indicates that there are undesirable side effects. Dr. Jerold Lucey goes even further in suggesting that a component of physiologic jaundice is due to "light deprivation."

I hope that the battle of the lights will not fall into dirty little skirmishes. Phototherapy has proved to be a great advance in management of jaundice in the neonate; nevertheless, it is necessary to view it with suspicion and to investigate with great care its potential long-term effects.—Ed.] ◄

Kernicterus in Small Sick Premature Infants Receiving Phototherapy. William J. Keenan, Paul H. Perlstein, Irwin J. Light and James M. Sutherland[7] (Cincinnati) describe the failure of phototherapy to prevent kernicterus in 4 small sick immature infants with gestational ages between 20 and 30 weeks. Two of the 4 infants had serum albumin levels below 2 Gm./100 ml. All of the infants were hypothermic sometime during the clinical course. One had a blood sugar of 28 mg./100 ml. while being treated for hyperbilirubinemia. All had significant acidosis. Two infants received protein hydrolysate intravenously and all received multiple medications. However, none of the infants received drugs that are known to potentiate the development of kernicterus.

All 4 infants died. In addition to kernicterus, all infants had other central nervous system pathologic findings. Three infants had infection in the central nervous system and 3 had subependymal or intraventricular hemorrhage. Autopsy of 1 infant revealed purulent meningitis and bilirubin staining of dentate, pontine and basal ganglions with extensive neuron necrosis. Another infant had patchy areas of severe atelectasis, necrotizing monilial laryngitis, monilial abscesses in liver and spleen, several small abscesses in the brain and neuronal necrosis and yellow pigmentation in the subthalamic nucleus. In the third infant there was marked nuclear kernicterus with neuron necrosis, extensive inflammation of the leptomeninges and a small subependymal hemorrhage. The fourth infant had a moderate degree of subependymal hemorrhage and neuronal necrosis with bilirubin deposition in the thalamus.

Maximal measured bilirubin concentrations were 17.8-10.5 mg./100 ml. The serum levels of bilirubin in each of the infants decreased when they were treated with phototherapy. Each infant had multiple complications that most likely potentiated the development of kernicterus at low concentrations of serum bilirubin. However, it is possible that if

(7) Pediatrics 49:652-655, May, 1972.

phototherapy had been used earlier in the clinical course of these infants the rise in serum bilirubin would have been less and kernicterus avoided.

► [Patients such as those presented here play right into the hands of that great advocate of phototherapy, Dr. Jerold F. Lucey, who, in a commentary in the same issue of *Pediatrics*, wrote that he feels such high-risk small premature infants should be placed on phototherapy shortly after birth and before the bilirubin level has risen to 10 mg./100 ml. He feels that this might be effective. Doctor Lucey is playing the game conservatively; he is not recommending that every small premature infant go promptly under the lights but only those with hypothermia, asphyxia, acidosis, hypoalbuminemia, hypoglycemia, sepsis, meningitis and drugs that affect albumin binding and those with a serum bilirubin above 10 mg./100 ml. I cannot fault him for such recommendations for this is the only way by which we can determine if phototherapy will prevent kernicterus under these circumstances. It is entirely possible that in the presence of meningitis or brain abscess, or inflammation of the meninges as noted in these infants, nothing can prevent staining of brain tissue by bilirubin, no matter how low the level of serum bilirubin is held. Do we know that the staining of the brain by pigment in these 4 infants represents the same significance as pigmentation of the brain in the absence of local inflammation or infection?

At any rate there is nothing to be gained by nit-picking. If it can be shown that immediate and continued phototherapy in these high-risk infants will not prevent the finding of kernicterus at autopsy, we shall have to find other methods of prevention or will have to accept the fact that when the brain or meninges are sufficiently damaged, kernicterus may be inevitable. It should be quite clear that prompt treatment of the asphyxia, acidosis, hypoxia, hypoglycemia or sepsis is vital to the management of the infant.

I would click the lights on at once for any premature infant at risk and would recommend phototherapy for healthy premature or small-for-date infants when the indirect serum bilirubin level reaches 10 mg./100 ml. In full-term infants who are healthy I would opt for phototherapy when the level reaches between 15 and 20 mg./100 ml. – Ed.] ◄

"Bronze" Baby Syndrome: Complication of Phototherapy is reported by Arthur E. Kopelman, Ralph S. Brown and Gerard B. Odell[8] (Johns Hopkins Univ.).

Girl was born after 7½ months of gestation. For the first 2 days she had mild to moderate respiratory distress. On day 3 jaundice was first noted, and by day 4 the total bilirubin was 21 mg./100 ml., with 8 mg./100 ml. direct reacting. She was exposed to a phototherapy lamp; within 48 hours (day 6), the skin had become brown and the hematocrit had fallen from 52 to 42%. Ampicillin was started for possible sepsis, although all cultures subsequently were sterile. On day 7 the skin had a dark gray-brown color, which did not change after administration of oxygen. The liver edge was felt 1.5 cm. below the right costal margin. The spleen was not palpable. Neurologic examination was normal. Blood smear revealed normal red blood cell morphology and platelets. Serum bilirubin concentration was 10 mg./100 ml., with a direct-reacting fraction of 2 mg./100 ml. The bilirubin saturation index was 6.3 (expected value for infants with this bilirubin concentration, 3). Serum glutamic oxaloacetic and pyruvic transaminases and alkaline phosphatase were elevated. The erythrocytes had a normal red color, whereas the serum after centrifugation of the erythrocytes was dark brown, similar to the patient's skin. The urine was also brown.

The baby was protected from bright light. The urine remained turbid brown for 2 days, and the stools were bulky and pale. Less than 3 mg. bilirubin per 24 hours was excreted in the stools. The gray-brown color of the skin and plasma gradually cleared over the next 3 weeks, but serum bilirubin values remained slightly elevated. At age 3 weeks the hematocrit was 24% and a transfusion of packed red blood cells was given to raise it to 30%. The infant was discharged at age 30 days.

The abnormal direct-reacting bilirubin in the serum before onset of light therapy and the elevation of serum transaminases associated with acholic stools suggest the likelihood of pre-existing liver disease. This may also have been responsible for the retention of the photo-oxidation products of bilirubin formed in vivo, which then may have led to the discoloration of the serum and skin. Current evidence indicates that

(8) J. Pediat. 81:466–472, September, 1972.

normally the photodecomposition products of bilirubin formed in vivo are rapidly excreted, primarily in bile and stool. It is not known whether these products are toxic when retained.

► [Dr. Jerold F. Lucey commented that this was an interesting, worthwhile report of a child with liver disease who received phototherapy and acquired a striking skin and serum discoloration. The discoloration was transient and benign as have been several other similar unreported cases. Infants with liver "disease" (elevated levels of direct-reacting bilirubin) should not receive phototherapy as it does not benefit them, and it could be harmful. This situation should not be confused with what occurs when a normal infant receives phototherapy. Doctor Lucey and his colleagues have not seen this type of skin or serum discoloration in over 600 "normal" premature infants treated with light in their nursery since 1966. The skin tanning noted in some infants (Woody, M., and Bradky, M.: Tanning from Phototherapy for Neonatal Jaundice, J. Pediat. 83:1042, 1973) is due to increased melanogenesis, a normal transient response to long-wave ultraviolet and visible light (Pathak, M., *et al.*: Melanogenesis in Human Skin Following Exposure to Long-Wave Ultraviolet and Visible Light, J. Invest. Dermat. 39:435, 1962). Doctor Lucey also writes that the evidence cited that this infant also had an "acute fall in hematocrit suggesting hemolysis" is extremely poor and unacceptable. The initial hematocrit on the 4th day of life was 52%, with a reticulocytosis of 4.6%, and at age 3 weeks it was 24%; these values are within the normal ranges for premature infants (Gorten, M., and Cross, E.: Iron Metabolism in Premature Infants, J. Pediat. 64:504, 1964). During the 3-week period of observation and study this infant had at least 24 blood studies done (and about 30 cc. blood withdrawn). He was known to have liver disease and suspected of having sepsis. Both of these conditions are associated with hemolysis and altered red cell survival time. The infant also gained weight from 1,250 Gm. to 2,030 Gm. He did not receive iron therapy. No stool studies to rule out blood loss were cited nor were the sampling sites for blood samples mentioned.

Doctor Lucey concludes:

"I therefore cannot accept the authors' evidence that this infant had hemolysis due to phototherapy. Several clinical studies have also not confirmed the presence of a higher incidence of anemia in infants who have received phototherapy.

"The other question the authors raise as a cause for concern is their finding of a high bilirubin saturation of albumin as determined by the salicylate saturation index. The initial study suggesting the clinical usefulness of this test has not been confirmed. It is apparently rarely used in other hospitals and has recently been discredited (Brattid, D.: Reserve Albumin Binding Capacity, Salicylate Saturation Index and Red Cell Binding of Bilirubin in Neonatal Jaundice, Arch. Dis. Childhood 48:393, 1973)."—Ed.] ◄

Photodynamic Action of Bilirubin on Erythrocytes was quantitated by Gerard B. Odell, Ralph S. Brown and Arthur E. Kopelman[9] (Johns Hopkins Univ.). Erythrocyte suspensions in bilirubin from a jaundiced infant who had experienced a sudden drop in hematocrit after exposure to a phototherapy lamp and from a normal adult were exposed to a fluorescent lamp. During irradiation none of the cell suspensions showed significant "immediate" hemolysis. After storage of these suspensions in the dark for 18 hours after 2 hours of irradiation, extensive "delayed" hemolysis was found in the irradiated samples in contrast to light-protected suspensions. The difference in delayed hemolysis between the suspensions of the patient and control suspensions was not significant. A suspension of the patient's cells that was irradiated without bilirubin exhibited no delayed hemolysis. If albumin was omitted from the suspensions, bilirubin caused hemolysis of erythrocytes without light exposure at concentrations as low as 2.5 mg./100 ml.

An initial loss of erythrocyte potassium occurred when the red blood cells were first suspended in the buffered medium, which contained no potassium. A subsequent loss of erythrocyte potassium occurred only in suspensions exposed to light, and the loss was linearly proportional to the duration of exposure. A further "delayed" loss of potassium occurred when the irradiated suspension was incubated overnight in the dark.

(9) J. Pediat. 81:473–483, September, 1972.

Potassium loss and subsequent hemolysis were more rapid in a suspension with a 2:1 molar ratio of bilirubin to albumin than in a suspension with a 1:1 ratio. This finding suggests that the hemolytic action of bilirubin is related to the concentration of free (diffusible) rather than protein-bound bilirubin.

Suspensions that were irradiated in air but in the absence of bilirubin exhibited no significant potassium loss. Elimination of oxygen from the suspensions by gassing them with carbon monoxide for 15 minutes before and during irradiation in the presence of bilirubin prevented the light-induced cation leak. The dependency of the induced potassium leak upon both light and oxygen as well as bilirubin suggests that the erythrocyte damage involves a photosensitized oxidation of an essential membrane constituent.

Caution should be exercised in application of phototherapy to newborns.

► [Dr. Jerold F. Lucey commented, "This study offers in vitro experimental evidence to support the view that phototherapy can cause 'acute anemia' in infants via a photodynamic action of bilirubin on erythrocytes. In view of the authors' previous unwillingness to accept in vitro evidence regarding the photodestruction products of bilirubin, one wonders why they are so willing to extrapolate from these in vitro observations made under highly abnormal light conditions to the human situation. It is too great a leap for me to accept. They also fail to explain why, if their hypothesis is true, severe anemia would not be more common in phototherapy 'victims.' I think they have found a cause for a 'disease' which may not exist." – Ed.] ◄

Controlled Trial Comparing Agar, Intermittent Phototherapy and Continuous Phototherapy for Reducing Neonatal Hyperbilirubinemia was carried out by Harold M. Maurer, Clare N. Shumway, David A. Draper and Ali A. Hossaini[1] (Med. College of Virginia, Richmond). Infants of low birth weight, aged less than 24 hours, were randomly assigned to one of four groups. Group 1 (17 infants) received 125 mg. agar by mouth every 3 hours for 4 days, beginning at 18 hours. Group 2 (18 infants) was exposed to 200–300 footcandles of blue fluorescent light intermittently, 12 hours daily for 4 days. Group 3 (19 infants) was exposed to blue fluorescent light continuously for 4 days. Group 4 (15 infants) was not treated. Infants with positive Coombs test or sepsis were excluded. Serum bilirubin concentrations were determined daily.

From the 2d day, infants who received continuous phototherapy had significantly lower mean serum bilirubin levels than those of any other group. Infants who received intermittent phototherapy or agar-supplemented feedings had mean values that were lower than those of controls on days 4–6 but the difference was significant only on day 4. Side effects of therapy in both light-treated groups consisted of occasional mild diarrhea. Agar supplementation was well tolerated and no significant weight loss occurred as a result of its potential laxative effect.

Continuous phototherapy during the first 4 days of life is significantly superior to either intermittent phototherapy or agar-supplemented feedings in reducing the concentration of serum bilirubin in low birth weight infants. The results do not confirm previous findings that agar supplementation in full-term infants prevents rise in neonatal serum bilirubin concentrations. Prophylactic use of continuous phototherapy

(1) J. Pediat. 82:73–76, January, 1973.

is not recommended for all low birth weight infants, only for those with serum bilirubin more than 10 mg./100 ml.

► [The authors of this article used USP Difco agar; Doctor Odell, who first pointed out the beneficial effects of agar therapy on bilirubinemia of the newborn, has stressed that the source of agar is important and that some preparations are more effective than others in their binding of bilirubin. Accordingly, the results reported here cannot be compared with those of Poland and Odell (1972 YEAR BOOK, p. 23).

In addition, the initial bilirubin levels of the infants treated with constant light were significantly lower than those of infants treated with intermittent phototherapy and 100% lower than those of infants treated with agar. Higher bilirubin levels on day 1 are usually associated with higher peak bilirubin levels on days 4 and 5. Finally, in the agar-treated group there were more male infants and more infants with shortened gestational ages and low birth weight than in the other groups. Such infants would be expected to have higher peak bilirubins.

F. H. Wirth, Jr., and S. E. Davis (Spring, 1973, Meetings of the Pediatric Societies, San Francisco) point out that the reabsorption of bilirubin from meconium is most pronounced in the 1st hours of life, and that there is a significant relationship between a delay of the first meconium passage and the incidence of hyperbilirubinemia. The authors studied two groups of healthy term infants. One group received one half of an infant glycerine suppository within 30 minutes after birth and every 4 hours just after feedings. The treated infants passed all their meconium at an average age of 27.6 hours as compared with 52.9 hours for the control group. Daily serum bilirubin levels were significantly lower in the treated group of infants on days 2, 3 and 4 of life. The amount of meconium and bilirubin excreted on day 1 was significantly greater in the study group.

It looks as though it is wise for the newborn to keep the bowels open. For that matter, it is probably beneficial for all of us. We will probably have several options in the future in treating the jaundiced newborn—purging, suppositories and enemas. Even blood letting may have its day. The acupuncturists are waiting to be heard.—Ed.] ◄

Intestinal Absorption of Immunoglobulins by Newborn Infants was studied by Leela Iyengar and R. J. Selvaraj[2] (Hyderabad, India). Paired samples of cord and maternal blood were collected from 31 mothers delivered at 40 weeks. Of these, 18 fed colostrum to their infants and then milk from the 4th day after delivery; the other 13 infants did not receive colostrum but were instead bottle-fed with formula milk until the 4th day, when they began to receive breast milk. Blood samples from all infants were obtained on the 5th day.

The IgG levels in cord serum were slightly lower than those of the maternal serum. Colostrum IgG concentration did not differ from that in serum, whereas the concentration in milk was low, being on the average only 11.7% of a reference serum. The concentrations of IgM and IgA in cord blood were considerably lower than the levels in maternal serum. These data indicate that transfer of these immunoglobulins across the placenta is not similar, there being a greater transfer of IgG than the other two. In colostrum, extremely high levels of IgA were found, fifteen times that of the reference serum, whereas the 5th day milk showed a dramatic decrease to approximately half of the reference serum level. The IgM levels in colostrum were 157% and in milk 46% of the reference serum.

Whereas levels of IgG in serum of infants who did not receive colostrum were reduced on the 5th day to 24% of the level at birth, the levels in colostrum-fed infants rose slightly from the initial level. The differences in IgG levels on the 5th day between the two groups were highly significant. Thus, reduction of IgG levels brought about as a result of catabolism was probably compensated by the intestinal absorption of IgG from the colostrum in the colostrum-fed infants.

Serum IgA levels in bottle-fed infants on the 5th day did not differ

(2) Arch. Dis. Childhood 47:411-414, June, 1972.