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PREMATURE AND NEWBORN INFANTS
Report of a Seminar

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The following report was prepared by a secretary-reporter chosen by the Editor to audit this seminar and summarize the information presented for the benefit of the readers of Pediatrics. The secretary-reporter and Editor assume full responsibility for the selection of the excerpts reported. [Ed.]

SURGICAL PROBLEMS OF NEWBORN AND PREMATURE INFANTS

Participating in the seminar's first session were Dr. William R. Richardson, Kings County Hospital, Brooklyn, New York, who served as moderator, Dr. Thomas Santulli, Children's Surgeon at Columbia-Presbyterian Hospital, New York City, Dr. Marel H. Harmel, Anesthesiologist at Kings County Hospital, and Dr. Lawrence K. Pickett, Chief of Surgery at the State University of New York Medical Center in Syracuse. All speakers emphasized the importance of closely co-operative effort by pediatricians, surgeons, radiologists, anesthesiologists and nursing personnel to facilitate early recognition, diagnosis and effective treatment of neonatal complications requiring surgery.

Diagnosis

Early recognition of surgical problems usually depends upon the observations of well-trained nurses. Any history of obstetric complications, especially breech presentation, a maternal history of hydramnios, any signs of respiratory distress, difficulty in swallowing at the time of the first feeding, emesis of bile-stained fluid, abdominal distention, or failure of the appearance of the first stool within 24 hours after birth should alert all observers to the possibility of complications which will require surgery.

As soon as respiratory or gastrointestinal complications are suspected, Dr. Pickett requests radiologic consultation. A roentgenogram of the chest, taken at this time, will delineate not only the infant's pulmonary status, but also the gas pattern of the intestinal tract. When the clinical picture suggests gastrointestinal obstruction, Dr. Pickett and his colleagues employ a No. 8 to 10 French soft rubber catheter, specially prepared by punching several holes in its terminal 1 cm portion. This tube is inserted under fluoroscopic control and passed cautiously to avoid traumatic puncture of any obstructing tissue which may be en-
countered. When esophageal atresia is recognized, the proximal esophageal pouch is carefully aspirated to remove pooled saliva. If the catheter passes easily into the stomach, gastric contents are aspirated and measured; Dr. Pickett believes that the presence of more than 30 ml of fluid within the neonate's stomach is abnormal and suggestive of duodenal obstruction. Air usually provides satisfactory contrast for roentgenologic studies. If a radio-opaque medium is needed, no more than 0.5 ml of Lipiodol® or non-oily Dionosil® is introduced through the rubber catheter under fluoroscopic control and then removed immediately. In Dr. Pickett's experience, a cystoscope serves as an excellent bronchoscope for examination of newborn infants, and has often been useful in locating small tracheal fistulas.

Transport and Preparation

When transport from one hospital to another is necessary for surgical treatment of gastrointestinal obstruction, Dr. Pickett recommends that the infant's head be elevated 45 degrees to prevent chemical irritation by regurgitated gastric juice, that continuous suction be employed to remove accumulating fluids from the bowel proximal to the site of obstruction, and that oxygen and humidifiers be liberally used when respiratory distress is also present. If transport by air is planned, one should be wary of possible closed-loop obstructions, in either the chest or the abdomen, within which trapped air may expand to cause rupture of a viscus.

Dr. Pickett recommends that at least 24 hours be allowed for stabilization and preparation of the infant prior to surgery. During this period, he gives nothing by mouth, and a solution of glucose without electrolytes parenterally to provide no more than 65 ml/kg/day. Overhydration and saline solutions are to be avoided during this preoperative period because they often lead to undesirable edema of the surgical wound and pulmonary edema. If pneumonia is suspected, appropriate antibiotics should be given, in addition to oxygen and humidity.

Resuscitation

Resuscitation of the newborn is best accomplished by mouth-to-mouth insufflation, according to Dr. Harmel. Oxygen may also be given by mask or by inhalator. The usefulness of most inhalators is limited by the narrow range of pressures which they provide. Because anoxia of more than 3 to 4 minutes' duration can produce irreversible damage to the central nervous system, Dr. Harmel stressed the importance of early and adequate resuscitation. Dr. Day questioned the validity of this traditional 3- to 4-minute margin of safety. He knows of no acceptable experimental data which establish upper limits of safe duration of anoxia for newborn infants, and none of the other participants could cite such data. Dr. Day's own clinical experience includes many infants who manifested no damage to the brain after experiencing anoxia of longer than 4 minutes' duration, and he believes that other variable factors, in addition to the amount of oxygen supplied to the brain, play significant roles. The use of respiratory analeptics is seldom indicated, according to Dr. Harmel, who compared their use to "whipping a tired horse"; he prefers to locate and remove the cause of respiratory obstruction whenever possible. Caffeine may occasionally be useful as a central nervous system stimulant, but only when the degree of nervous depression is slight.

Intestinal Obstruction

The preoperative problems presented by newborn infants with intestinal obstruction were discussed by Dr. Santulli. He is convinced that any infant who vomits bile or who develops abdominal distention deserves roentgenologic examination in three positions, upright, horizontal and inverted, using air as the contrast medium. If these initial films do not clearly demonstrate the site of obstruction, a small barium enema should be used, because it is often difficult to differentiate gas patterns of the colon from those made by gas in the small bowel. A cautious barium enema will demonstrate the presence of: (1) congenital megalcolon, which can cause intestinal obstruction during the newborn period and usually should not require operation at this time; (2) an obstructing meconium plug which may be removable by vigorous irrigations using one-third strength hydrogen peroxide without resort to laparotomy, and (3) malrotation of the intestine.

Dr. Santulli has reviewed the surgical experience at New York Babies' Hospital from 1939 through 1955. The most common causes of intestinal obstruction in newborn infants
were atresias and stenoses (57 cases, mortality 58.0%), meconium ileus (37 cases, mortality 67.5%), malrotations (30 cases, mortality 16.6%) and aganglionoses (28 cases, mortality 28.8%). Less frequent causes included inguinal hernias, congenital peritoneal bands and local volvulus.

Meconium ileus has been the presenting problem of 10% of all patients with cystic fibrosis of the pancreas being followed at Babies' Hospital. The typical surgical picture presented by these patients includes dilatation and hypertrophy of the proximal ileum, volvulus and/or gangrene of the mid-ileum, and “hypoplasia” of the colon. Meconium ileus has often been associated with additional anatomic abnormalities; in the Babies' Hospital series of 37 patients, volvulus of the small intestine has been present in 16, congenital peritoneal bands in 4, malrotation in 3 and meconium peritonitis in 7 cases. Twenty-five of these thirty-seven patients died after surgery; of the 12 who survived surgery, 7 have subsequently succumbed to pulmonary infections, and 1 has died because of malnutrition and dehydration. Among the four currently surviving patients, three are in excellent clinical condition with radiologically normal lungs, but one has severe pulmonary changes.

Of 28 patients admitted to Babies' Hospital during the neonatal period with intestinal obstruction due to congenital megacolon, 13 came to surgery during this early period, but 15 responded initially to conservative treatment and could be treated surgically at a later age. The eight deaths in this group were attributed to anasarca, perforation, bacteremia and acute membranous colitis, which may occur in association with any surgical treatment of colonic obstruction.

Major causes of mortality in the total group of patients were prematurity, shock, electrolyte and water imbalances, malnutrition, breakdown of anastomotic sites and nonfunctioning anastomoses, peritonitis, and aspiration of vomitus. Mortality rates can be decreased by early diagnosis and surgical treatment, conservative administration of parenteral water and avoidance of salt-containing fluids during the pre- and postoperative periods, and improved anesthesiologic and surgical techniques.

Rupture of the Stomach or Intestines

The infant who suddenly develops abdominal distention and circulatory collapse, usually during the first week and rarely after the second week of life, should be considered to have rupture of the stomach or intestine, for which early surgical treatment is essential. Such rupture may be due to a muscular defect in the gastric wall, sepsis, or trauma produced by polyethylene tubing. A roentgenogram of the upright abdomen will demonstrate free air under the diaphragm and it is not necessary to further localize the point of rupture preoperatively, according to Dr. Santulli. Dr. Day called attention to the importance of properly selecting and preparing polyethylene tubing for use in gavage. The tubing's outside diameter should not be greater than 0.38 cm, and the tip must be rounded and smoothed. When tubing is cut by scissors, the tip is sharp enough to perforate a rubber glove easily. Dr. Santulli urged caution in the use of indwelling gavage tubes, because of the danger of perforating the gastrointestinal wall. When tube-feedings are needed, he uses an indwelling polyvinyl tube.

Postoperative Problems

During the general discussion which ended this session, Dr. Pickett pointed out that intestinal obstruction by a meconium plug may be the initial manifestation of either cystic fibrosis of the pancreas or of congenital megacolon. In his experience, 50% of the infants who had obstructing meconium plugs during the newborn period have subsequently developed other signs of cystic fibrosis of the pancreas. Dr. Harry Gordon stressed the importance of carefully and cautiously observing any infant who fails to pass his first stool within 24 hours post partum. Dr. Richardson believes that the product of any complicated delivery, especially an infant born by breech presentation, should be carefully observed because the incidence of traumatic complications such as visceral ruptures is high in this group of infants. Dr. Santulli warned against the use of tap-water enemas if congenital megacolon is suspected, because of the danger of water intoxication; saline enemas in small quantities should be used in such cases. When poor healing or complicating infection occur after circumcision of an infant, Dr. Pickett recommends that both diaper and dressing be removed from the infant so that the penis may be exposed to air. The use of high concentrations of oxygen during surgical anesthesia of premature infants may involve risk of subse-
quent development of retrolental fibroplasia, but Dr. Harmel believes that the benefits derived from oxygen administered during surgery far outweigh this possible danger. According to Dr. Day, no one knows whether exposure to high concentrations of oxygen for only 1 to 2 hours is safe or not, but the available evidence does suggest to him that there is a lessened risk associated with administration of oxygen when it is really required.

HEMATOLOGY

Participants in the session on hematology were Dr. R. Janet Watson, Dr. Walter J. O'Connor and Dr. Richard L. Day of the State University of New York, and Dr. James A. Wolff, of the College Physicians and Surgeons, Columbia University.

Iron-deficiency Anemias

Current concepts of the physiologic anemia of the newborn and the anemia associated with prematurity were reviewed by Dr. Wolff. He prefers to think of the newborn's physiologic anemia as having two phases. The earlier phase, extending through the first 3 or 4 months of life, is primarily due to decreased hematopoiesis. During this period transplacentally acquired stores of iron are sufficient to satisfy the infant's modest requirements and iron derived from dietary sources is not utilized for the production of hemoglobin. The later phase is a manifestation of iron deficiency to which both endogenous and exogenous factors may contribute. Endogenous variables which may predispose to anemia include hemoglobin concentration at the time of birth, total blood volume at birth, total body content of iron (Dr. Wolff considers that values within a range from 100 to 300 mg of elemental iron are normal), volume of placental blood permitted to enter the infant before the umbilical cord is cut, and rate of physical growth during early infancy. Among the more important exogenous factors is variation in the absorptive capacity of the infant's gut which may be a limiting factor if less iron can be absorbed than is required for optimal hematopoiesis. These same endogenous and exogenous factors contribute to the development of the anemia of premature infants, which may become quite severe because of the rapid growth of these infants.

Basing therapy on these concepts, Dr. Wolff prescribes iron for all premature infants, starting at the time of discharge from the hospital, in an initial dosage calculated to supply 16 mg of elemental iron per day. The dosage is subsequently changed to 5 to 10 mg/kg/day as the infant grows. He prefers to give the iron-containing liquid medication between meals and has not observed any manifestations of intestinal toxicity. Dr. Wolff stated that blood transfusion is rarely necessary in the anemia of prematurity, and is reserved for those infants who have other complications in addition to severe anemia. He usually finds that premature infants do well without therapeutic iron after 6 months of age if dietary sources of iron are adequate.

Dr. Wolff and Dr. Watson commented upon the use of combinations of cobalt with iron for the treatment of premature infants with anemia. Both speakers called attention to the potential toxicity of cobalt, which has been shown to cause thyroid dysfunction and may also have a basically toxic effect upon hematopoiesis. Dr. Watson made a strong plea that cobalt not be used for the treatment of any anemia unless special research is being conducted. She does not know of any hematologist who has had 5 years' experience with cobalt therapy and still prescribes it.

When to sever the premature infant's umbilical cord received comment from Dr. Day, who balanced the desirable 30 to 40% increase in blood volume gained by delaying severance of the cord till all placental blood has drained into the infant against the potential hazard of producing right heart failure by overloading the premature's cardiovascular system. Dr. Day believes that the practice of milking the umbilical cord may be dangerous for this reason, but prefers to await the collection of further data before making a final decision.

Bilirubin Metabolism

Dr. Day attempted to reach conclusions concerning whether, and when, exchange transfusions should be done on the sole indication of hyperbilirubinemia. He has studied a strain
of rats in which jaundice and kernicterus occur spontaneously in a high percentage of newborns (cf., Malloy, Helga T. and Lowenstein, L.: Hereditary jaundice in the rat. Canad. M.A.J., 42:122, 1940), due to a single recessive gene which produces a metabolic defect in the liver. Studies of these newborn rats, and also of certain protozoa, Tetrahymena, have shown that bilirubin inhibits the uptake of oxygen by fresh tissue, and in high concentrations (exceeding 120 mg/100 ml) prevents the clotting of blood. The experiments with rats suggest that a "maturity factor" of neural tissue may determine the concentration of bilirubin in blood which produces toxic effects. The experiments with Tetrahymena demonstrated the ability of cytochrome C to counteract the toxic effects of bilirubin, but this counteractivity was not apparent when cytochrome C was given to jaundiced newborn rats and Dr. Day stated that cytochrome C has absolutely no justifiable use in the treatment of humans.

Dr. Day's clinical experience suggests that 5 to 10% of premature infants develop bilirubinemia greater than 20 mg/100 ml. Many factors are involved and must be considered before therapeutic decisions are made. English workers have observed the incidence of hyperbilirubinemia to be increased when infants are given 10 mg of Vitamin K daily for several days. American reports suggest that Gantrisin® may predispose to the development of kernicterus even when the concentration of bilirubin in serum never exceeds 15 mg/100 ml. Hepatic immaturity also affects the development of hyperbilirubinemia in premature infants.

Because of the paucity of basic knowledge concerning the mechanism of toxicity of bilirubin, Dr. Day does not use hyperbilirubinemia as a sole criterion for exchange transfusion. He prefers to individualize treatment on the basis of the patient's complete clinical picture, while remaining fully aware that any course of treatment involves risks. Following the English reports cited above, Dr. Day recommends that the individual dose of Vitamin K administered to newborns be less than 5 mg and that doses be given no oftener than every third day. He also believes that the administration of Gantrisin® and sulfadiazines to premature and newborn infants is contraindicated because of demonstrated potentiation of bilirubin's toxicity.

**Placental Hemorrhage**

Dr. O'Connor has studied 17 mother-infant pairs in whom he believes that transplacental hemorrhage was responsible for progressive anemia of the neonate. During a survey conducted at King's County Hospital, Brooklyn, New York, Dr. O'Connor suspected 24 such cases among 9,000 deliveries but 7 cases were eliminated from the reported series because of insufficient postnatal data. Photometric demonstration of more than 1% fetal hemoglobin in the mother's blood immediately post partum, plus subsequent proof of the disappearance of this fetal hemoglobin from the maternal circulation within 2 or 3 months, established the diagnosis. Transplacental hemorrhage was associated with other obstetric complications in 9 of the 17 mothers, and with premature delivery in 7 cases. Dr. O'Connor compared concentrations of hemoglobin obtained by heel puncture of these 17 infants with those of 24 normal newborns. The mean concentration for the anemic group was 13.3 gm/100 ml, in contrast to a mean value of 18.1 gm/100 ml for the control group. The difference, 4.8 gm/100 ml, is highly significant (P < 0.001).

Fourteen mother-infant combinations in which bleeding from the maternal vagina had occurred during labor were also studied. Fetal hemoglobin was present in the vaginal blood from 8 of these 14 cases, indicating that hemorrhage may arise from the fetal as well as from the maternal surface of the placenta leading to transvaginal loss of blood.

Dr. O'Connor believes that the possibility of prenatal transplacental hemorrhage should be considered as a likely explanation for progressive anemia during the first 12 to 24 hours of life if serologic incompatibilities cannot be identified and the infant is not jaundiced. He favors the conservative use of transfusions of whole blood in the treatment of these infants.

**Blood Dyscrasias**

Blood dyscrasias which may occur during the neonatal period were discussed by Dr. Watson, who stressed the rarity of all of these conditions in comparison to the relative frequency of Rh- and ABO-incompatibilities and of septicemia. Congenital spherocytosis and congenital ovocytosis may produce jaundice and severe anemia during the neonatal period,
requiring exchange transfusion. In Dr. Watson's experience sickle-cell anemia and thalassemia have not been recognized in infants under 4 months of age.

**Hemorrhagic Diseases**

Hemorrhagic diseases of the newborn may be due either to platelet defects, which are usually manifested clinically by the appearance of petechiae, or to defective coagulation mechanisms, which usually produce ecchymoses without petechiae. About 50% of the infants born to thrombocytopenic mothers have transient thrombocytopenia, but the infants' platelet counts usually return to normal within 1 to 3 months. Dr. Watson uses adrenocortical steroid therapy when such a newborn infant's platelet count is less than 50,000/mm³ and petechial hemorrhages are present. Congenital deficiencies of nearly all of the protein factors known to promote coagulation of blood have been reported. All of these are manifested by prolongation of the coagulation time and prothrombin-consumption time, and all can be corrected by the administration of fresh whole blood. Therefore, Dr. Watson believes that it is not necessary to identify the specific coagulation defect when a hemorrhagic emergency exists. She prefers to utilize the small sample of blood usually obtainable for proper typing and cross-matching of the fresh blood which the infant needs. In extreme emergencies she willingly uses fresh unmatched type O, Rh-negative blood.

Dr. Watson also called attention to the recent paper by L. C. Y. Sun and A. E. Rakoff (Evaluation of the peripheral blood smear test in the detection of chromosomal sex in the human. J. Clin. Endocrinol. & Metab., 16:55, 1956) which reports sex-related differences in segmented polymorphonuclear leucocytes. Pedicled extrusions of dense chromatin, somewhat resembling drumsticks, occur in the nuclei of 5 to 6% of female polymorphonuclear leucocytes and do not occur in male white blood cells. Dr. Watson has found this difference useful in identifying the chromosomal sex of hermaphroditic infants.

**NUTRITION OF PREMATURE AND FULL-TERM INFANTS**

This topic was discussed by Dr. Samuel Z. Levine, Cornell Medical College, and Dr. L. Emmett Holt, Jr., New York University, during the seminar's third session.

**Fluid Requirement**

In discussing fluid requirement, Dr. Levine utilized data accumulated in the premature metabolic unit of the New York Hospital by Dr. Harry Gordon and himself. Table I summarizes data presented concerning the fluid metabolism of premature and full-term newborn infants. Both groups were ingesting 140 to 150 ml/kg/day of formula.

The volume of fluid necessary for maintenance of premature infants appears to be about 125 ml/kg/day. Larger volumes cause excretion of more dilute urine while the positive water balance remains essentially constant. When premature infants receive less than 125 ml/kg/day, fever and weight loss (signs of negative fluid balance) tend to appear. Overfeeding is to be avoided, and therefore it is recommended that small infants not be given more than 140 to 150 ml/kg/day of formula, which will provide adequate water without danger of overfeeding.

**Caloric Requirement**

In discussing the caloric requirement of premature infants, Dr. Levine employed data from studies by Dr. Harry Gordon, conducted on infants maintained in a respiration chamber except during feedings (Table II).

It was emphasized that these are average
TABLE II

<table>
<thead>
<tr>
<th>Caloric Expenditure</th>
<th>Mean Range (calories/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal (sleeping) activity</td>
<td>60  50–75</td>
</tr>
<tr>
<td>Non-sleeping activity</td>
<td>10  5–15</td>
</tr>
<tr>
<td>Fecal losses</td>
<td>20  10–30</td>
</tr>
<tr>
<td>Total maintenance</td>
<td>90  75–100</td>
</tr>
</tbody>
</table>

Calories required to permit daily weight gain of 12.5 gm/kg/day

\[= 12.5 \times 2.5 \]

= 30  25–35

Total caloric requirement

| 120  100–135 |

figures derived from studies of large groups of premature infants. Some infants will require more calories and some will thrive while receiving less; therefore, in practice each must be treated individually. In response to a question concerning the caloric requirements of premature infants suffering severe respiratory distress or other neonatal complications which may require increased expenditure of energy, Dr. Levine stated that it is preferable to depend upon the infant's fat stores as a source of additional calories under these circumstances. It is hazardous to increase the caloric intake during such a period in the face of the infant's susceptibility to gastrointestinal disturbances. Simple glucose solution is frequently preferable in this situation.

Another question directed to Dr. Levine concerned the infant on a self-regulated feeding schedule who appears to take larger volumes of fluid than Dr. Levine recommends and still seems to be hungry. He replied that neurologic control of appetite in the premature may be unreliable and lead to a vicious cycle of excessive crying, apparently due to hunger, and consequent excessive expenditure of energy leading to further hunger. The basal metabolism of so-called hungry infants has been found to be normal. This type of infant may also lose more calories in the feces.

Dr. Levine outlined his present program for feeding premature infants. Nothing is offered by mouth for the first 12 hours. Feeding is instituted with 5% glucose in water, 2 to 5 ml per feeding initially, and volumes are then gradually increased to 10 ml per feeding as tolerated. The glucose solution is then gradually replaced by a suitable formula of cow's milk or human milk and the volume increased every 2 or 3 days until maintenance requirements of fluid and calories are provided. Feeding by gavage is employed if sucking is inadequate, sometimes for as long as 60 days. A rubber tube is preferred to plastic tubing because the latter has become associated with more undesirable secretions from the respiratory tract and unnecessary trauma.

**Protein Requirement**

Dr. Holt continued the discussion with a consideration of the infant's requirement for protein. The minimal requirement is that which will permit most infants to gain weight at a normal rate and varies according to age, in direct proportion to the rate of growth. The protein requirement for the newborn full-term infant is approximately 2.2 gm/kg/day. There are insufficient data to permit a valid estimate of the minimal requirement of protein for premature infants. By extrapolation of the curve describing protein requirements during infancy, a value of about 3 gm of protein per kg per day was offered as the minimal requirement for the premature infant. The requirement of a given type of protein is dependent upon its content of so-called essential amino acids. Present opinion favors provision of approximately 25% more than the calculated minimal requirement.

Dr. Holt cautioned that one should also consider the possibility that there is a maximal intake of protein which an infant may be expected to tolerate without such ill effects as hypertrophy of the kidneys and increased requirement for water. In response to this concern, Dr. Levine referred to experience in his clinic with groups of premature infants who received human milk, a standard formula of evaporated milk, and a formula of half-skimmed milk. The best gains in weight were observed in those infants receiving the high-protein formula, half-skimmed milk. No ill effects were observed from the high-protein feeding, and because the weight gain was superior and the rate of survival equivalent, it was concluded that the high-protein formula did not harm these premature infants.

Participants received the following answers to questions asked at this point in the discus-
On Dr. Holt’s service, the currently routine feeding for premature infants is Olac®. On Dr. Levine’s service, small premature infants receive a formula prepared from half-skimmed milk powder, and larger premature infants get an evaporated milk formula. Dr. Holt believes it is essential to increase the protein content of any diet slowly and cautiously, especially if significant protein deficiency is to be treated. Time is required to permit the body’s metabolism to adapt to a high-protein load, as has been shown by recent experience of nutritionists treating kwashiorkor in Uganda.

Dr. Levine recommends that the use of concentrated feedings be discontinued because the infant cannot maintain internal iso-osmolarity indefinitely when offered hyperosmolar fluids. The transient edema which is occasionally observed in premature infants may be due either to hypoproteinemia, or to transient excessive retention of electrolytes, according to Dr. Levine. Dr. Holt thinks that certain of these infants do not actually have edema but are manifesting a spurt in weight which can occur at any age if carbohydrate is substituted for fat as the body’s chief source of calories. Concerning the addition of specific amino acid supplements to the infant’s diet, Drs. Levine and Holt were in agreement that normal utilization of amino acids depends not only on the total amounts available, but also upon their symmetrical availability in accordance with proportional requirements. Amino acid imbalances, such as can be produced by specific supplementation, may be deleterious.

**Fat Requirement**

As a preface to his discussion of the fat requirement of premature infants, Dr. Holt admitted that the subject is presently open to debate. He believes that there are adequate data to show that the average premature infant absorbs fat poorly, although there is a wide range of absorptive ability among individual infants. Whereas the full-term infant can absorb about 90% of ingested butter fat, premature infants absorb only 60 to 70% (range 38 to 80%) of ingested butter fat and 70 to 90% of ingested olive oil. It is desirable to promote absorption of fat, not only for its caloric value, but also to provide essential fatty acids and fat-soluble vitamins. The percentage of ingested fat which is absorbed by the premature infant can be increased either by modifying its chemical character or by changing its physical state. Balance studies have demonstrated that absorption can be improved by selecting short-chain fats or fats which contain many unsaturated carbon bonds, such as olive oil, corn oil or soya bean oil. Improved absorption also follows the modification of the physical state of the fat by emulsification. The total quantity of fat which is absorbed may also be increased by increasing the fat content of the diet, because absorption is directly related to the fat content of the bowel. Dr. Holt believes that fat provides an excellent source of calories for the infant, and points out that even when the infant absorbs only 50% of ingested fat, he derives more caloric benefit from fat, gram for gram, than he would obtain from equivalent amounts of ingested carbohydrate (e.g., 1.0 gm carbohydrate yields 4.1 calories and is 99% absorbed, thus providing approximately 4.1 calories; in comparison, 1.0 gm of fat yields 9.3 calories and, even if only 50% is absorbed, will yield approximately 4.6 calories). Dr. Holt has found that corn oil is a useful component of formulas for premature infants on his service, and has not observed such complications as diarrhea, constipation, electrolyte imbalances, or vomiting.

In reply to a question from Dr. Day concerning the minimum requirement for fat to permit normal growth of an infant, Dr. Holt stated that very little useful data is available. It is known that Eskimo children, who receive a very low fat diet consisting mainly of pre-chewed lean meat, grow well. Dr. Holt suspects that a true requirement for fat is probably negligible, but believes a positive advantage can be gained by administering fat for its caloric value.

In commenting upon Dr. Holt’s remarks, Dr. Levine considered these efforts to improve absorption of fat very promising and potentially worthwhile if final results suggest practical and economically feasible methods of providing calories to small infants. However, he felt that it would be uneconomical to over-stoke a machine with poorly utilized fuel, such as fat, when the same calories could be derived from a fuel known to be more efficiently utilized, such as carbohydrate or protein. His own data indicate to Dr. Levine that fecal losses of fat in the stools of premature infants may be twice those of full-term infants.
(20 calories/kg/day as compared to 10 calories/kg/day). Although he does not insist on any particular type of feeding for premature infants, Dr. Levine is convinced that premature infants need more protein and less fat than larger infants, and that they need more concentrated feedings than are provided by unmodified human milk in terms of protein, calcium and phosphorus. In his own hospital practice, Dr. Levine finds that smaller premature infants progress best when given a properly modified cow's milk mixture, and he still prefers to rely upon carbohydrate and protein as sources of calories.

**Carbohydrate Requirement**

According to Dr. Holt, the medical literature contains very few observations which indicate an actual requirement for carbohydrate. Balattice studies have been difficult to do because of the complexity of the degradation products which appear in the feces. Recently, Dr. Holt and his co-workers have used C 14- and C 13-tagged glucose and sucrose to study absorption and utilization of carbohydrate. In all of eight normal subjects studied, more than 99% of ingested sugar was absorbed. Two premature infants were also given C 13-labelled sucrose and absorbed 98.4% and 98.6% of this sugar, respectively. Only a portion of the administered sugar was tagged, but Dr. Holt believes that these studies demonstrate that premature infants are able to absorb carbohydrate just as efficiently as older infants do. It was also demonstrated that the absorbed carbohydrate is utilized rapidly. More than 90% of the ingested, tagged sugar was expired as carbon dioxide within 2 hours from the time of ingestion.

**INFECTIONS AND ENVIRONMENTAL CONDITIONS**

The fourth and final session was devoted to consideration of infections and environmental conditions as these affect the progress of newborn and premature infants. Discussants were Dr. Hattie E. Alexander and Dr. William A. Silverman, of the College of Physicians and Surgeons, Columbia University. Dr. Silverman also read a paper prepared by Dr. William Blanc, pathologist at Babies' Hospital, New York, who was unavoidably absent.

**Amniotic Infection**

The etiologic role of amniotic infection in perinatal pathology was discussed in Dr. Blanc's paper. Bacterial contamination of the amniotic fluid, fetal membranes, placenta, and fetus may occur in the presence of prematurely ruptured amniotic membranes, or during prolonged difficult labor with anoxia and fetal distress. Involvement of all tissues is rare, but several fetal tissues are frequently affected. Pneumonitis is the most common manifestation. Dr. Blanc believes that the majority of infants who succumb to pneumonia during the first 3 days of life acquired their infection during the last phase of intra-uterine life. In support of this concept, he reported results of his own studies in several related areas. Bacteriologic examination of the maternal vaginas, amniotic fluids, and aspirated gastric fluids from newborn infants whose births were complicated by premature rupture of amniotic membranes or prolonged labor has yielded identical organisms from each of the three sources. The incidence of perinatal pneumonitis has also been found to increase with the passage of time after the onset of labor or rupture of amniotic membranes. In Dr. Blanc's series, only 5% of infants born within 6 hours of the onset of labor showed signs of infection, whereas 60% of infants born after 6 to 12 hours of labor showed such signs. Comparing the necropsy experience of two hospitals, Macgregor found that 19% of all the necropsies in each hospital were performed on the bodies of infants dying within the first week of life with pneumonia. In contrast, the two hospitals had quite different records concerning infants dying after the first week (13.7% versus 0.8% of all necropsies); this difference appeared to be due to better prophylaxis against postnatal infections in the second hospital. Dr. Blanc interprets this data as evidence of the incidence of fatal infections acquired prenatally in the two hospitals studied.

The placentitis which occurs in association with amniotic infection is pathologically unique because it involves reaction of two different tissues to the same infecting organism. Both the maternal and the fetal surfaces of the placenta usually show acute inflammatory reactions, but if fetal death occurs only the
maternal side shows leukocytic infiltration. Pathologic examination of the lungs of infants succumbing to prenatally acquired pneumonia reveals purulent amniotic exudate within the pulmonary system. Usually no fibrinous exudate is present, and occasionally the infection appears to be limited to the larger bronchi, death being due to bronchial obstruction.

To aid the clinician in recognizing those infants who may have acquired infection prenatally, Dr. Blanc suggests that two studies be done routinely on all obstetric and newborn services. A smear of the placental surface at the maternal-fetal junction should be examined for evidence of increased numbers of leucocytes, suggesting amniotic infection and placentitis. Immediately after birth, gastric fluid aspirated from the newborn infant should be smeared and stained with methylene blue. Dr. Blanc has found that large numbers of leucocytes are present in the gastric contents of 80% of newborn infants who subsequently develop pneumonitis during the first week of life. Culture of the gastric fluid should be done when the smear arouses suspicion, to provide guidance in the choice of effective antibiotics if pneumonitis subsequently develops.

Antibiotic Therapy

Proper use of antibiotics in the treatment of premature infants was discussed by Dr. Alexander, whose theme was "To treat or not to treat, that is the question." She prefaced her remarks with an appeal for a well-controlled study designed to show the actual contribution of primary infection to the mortality of prematures. Dr. Alexander believes that if cases in which infection secondarily complicates severe underlying anatomic or metabolic defects be excluded, the number of deaths due to infections is quite small. Nevertheless, she favors study of the effects of routine use of antibiotics in premature infants because of their well-known inability to manifest acute infection by the usual systemic signs. She dislikes the concept of "prophylactic antibiotics" in relation to treatment of prematures, because truly therapeutic dosages are indicated if antibiotics are to be used at all.

Choice of antibiotic agents should be based upon knowledge of the susceptibilities of those organisms which most commonly infect prematures, the staphylococci, coliform bacilli and other enteric pathogens. In addition, antibiotics to be used routinely should satisfy certain essential criteria. They should be safe for general use. They should tend to discourage the development of resistant strains within the flora of the nursery. They should be capable of providing adequate but not excessive concentrations within the premature's body during the first few days of life, without undue dependence upon the functional capabilities of immature kidneys. Preferably they should be effective when administered by mouth and be rapidly and efficiently absorbed from the gastrointestinal tract.

Basing her choice on these criteria, Dr. Alexander suggested that the following combination of antibiotic agents would be worthy of trial in the treatment, during the first week of life, of all infants whose birth weights are less than 2000 gm:

1. Chloramphenicol, 100 mg/kg/day in divided doses by mouth.
2. Erythromycin, 50 mg/kg/day in divided doses by mouth.
3. Sulfadiazine, 100 mg/kg every other day by mouth.

The combination of chloramphenicol and sulfadiazine is considered to be effective against most gram-negative organisms. Chloramphenicol and erythromycin have a good combined action against staphylococci. Sulfadiazine is administered every other day because experience has shown that effective blood levels persist for 48 hours when 100 mg/kg of this agent are given intramuscularly on the first day of life, presumably because of delayed renal excretion.

If it be necessary to administer the antibiotics intramuscularly, Dr. Alexander believes that a combination of chloramphenicol (50 mg/kg/day) and sulfadiazine (100 mg/kg every other day) may be adequate, without the addition of erythromycin.

Considerable discussion followed these remarks. Dr. Levine stated that he has adopted the policy of not ordering antibiotic therapy for any patient unless specific indications are present, and that he believes this to be especially important in treating prematures, because so little is known concerning potentially harmful effects of antibiotic agents. He recognizes only three indications for the administration of antibiotics to premature infants, namely: (1) a history of prematurely ruptured...
amniotic membranes 24 to 48 hours before delivery; (2) transport of the premature infant from another service into a premature nursery center, and (3) gross evidence of infection. Dr. Levine believes that the premature infant is no more susceptible to most bacteria than is the full-term infant, but accepts the possibility that staphylococci and coliform bacilli may thrive better in premature infants. In response to a question concerning the use of chloromycetin palmitate, Dr. Alexander stated that the palmitate is not absorbed from the gastrointestinal tract as well as crystalline chloramphenicol, and she would therefore not recommend the use of the palmitate preparation.

The panel was asked whether experience would suggest that sulfadiazine therapy is associated with the same increased incidence of kernicterus which has been reported to follow the use of Gantrisin®. Dr. Silverman stated that two nursery centers where sulfadiazine has been used prophylactically for a long time have rarely found kernicterus in premature infants coming to necropsy, however this negative evidence must be accepted with caution. Another question called for comments concerning the advisability of routinely administering gamma globulin to all premature infants. Dr. Silverman stated that prematures have been shown to possess high levels of gamma globulin at the time of birth, and that limited studies have failed to demonstrate any benefits from the administration of gamma globulin to premature infants.

Environmental Conditions

The current status of knowledge concerning optimal environmental conditions within the premature infant’s incubator was reviewed by Dr. Silverman.

Oxygen

Oxygen should be ordered explicitly in terms of the concentration desired within the incubator being used, and not in terms of rate of flow. Dr. Silverman currently favors the administration of 36% oxygen to cyanotic premature infants until the cyanosis is relieved, at which time he attempts to discontinue oxygen administration. A recent co-operative study suggests that it is not wise to administer additional oxygen routinely to all premature infants, no matter what concentration be chosen. This study has demonstrated that the incidence of retrolental fibroplasia increases with each increase in oxygen concentration above normal atmospheric level. Therefore, Dr. Silverman believes additional oxygen should not be given unless there is a specific indication for it, and that the only reasonable indication is cyanosis. Intercostal and sternal retractions, without cyanosis, should not be assumed to indicate need for oxygen therapy; in such cases, one should suspect and try to remove respiratory obstructions. Dr. Silverman was asked whether an infant who has been receiving oxygen in a concentration of 34 to 36% for more than 24 to 36 hours should be abruptly removed from the high oxygen environment, or weaned gradually. In reply, he stated that evidence from animal experimentation indicates that one should remove the infant from the high oxygen environment abruptly, and should not wean the infant from oxygen gradually. The longer the premature infant remains in an environment where the oxygen concentration is greater than atmospheric, the longer he is exposed to the vaso-obliterating effects of oxygen upon retinal vessels, and the greater are his chances of developing retrolental fibroplasia.

Questioned about maximal oxygen concentrations to be recommended, Dr. Silverman stated that in his own nursery he had found it necessary to increase oxygen concentration above 40% in only three cases in the past year, all three were in severe respiratory distress and did not survive.

Humidity

Optimal humidity within the incubator was considered next. The history of the use of high humidity in the treatment of premature infants was traced from the early experience of Blackfan and Yaglou, using 65% humidity, through the period when supersaturated environments were recommended, to the more recent popularization of detergents. Papers championing these various therapeutic methods have created considerable confusion and the evidence supporting these practices was considered meager by Dr. Silverman. He therefore undertook a study designed to redefine optimal environmental humidity for the premature infant. Preliminary findings suggest that the major beneficial effect of high humidity surrounding the premature infant is a reduction in losses of body heat, and not an effect upon pulmonary function. Blackfan and Yaglou found that pre-
mature infants living in environments with 20% humidity required higher bed-heat temperatures to maintain stable body temperature than did those prematures who were kept in environments with 65% humidity. It would appear that stabilization of body temperature by conservation of body heat may be even easier for the premature in 80 to 90% humidity.

Dr. Silverman’s study of the effects of varying relative humidity within the premature’s Isolette® was commented on by Dr. Day, who pointed out that Dr. Silverman had arbitrarily selected 84°F as the air temperature to be employed in his study. Adult subjects, unclothed and quiet on beds maintained at bed-temperatures of 85 to 88°F, will experience continuous decline of body temperature till chilling occurs at the so-called “zone of thermal neutrality,” which is about 85°F. Below 85°F, control of body temperature can be achieved only by means of shivering. Because the premature infant is incapable of shivering, it is possible that all of the infants studied by Dr. Silverman were under a significant physiologic disadvantage. Dr. Silverman accepted the validity of this comment and noted that the difference in mortality which was observed in the two contrasting conditions of ambient humidity might not hold true at higher environmental temperatures. He proposed additional studies, using 88°F as the air temperature for the environments.

Body Temperature

What should the premature infant’s body temperature ideally be? Dr. Silverman believes that one should try to maintain the infant’s body temperature near 96 to 97°F, depending upon the degree of maturity of the infant. To do so usually requires the maintenance of the incubator’s bed at 85 to 90°F. If the bed heat is increased above 90°F, dangerous bouts of hyperthermia may occur.

In summary, Dr. Silverman recommends that the environment for the premature infant whose body weight is less than 2 kg should provide an air temperature of 88 to 90°F and 80 to 90% relative humidity. Oxygen should not be added unless the infant is cyanotic and should rarely exceed a concentration of 36%.
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Richard L. Day and William A. Silverman
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