GUIDELINES

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For

NEWBORN CARE

PREPARED BY

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Department of Pediatrics
University of Iowa College of Medicine
and
Statewide Perinatal Care Program

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INTRODUCTION

This booklet has been prepared to assist the physicians and nurses caring for newborn infants in the State of Iowa. The items discussed were determined on the basis of need (hospital survey) and are discussed from the standpoint of the ability of the individual hospitals (any size) to render the care indicated.

We feel that a reasonable adherence to the guidelines for neonatal care will insure an adequate standard of care for all infants in the State of Iowa.

These guidelines are presented with no associated regulatory authority. Since the physicians and nurses practicing in Iowa hospitals are all health care professionals, we do not feel that regulatory measures are required to insure adequate care.

Herman A. Hein, M.D.

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GUIDELINES FOR NEWBORN CARE

1. NEWBORN EXAMS: We strongly encourage physicians to do a newborn as well as a discharge exam on each infant. Due to the marked changes that take place in the first days of life, we feel the discharge exam is particularily warranted. For example, a newborn may have good femoral pulses at birth, however, when examined on the third or fourth day the pulses are no longer palpable. This situation is created by a coarctation of the aorta that was previously being fed by a ductus arteriousus. When the ductus closes, the blood supply distal to the coarctation is markedly decreased.

PHYSICIAN'S RECORD OF NEWBORN INFANT

THIS FORM NOT ACCEPTABLE AS A PERMANENT RECORD UNLESS PROPERLY FILLED OUT

( ) Male ( ) Female child of _____ (Family name) _____ (Mother's given name) _____ (Infant's given name)	Color ( ) W ( ) non-W	Hosp. No.

Mo. Day Year Time: BIRTH: ____a.m. ____p.m.	Weight	Length	Chest circ.	Head circ.	Attending physician
	lbs. oz.	inches			

*Code each item as follows:

O No abnormality
X Abnormality (describe abnormal findings objectively)

	ADMISSION EXAMINATION		DISCHARGE EXAMINATION	
	Code*	Description of abnormal findings	Code*	Description of abnormal findings
1. GENERAL APPEARANCE (maturity, activity, tone, cry, color, nutrition, edema)				
2. SKIN (icterus, rashes, hematoma)				
3. HEAD, NECK (molding, caput, craniotabes cephalohematoma)				
4. EYES (abnormalities, conjunctiva. red reflex)				
5. EARS, NOSE & THROAT (lips, gums, palate)				
6. THORAX (including breast hypertrophy)				
7. LUNGS				
8. HEART (including femoral pulse)				
9. ABDOMEN (including umbilicus)				
10. GENITALIA (testes, circumcision; meatus, discharge)				
11. ANUS				
12. TRUNK AND SPINE				
13. EXTREMITIES (including clavicles and abduction of hip joints)				
14. REFLEXES (Moro, grasp, sucking, swallowing)				

Impression at admission:	Impression and discharge diagnosis:

Date	Time	Physician's signature	Date	Time	Physician's signature

(OVER)

This form is recommended by Committee on Maternal and Child Care, American Medical Association, and the American Academy of Pediatrics. 0138:30M:663-J:10/73 OP-186

PHYSICIAN'S RECORD OF NEWBORN INFANT — (reverse side)

PHYSICIAN'S ORDERS

Date	Orders	Doctor's Signature	Nurse's Signature	Time Checked

PROGRESS NOTES

Date	

WARMTH, PHISOHEX, BATHING

2. WARMTH: The most critical time for the maintance of the neonate's normal body temperature is immediately post delivery and for the following 8 hours. The chilled infant is clearly at risk for a hypoglycemia episode.[1] Newborns have poor temperature control and are frequently not able to maintain their body temperature. The temperature drops ⟶ Blood PH drops ⟶ causing acidosis ⟶ Blood sugar drops ⟶ (Hypoglycemia commonly leads to CNS damage).

How does cooling occur:

Delivery Room-

1. The infant is set aside while the mother is cared for
2. Prolonged length of stay in the delivery suite
3. Procedures on the infant are done too soon (ex: circumcision in DR)

Nursery-

1. Bathing of the infant is done too soon - has to look nice for Mom and Dad!
2. Baby is taken from the heated environment prior to being stabilized

We feel that the baby should not be bathed until he has a chance to stabilize, therefore, no earlier than 8 hours after delivery. It can be safely stated that there are no real indications medically for bathing newborn infants, and in fact, the first bath is done early to please the parents. Indeed chilling is a very important factor but also the fact that the baby's protective vernix is removed should not be taken lightly. We agree that excessive amounts of blood and meconium should be removed, and an infant born with foul smelling amniotic fluid should be cleansed, but until the baby has stablized we see no use for any further cleansing.

There has been considerable controversy over the use of phisohex for newborn bathing. The FDA ruling has clearly put the burden of responsibility on anyone who wants to use this preparation routinely. There is a growing accumulation of evidence that would seem to support a single phisohex bath as a reasonable effort to reduce Staphylococcal colonization in the newborn. However, until further evidence is presented, we feel that the most reasonable approach is to delete the use of phisohex in the care of the routine newborn infant. In general, good handwashing techniques of personnel caring for infants, (i.e. wash between infants), proper gowning, and the use of common sense will generally preclude Staphylococcal epidemics from the newborn nursery.[2]

There is no point in doing circumcisions in the delivery room other than for the convenience of the physician. Delivery rooms are generally cold and there is considerable concern with the ability of even the best overhead warmer to keep the immediate newborn adequately warm when a procedure is performed in the delivery room. Futhermore, we really do not know in that first hour or so of life if this youngster might be thrombocytopenic, or might have some other problems with a hemorrhagic disease, and for this reason, also, we would discourage early circumcisions.

The importance of providing environmental warmth to minimize loss of body heat cannot overemphasized. At birth, a major cause of heat loss is the evaporation of amniotic fluid that covers the infant's skin. He must therefore be dried rapidly, preferably by another individual, while the nurse removes sevretions with a bulb syringe. Wrap and rub the infant dry in a warm warm blanket and place him in a heated area. Avoid undue exposure to room air because any chilling rapidly lowers the body temperature and increases the need for oxygen. The provision of warm, moist oxygen is important. Do not

use cold oxygen, if possible, because with a stressed infant, the thermal skin receptors in the face are more responsive to environmental temperature change than those in any other part of the body. (Cold oxygen will cause accelerated chilling.)

Do not leave the baby in the delivery room too long. Transport of the baby to the nursery must be rapid. He should be wrapped in a warm blanket and carried to the nursery.

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[1] Pagliara, Anthony, MD, et al, "Hypoglycemia in Infancy and Childhood, Part I", The Journal of Pediatrics, March 1973, Vol. 82, No. 3, p. 365 - 379.

[2] "American Academy of Pediatrics, Committee on Fetus and Newborn Statement": Hexachlorophene and Skin Care of Newborn Infants, Newsletter Supplement, January 1, 1972. Also, Pediatrics, Vol. 52, No. 2, August 1973, p. 264.

Newsletter Supplement - January 1, 1972

COMMITTEE STATEMENT

Committee on Fetus and Newborn
American Academy of Pediatrics

HEXACHLOROPHENE AND SKIN CARE OF NEWBORN INFANTS*

The question of safety has been raised by the recent evidence that levels of hexachlorophene in the blood of newborn infants receiving daily baths with a 3% solution are close to levels which are neurotoxic for adult rats.[1] Hexachlorophene is widely used in newborn nurseries, but techniques vary considerably; they range from meticulous, double, early bathing followed by daily baths,[2] to alternate day washing with a diluted solution followed by rinsing off.

With chronic oral administration, blood levels associated with leg weakness progressing to paralysis in the adult rat have ranged from 0.985 to 1.48 p.p.m.[3] Toxic manifestations have not been observed nor recognized in newborn infants with "meticulous" daily washing. The chemical is readily absorbed from the skin, resulting in blood levels of 0.009 to 0.646 p.p.m.[1] The compound is excreted as a monoglucuronide in the bile and feces. Convulsions have been reported in an infant 4 days after repeated application of the 3% emulsion to the skin without subsequent rinsing;[4] and, toxic manifestations have been observed in burn patients, but at relatively high serum levels (29 μg/ml), after denuded areas have been washed with hexachlorophene.

It is not known whether or not this substance as currently used on infants is toxic. Although the symptoms observed in adult man and adult rats are similar, the actual blood levels at which symptoms are produced in man appear to be much higher. Symptomatology in the rat with chronic oral administration was accompanied by brain lesions, cerebral edema, and cystic spaces in the white matter of the brain; these lesions were reversible over a period of 6 weeks when hexachlorophene was discontinued.[3] Similar lesions have been produced in experimental intoxication of monkeys following both subcutaneous administration and application of hexachlorophene to the skin.[5] The animals did not demonstrate abnormal neurological signs even with plasma levels of 3.1 μg/ml, although papilledema was found at autopsy in some instances. It is not presently known whether the lesions are reversible when hexachlorophene is discontinued.

For a number of reasons, it appears that, at this time, there is little justification on microbiological grounds for routine, daily hexachlorophene baths for the newborn infant. With the "meticulous" techniques, the rate of colonization with coagulase-positive staphylococci and the incidence of skin lesions is reduced.[2,6,7] However, there is no documented experience where this technique has arrested a serious nursery epidemic. It is also well established that the use of hexachlorophene increases colonization with gram-negative organisms[8,9] as well as the incidence of gram-negative disease.[9] Finally, for reasons that have not been defined, the problem of serious staphylococcal disease in the nursery has not been of major importance during the last 5 years, as it was 10 to 15 years ago, whether or not hexachlorophene has been used for skin care of newborn infants.

Until further evidence is forthcoming, the Committee feels that the following cautionary warning is appropriate:

WARNING: The safety of daily bathing of infants with hexachlorophene-containing solutions has not been established. Blood levels found in newborn infants bathed daily in 3% hexachlorophene solutions have been shown to approach levels known to be neurotoxic in experimental animals. Therefore, the use of hexachlorophene for total body bathing of newborn infants in hospital nurseries or at home is contraindicated.

RECOMMENDATIONS

At present the Committee recommends dry skin care; washing with plain, nonmedicated soap and tap water; or washing with tap water alone for skin care of the newborn infant. It should be emphasized that the two most important factors in the transmission of infection from infant to infant are hand contact and breaks in technique. These factors can be minimized by scrupulous hand washing before entering the nursery as well as just before and just after handling each infant. Either iodophor preparations or 3% hexachlorophene emulsion are recommended for hand washing.[10]

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*This statement has been reviewed and approved by the Chairmen of the Committee on Environmental Hazards and the Committee on Drugs.

THERMOREGULATION

Man shares with other homeothermic animals the ability to maintain his internal body temperature in the face of a cooler environmental one. To do so requires the generation of heat which is reflected in and can be readily measured as oxygen consumption. The so-called "neutral zone" of ambient (environmental) temperature is defined as the zone at which oxygen consumption is minimal yet sufficient to maintain body temperature. For adult man this zone ranges from 25 to 30°C., i.e., slightly above that of the temperature of a normal room. In the newborn infant the zone is higher and narrower (32 to 34°C.). Lowering the environmental temperature even slightly below this range results in a steep rise in oxygen consumption,[9, 76] an increase which can only be met by increasing minute ventilation.

For the infant with respiratory distress, already breathing at rates exceeding 100 per min., this increased demand may be impossible to meet and can on occasion prove to be the final stimulus precipitating respiratory failure. Conversely, the inability to meet this demand because of his respiratory impairment also results in an easy tendency to hypothermia, as evidenced clinically by a falling body temperature with increased requirements for external heat in an effort to maintain it.

In the attempt to maintain a minimal yet satisfactory metabolic rate, attention must be paid to thermal factors other than the temperature of the environment. Evaporative heat loss from the lungs (see above) and skin can to some extent be reduced by providing adequate humidity. Convective heat losses due to air currents are to be avoided (a major source of such losses are injudiciously used air conditioners in a nursery), as are conductive losses. Placing a newborn infant directly on a cold steel delivery table, wrapped in a wet towel, is an example of this avenue of heat loss. Finally it must be remembered that radiant heat loss is independent of the air temperature, and thus placing the infant too close to a cold outside wall will result in large heat losses even in the face of an adequate temperature inside the incubator.

A major source of cold stress often ignored is the administration of oxygen. Unless humidified and heated, either via the incubator or a warmed humidifier, oxygen from a wall or tank source is both cold and dry. Moreover it has been clearly shown that the administration of such cold, unhumidified oxygen over the forehead or trigeminal area (via a

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face mask) will result in large increases in oxygen consumption even when the rest of the body is kept at adequately warm conditions.[59, 63]

The metabolic results of hypothermia may have additional detrimental effects on the infant. Exposure to cold results in a rise in serum nonesterified fatty acids (NEFA),[67] which are in turn competitive anions for albumin binding sites with bilirubin,[12, 61] a derangement which can ultimately have serious effects in the induction of kernicterus at low levels of bilirubin (see below). The NEFA increase on cold exposure is mediated in the newborn by the release of norepinephrine.[67, 76] This release of norepinephrine has been implicated as a causative mechanism in the lowering of arterial Po_2 levels in normal infants exposed to a cool environmental temperature,[72] with the suggestion that the vasoconstrictive effect of norepinephrine in the lung would increase the amount of lung "shunting" with resultant disturbances in the V/Q ratio (see above). The menace of such a mechanism for the infant with the respiratory distress syndrome who is already handicapped by a severe ventilation/perfusion abnormality with a large "shunt" is obvious.

Severe hypothermia results in vasoconstriction and ultimately in acidosis. Moreover the hypothermic baby may become profoundly hypoglycemic,[18] presumably as a result of the known inverse NEFA-glucose relationship.[24] The hypoglycemia occurring under such circumstances is often resistant to correction with intravenous glucose alone until the infant is rewarmed. Because of this, true glucose levels, either clinically or experimentally, need always to be measured with the infant at thermoneutral conditions.

Symposium on Pediatric Pharmacology, "Therapy of the Respiratory Distress Syndrome", Stern, Leo, MD, Pediatric Clinics of North America, Vol. 19, No. 1, February, 1972, p. 221-239.

VITAMIN K_1 OXIDE

3. VITAMIN K: The newborn appears to have limited stores of vitamin K at birth. If additional vitamin K is not supplied these stores may be exhausted, with resulting cessation of hepatic synthesis of the prothrombin complex. Thereby, the normally low levels of factor II, VII, IX, and X may be severely compromised. These clotting factors disappear from plasma in accord with their half-times: factor II, 2 to 5 days; factor VII, 2 to 6 hours; factor IX, 1 day; factor X, 1 to 2 days. In line with these decay rates, the greatest risk of hemorrhage occurs between 2 and 7 days of life. The most frequent sites of bleeding are the skin and mucous membranes, particularily the gastrointestinal tract. Prolonged bleeding following circumcision or from skin puncture to obtain routine capillary blood samples may be isolated signs of hemorrhagic disease, or there may be fulminating, generalized bleeding.

Hemorrhagic disease of the newborn as a result of vitamin K deficiency is relatively uncommon today because most newborn infants receive prophylactic intramuscular injection of vitamin K immediately after birth. A single dose of 1 mg. in the full term infant and $\frac{1}{2}$ mg. is adequate for the premature infant of less than 5 lbs.[3]

We strongly encourage each physician to institute a policy of routine administration of vitamin K_1 oxide to all newborns. Preparations of vitamin K_1 oxide currently available are AquaMephyton, Konakion, Synkamin, and Mephyton Vitamin K-1.

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[3] Pediatric Clinics of North America, November 1972, p. 1033 - 1034.

Neonatal Vitamin K Deficiency: "Hemorrhagic Disease of the Newborn"

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Hemorrhagic disease of the newborn as a result of vitamin K deficiency is relatively uncommon today because most newborn infants receive prophylactic intramuscular injection of vitamin K immediately after birth. A single dose of 1 mg. is effective and entirely sufficient. High doses of synthetic vitamin K have been associated with hemolytic anemia and significant hyperbilirubinemia, particularly in premature infants.[10] Treatment of hemorrhage caused by vitamin K deficiency, usually associated with omission of prophylaxis, consists of intravenous injection of a single 1 mg. dose of vitamin K_1. The response to therapy is dramatic, with cessation of bleeding within 1 to 2 hours and substantial correction of clotting abnormalities within 24 hours.

** PEDIATRIC CLINICS OF NORTH AMERICA, November 1972, p. 1033-1034

NURSING RESPONSIBILITIES

4. VITAL SIGNS AND NURSES CHARTING: We strongly encourage frequent observations and attempt to familiarize nurses with a problem oriented approach to the newborn, recording things that really are significant in the child's course, and simply not to record that he had a "good 8 hours".

All newborn infants should have specific, timed observations. The first 8 hour segment of life is a very critical time during which the infant is stabilizing; Frequent observations should be noted and charted hourly on each infant for a period of 8 hours and then every 4 hours for the duration of the infant's hospital stay. This is important, not only from the standpoint of the infant but also to establish a resonable medio-legal record. There are 6 major observations that require notation:

1. Heart rate at rest
2. Respiratory rate at rest
3. Character of respirations
4. Color
5. Temperature
6. Infant's behavior - (active, alert, moves all extremities, good suck, irritable, lethargic, and high pitched cry, etc.)

EYE PROPHYLAXIS

5. EYE CARE: The instructions for eye care are essentially routine. We find most hospitals are using the Crede method with silver nitrate. Ilotycin, also, is frequently used. We want to emphasize that the instillation of 1% silver nitrate solution into both eyes should be within the first hour after birth. The Committee on Opithalmia Neonatorum does not recommend irrigating the eye after instillation of 1% silver nitrate.[4]

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[4] A Statement by the NSPB Committee on Ophthalmia Neonatorum, Control of Ophthalmia Neonatorum. Copyright 1973 by the National Society for the Prevention of Blindness, Inc.

Prophylaxis

The Committee recommends continued use of 1% silver nitrate in single-dose containers as the prophylactic agent of choice. Because there is concern about the remote possibility that babies might develop a sensitivity to any antibiotic that might be used, and because use of antibiotics might encourage the colonization of antibiotic-resistant organisms in babies in a nursery, their routine use as prophylactic agents is inadvisable until further research produces more precise information than is presently available.*

The Committee urges that cervical cultures from all expectant mothers be taken for the detection of an asymptomatic gonococcal infection.

Treatment

The Committee recommends the prompt culturing for gonococci as well as prompt treatment of any ocular infection or other inflammation in the newborn. Antibiotics may be used for treating infection. The importance of reexamination of the baby after hospital discharge when any inflammatory condition or infection has been detected or suspected is emphasized.

Proper Instillation of Silver Nitrate

Gonococcal ophthalmia neonatorum can usually be prevented by the proper application of the Credé prophylaxis. This procedure calls for the instillation of 1% silver nitrate solution into both of the infant's eyes within the first hour after birth. The Committee on Ophthalmia Neonatorum stresses the importance of performing the instillation so that the silver nitrate reaches all parts of the conjunctival sac. This can be accomplished by careful manipulation of the lids with the fingers to insure spreading of the drop. If the medication strikes the lids and lid margins only and fails to strike the cornea, the instillation should be repeated. If the Credé prophylaxis is properly performed, a mild chemical conjunctivitis should result. The Committee on Ophthalmia Neonatorum does not recommend irrigating the eye after instillation of 1% silver nitrate.

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* Nothing is presently known about the production of resistant strains of gonococcus and other organisms in nurseries as a result of the use of antibiotics for prophylaxis. This lack of knowledge and the impracticability of having fresh solutions of the antibiotics always at hand cannot be emphasized too strongly.

Failure of this method to prevent infection can occur especially if an infected mother's membranes rupture prematurely, exposing the baby's eyes to infection for hours or days prior to delivery. Since ophthalmia may also be a manifestation of neonatal sepsis, one should be alert to this possibility to insure prompt recognition and vigorous treatment.

Another important type of ophthalmia neonatorum, inclusion conjunctivitis, is not preventable by the Credé prophylaxis, nor does silver nitrate affect staphylococci and other types of infectious agents causing conjunctivitis in the newborn.

Legislative Requirements*

The use of a prophylactic agent in the eyes of all newborn babies is required by law or regulation in 47 states and the District of Columbia. In the remaining three states, the requirement is limited as follows: "to births attended by midwives;" and "to cases in which the presence of disease is suspected." The regulations in these states also direct the "State Department of Health to furnish free prophylactic." In 10 states, the requirement may be waived if parents object.

Silver nitrate is the only prophylactic agent specified or approved for use in 15 states; in 33 states and the District of Columbia, silver nitrate or "other equally effective agent" may be used. In two states, a particular prophylactic agent is not designated.

Reporting

The Committee recommends that all physicians and hospitals be required to report their gonorrheal ophthalmia neonatorum cases to state or local health departments, or both, so that incidence data may be obtained to determine the effectiveness of the control measures.

* A summary of the laws and regulations requiring use of a prophylactic for the prevention of ophthalmia neonatorum, in effect as of August 1968, is available from the National Society for the Prevention of Blindness, Inc., 79 Madison Avenue, New York, New York 10016.

6. EARLY FEEDINGS: Many hospitals are offering newborns their first feedings relatively late. We realize that the reason for this is the fear of aspiration. Very few babies stand the risk of aspiration, and those babies can be hand picked prior to feeding. We are talking, of course, about the immature infant who is not capable of sucking. If this baby cannot suck, if he cannot tolerate gastric tube feedings, we think that he probably should be referred to a center where intravenous therapy can aliment him for a resonable period of time. The infant with excessive mucous should also have special attention since esophageal atresia should be ruled out prior to the first feeding.

The importance of the prevention of hypoglycemia can not be over stressed. This is indeed our main objective in encouraging the early feeding or otherwise providing for a source of glucose for the newborn infant. The newborn is deficient relative to glucose stores. He has very little liver glycogen to convert to glucose. Immature babies have the most profound problem in this regard. We find there is no advantage and great potential harm in delaying the first feeding beyond 4 hours.[5]

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[5] Pagliara, Anthony, MD, et al, "Hypoglycemia in Infancy and Childhood, Part I", The Journal of Pediatrics, March 1973, Vol. 82, No. 3, p. 365 - 379.

7. HYPOGLYCEMIA: Hypoglycemia is potentially a common problem in the newborn and the results of a hypoglycemic episode may be devastating. We feel that each nurse caring for newborns should be aware of the signs and symptoms of this disorder. Unfortunately there is no precise clinical pattern that hypoglycemia follows and the nurse and physician must exercise a high degree of clinical suspicion. The following signs and symptoms have all been associated with hypoglycemia:

1. "Jitters" - the baby may be very irritable all the time or alternate between "jitters" and lethargy. "Jitters" may progress to frank convulsions.
2. Eye - rolling (grave suspect)
3. Respiratory rate above 60 or has tachypnea
4. Poor eater - may be the one that will suck soon after birth, but as hypoglycemia progresses he loses the ability to suck and swallow. It is not unusual to read the nurse's notes and find a good description of hypoglycemia, with nothing being done to correct the condition.
5. Cyanosis

In addition, the following historical data tends to predict a baby who is a likely candidate for hypoglycemia: the immature infant, small for dates baby, infant of a diabetic mother, the second twin, and infants who undergo exchange transfusions.

The use of dextrostix is a simple, effective method for determining low blood glucose levels on the newborn infant, and we recommend that nurses be allowed to do this procedure if any question of hypoglycemia exists. We have demonstrated this technique in many hospitals, and of course, encourage that

600 Gm. of muscle mass) or 4.2 Kg. of muscle mass per week. Since adults are capable of sustaining total caloric deprivation for prolonged periods of time, it is obvious that adaptive mechanisms must supervene to prevent the inanition and death which would rapidly occur due to the loss of funtional and structural protein secondary to the glucose demands of the organism. The only known source for net de novo glucose synthesis is protein (net conversion of fat to glucose requires a dicarboxylic acid cycle which is not present in mammals); thus it seems obvious that the only feasible conservation mechanism involves a decrease in the glucose requirements of the organism.

It is well recognized that the brain, formed elements of the blood, and the renal and the adrenal medulla have an obligate requirement for glucose as their source of energy (Fig. 1). Indeed, in the case of the red blood cell mass, the absence of mitochondria makes this tissue totally dependent on glycolysis as a source of energy. Since approximately 80 per cent of the total basal glucose requirements of the individual is represented by the metabolism of the central nervous system, the only adaptation which the organism could make which would significantly reduce glucose requirements would be in this tissue. One of the more exciting developments in the past 5 years has been the demonstration that the brain can adapt during fasting to the utilization of ketone bodies and, indeed, derives over half of its energy by the oxidation of ketones under these conditions. This adaptation results in a marked decrease in the demand for de novo glucose synthesis and consequently permits the organism to conserve its vital protein stores.[12]

It becomes evident from the above considerations that the newborn infant and young child are at a precarious balance between their obligatory glucose requirements and their ability to maintain this supply during caloric deprivation. Specific measurements of glucose requirements in the young child are lacking but on the basis of animal studies, it would appear that they are 2- to 3-fold greater than in the adult.[13] Despite this increase, the glycogen stores of the liver are sufficient to meet these demands for at least 8 to 12 hours. For example, a 10 Kg. youngster has approximately 20 to 25 Gm. of stored hepatic glycogen, sufficient to meet a glucose requirement of 4 to 6 Gm. per kilogram per day for approximately 12 hours. After 24 to 36 hours, the young child is totally dependent on gluconeogenesis for glucose supply—this is clinically evident in many by a poor glycemic response to glucagon under these circumstances.[5, 13a] As pointed out previously,[14] one of the factors which probably contributes to the high glucose requirement of the young child is the relative increase of brain mass to total body mass in this age group. However, agreement is not uniform that the glucose requirements of the neonate and young child per kilogram of body weight are significantly greater than in the adult. Even if the glucose requirements were the same, the immature individual is still less able to defend his blood glucose, since his gluconeogenic potential may be significantly less than that of his adult counterpart. As noted in the preceding paragraphs, over 50 per cent of de novo glucose production is derived from protein stores. The protein mass of the newborn infant and young child, relative to total body mass, is significantly smaller than in the adult; hence the ability to mobilize an adequate supply of endogenous gluconeogenic substrate may be compromised in this age group. These considerations emphasize the importance for specific quantitative studies of these various parameters in different pediatric age groups.

HEPATIC GLYCOGENOLYSIS AND GLUCONEOGENESIS

In the following sections, the key enzymes involved in glycogen degradation and synthesis and gluconeogenesis will be discussed with particular emphasis on those in which deficiencies have been implicated as the cause of hypoglycemia. Additional biochemical details on these enzymes are available in several excellent recent reviews.[15, 16] Although it has been well documented that the kidney is capable of gluconeogenesis, studies in adult human beings indicate that the net glucose con-

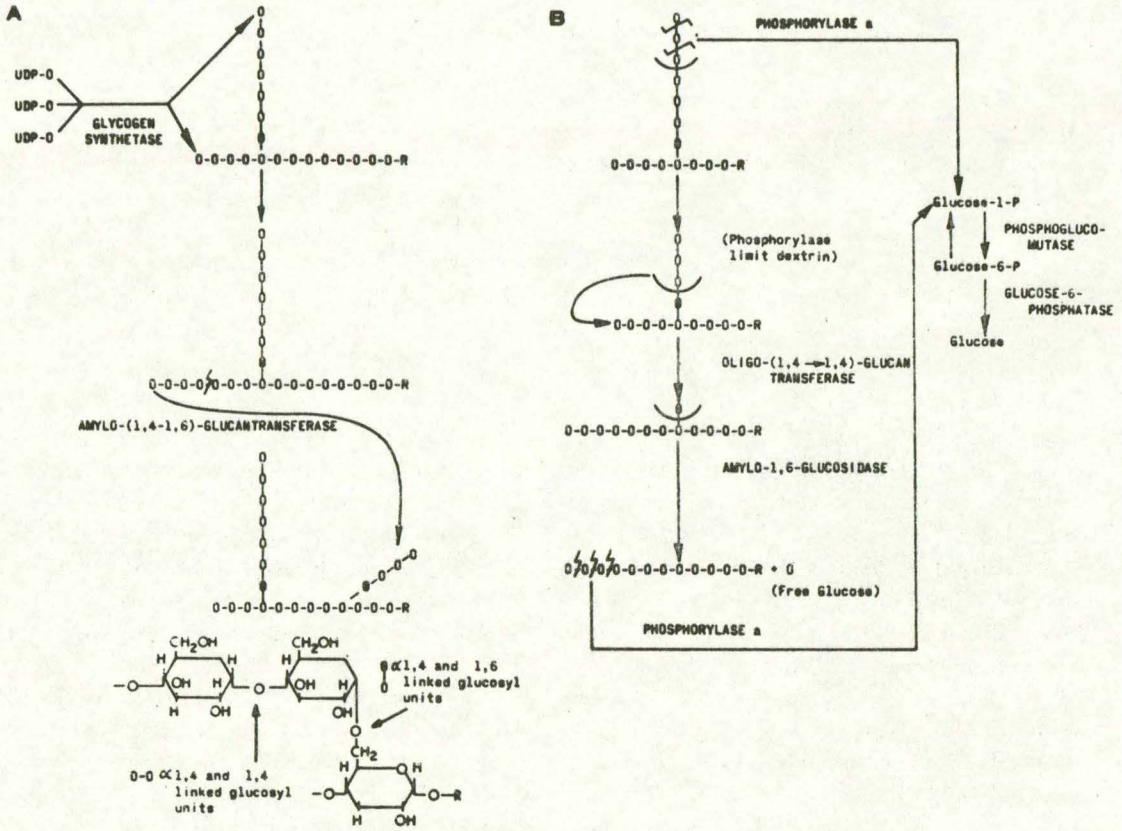

Fig. 2. *A*, Synthesis of glycogen. *B*, Degradation of glycogen. *0* = glucosyl monomer, *UDP-0* = uridine diphosphoglucose.

tribution of this organ is relatively small until after very prolonged periods of fasting (4 to 6 weeks).[2] In dogs, renal glucose production, even after such severe gluconeogenic stimuli as 2 to 4 weeks of fasting, ethanol, or insulin-induced hypoglycemia, still represented less than 10 per cent of the glucose released from the liver.[17] For these reasons, it would appear that the kidney is not a site for the physiologic control of glucose homeostasis in the early postprandial period (24 to 48 hours).

Glycogen synthesis.

Glycogen synthetase and amylo-(1,4 → 1,6)-glucantransferase. Hepatic glycogen synthetase (UDP-glucose-glycogen glucosyl transferase) transfers a glucose residue from uridine diphosphoglucose (UDPG) to an outer chain of glycogen in α-1,4 linkage. When the peripheral chain of glycogen reaches a length between 7 and 21 glucosyl units, a second enzyme, amylo-(1,4 → 1,6) glucantransferase (brancher enzyme), transfers a number of 1,4-linked glucosyl units from the end of a glycogen chain to another section of the glycogen molecule in α-1,6 linkage (Fig. 2, *A*). Glycogen synthetase exists in an active dephosphorylated (glycogen synthetase a) and inactive phosphorylated (glycogen synthetase b) form. Control of this enzyme is mediated, at least in part, by factors altering the intracellular level of adenosine 3′,5′-monophosphate (cyclic AMP). For example, glucagon and epinephrine increase the concentration of cyclic AMP and thereby stimulate a protein kinase which phosphorylates glycogen synthetase a to the inactive form b, and hense inhibits glycogen formation (Fig. 3).[18, 19]

Glycogenolysis.

Phosphorylase, oligo-(1,4 → 1,4)-glucan transferase and amylo-1,6-glucosidase (debrancher enzyme). Phosphorylase is the rate-limiting enzyme which initiates glycogenolysis and catalyzes the cleavage of α-1,4 glu-

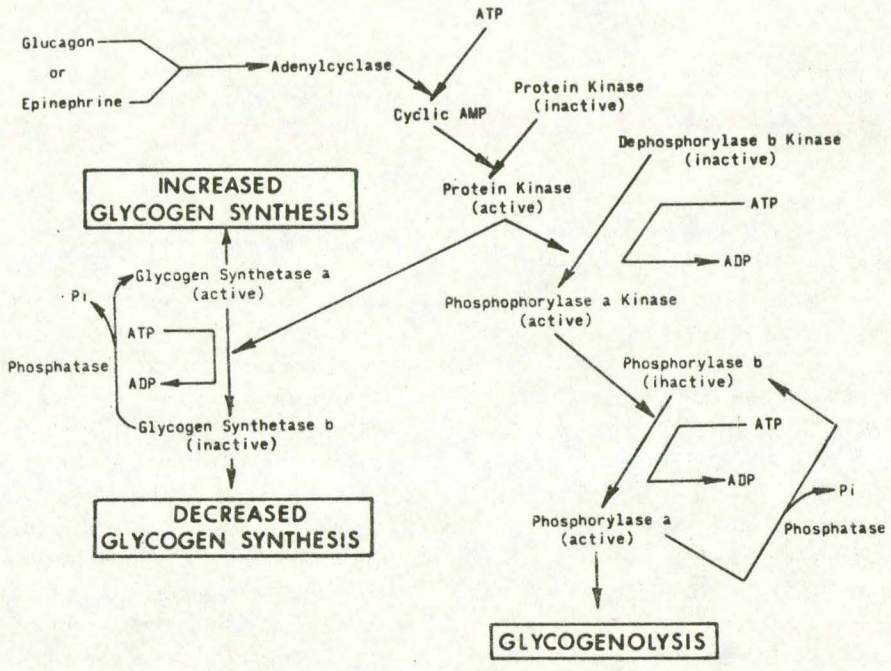

Fig. 3. Schematic representation for activation and deactivation of phosphorylase and glycogen synthetase.

cosyl units (Fig. 2, *B*). Although this enzyme can catalyze both glycogen degradation and synthesis in vitro, its specific function in vivo is glycogenolysis.[20] Phosphorylase hydrolyzes successive glucose residues until four glucosyl units remain on each branch; at this point, the glycogen molecule is termed a phosphorylase "limit dextrin".[20] Phosphorylase action can proceed no further until the α-1,4–linked trisaccharide is removed from the 1,6-linked glucose by a second enzyme, oligo-(1,4→1,4)-glucan transferase. The α-1,6 glucosyl unit is then removed as free glucose by amylo-1,6-glucosidase (debrancher enzyme) (Fig. 2, *B*). These two functions of debrancher enzyme (i.e., amylo-1,6-glucosidase and oligo-(1,4→1,4)-glucan transferase activity) have not been clearly separated.[21]

The control mechanisms regulating the relative amounts of active and inactive phosphorylase[22] are shown in Fig. 3. Glucagon and epinephrine, which activate the enzyme adenyl cyclase present in the plasma membrane, initiate a cascade of reactions which can be summarized as follows: (a) the increased intracellular level of cyclic AMP activates a protein kinase which (b) phosphorylates dephosphophosphorylase b kinase to phosphophosphorylase a kinase, which (c) catalyzes the activation of inactive phosphorylase b to active phosphorylase a. The inactivation of phosphorylase a is catalyzed by a highly specific phosphatase (Fig. 3).

Since cyclic AMP-dependent protein kinase activates the phosphorylase system and inactivates glycogen synthetase, it is evident that these two events are controlled synchronously by those factors influencing the adenyl cyclase-cyclic nucleotide phosphodiesterase complex (i.e., glucagon, epinephrine, methyl xanthine, and possibly insulin).

Phosphoglucomutase catalyzes the only physiologically reversible step in glycogen synthesis and degradation (Fig. 2, *B*). This enzyme transfers phosphate between the 1 and 6 positions of glucose and is not a site of physiologic regulation of glycogen synthesis or degradation.

Gluconeogenesis. Four enzymes which catalyze physiologically irreversible reactions and which function as rate-limiting steps in the gluconeogenic sequence are glucose-6-

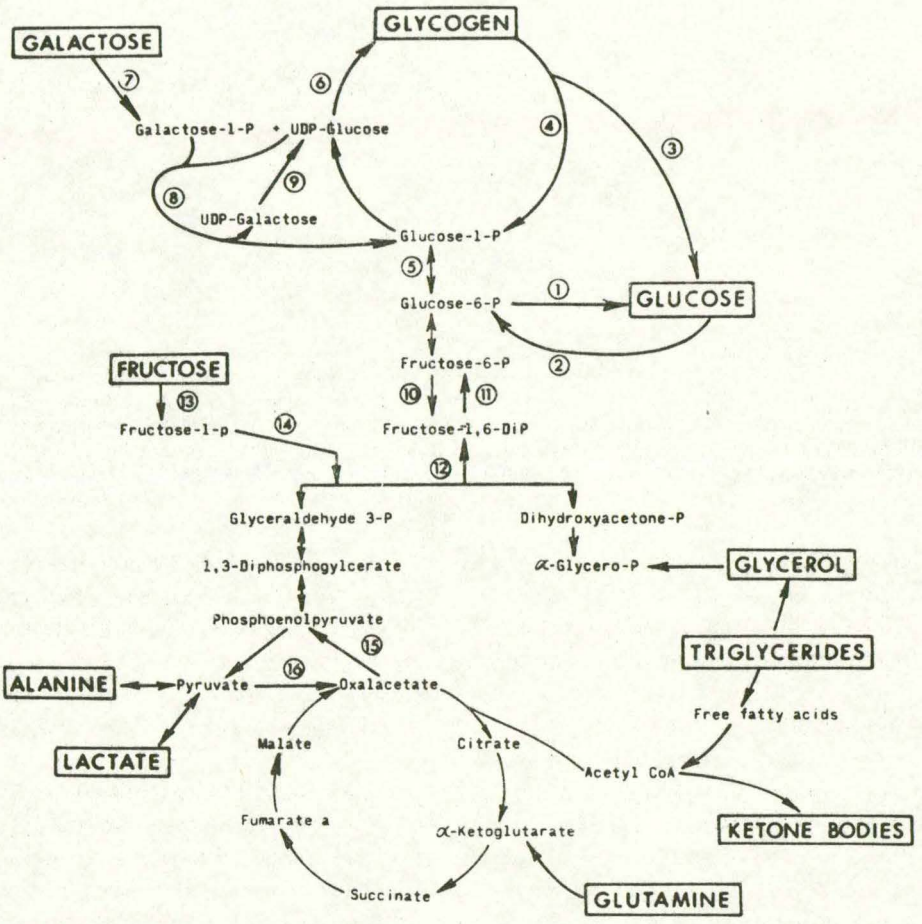

Fig. 4. Metabolic pathways involved in glycogen synthesis and degradation and gluconeogenesis. Key enzymes are designated by number. (1) glucose-6-phosphatase, (2) glucokinase, (3) amylo-1,6-glucosidase, (4) phosphorylase, (5) phosphoglucomutase, (6) glycogen synthetase, (7) galactokinase, (8), galactose-1-phosphate uridyl transferase, (9) uridine diphosphogalactose-4-epimerase, (10) phosphofructokinase, (11) fructose-1,6-diphosphatase, (12) fructose-1,6-diphosphate aldolase, (13) fructokinase, (14) fructose-1-phosphate aldolase, (15) phosphoenolpyruvate carboxykinase, (16) pyruvate carboxylase.

phosphatase, fructose-1,6-diphosphatase, phosphoenolpyruvate carboxykinase, and pyruvate carboxylase. These enzymes appear to function in a coordinate manner—their activities are increased by fasting and cortisone and decreased by feeding or insulin treatment.[28]

Glucose-6-phosphatase. This enzyme hydrolyzes glucose-6-phosphate to glucose and is the final enzymatic step by which the liver releases free glucose derived from either glycogenolysis or gluconeogenesis. Its complete absence, therefore, precludes glucose formation by either glycogenolysis or gluconeogenesis except for approximately 8 per cent of liver glycogen which can be converted to free glucose through the action of amylo-1,6-glucosidase (Fig. 2, *B* and 4). The enzyme is bound to microsomal membranes and, since it has not been highly purified, little is known about the molecular mechanisms by which its activity is regulated.

Fructose-1,6-diphosphatase. Fructose-1,6-diphosphatase catalyzes the hydrolysis of fructose-1,6-diphosphate to fructose-6-phosphate. As noted in Fig. 4, this enzyme is involved in glucose production from glycerol and fructose as well as from lactate, pyruvate, and amino acids.

Pyruvate carboxylase and phosphoenolpy-

rate carboxykinase. These two enzymes catalyze the formation of phosphoenolpyruvate from pyruvate (Fig. 4). Although pyruvate carboxylase is present in the mitochondria while phosphoenolpyruvate carboxykinase is present in both the cytosol and intramitochondrial space in man,[24] these two enzymes generally exhibit synchronous activity. Exton and associates[25] have suggested that the acute effect of glucagon and epinephrine on gluconeogenesis is at the level of the conversion of pyruvate to phosphoenolpyruvate. It has recently been shown in the fetal rat that both enzymes are present at very low levels and that glucagon and cyclic AMP induce the formation of phosphoenolpyruvate carboxykinase but not pyruvate carboxylase.[26]

Another potential rate-limiting step in gluconeogenesis may involve the transamination of alanine to pyruvate by glutamic-pyruvic transaminase. This transaminase is also increased by fasting, glucagon, and cortisone, and is depressed by feeding and insulin.[6]

Galactose and fructose metabolism. The conversion of galactose to glucose involves a series of reactions catalyzed in sequence by galactokinase (formation of UDP galactose) and uridyl diphosphogalactose-4-epimerase (formation of UDP glucose). UDP glucose may then be converted directly to glycogen by glycogen synthetase or may react in the galactose-1-phosphate uridyl transferase reaction to form glucose-1-phosphate (Fig. 4). Consequently, the only gluconeogenic enzyme required for the conversion of galactose to glucose is glucose-6-phosphatase.

The major pathway for fructose conversion to glucose involves the sequential action of fructokinase (formation of fructose-1-phosphate), fructose-1-phosphate aldolase (formation of D-glyceraldehyde-3-phosphate and dihydroxyacetone phosphate), and fructose-1,6-diphosphate aldolase (formation of fructose-1,6-diphosphate). In the case of fructose, therefore, both fructose-1,6-diphosphatase and glucose-6-phosphatase are required for conversion of this sugar to glucose.

THE ENDOCRINE SYSTEM

Insulin is the predominant hormone regulating the blood glucose level, since it is the only hormone whose direct action is to decrease the influx of glucose and accelerate the efflux of glucose from the vascular space. Insulin stimulates the transmembrane movement of glucose into skeletal and cardiac muscle and adipose tissue and the conversion of glucose to glycogen and triglyceride, as well as the intracellular transport of amino acids in these tissues and their incorporation into protein.[27] The hormone, at even low concentrations, is a potent inhibitor of adipose tissue lipolysis.[28] The net effect of these actions on peripheral tissues is to accelerate glucose disappearance from the blood and to decrease the supply of gluconeogenic substrates (i.e., glycerol and amino acids) presented to the liver. In concert with these peripheral actions, insulin stimulates hepatic glycogen synthesis, impairs glycogenolysis, and markedly depresses hepatic gluconeogenesis. Current information suggests that these hepatic effects reflect an action of the hormone on the adenyl cyclase-cyclic nucleotide phosphodiesterase system resulting in a decrease in the cellular concentration of cyclic AMP.[25] This action would result in activation of glycogen synthetase, inhibition of the phosphorylase system, and an ultimate decrease in the levels of gluconeogenic enzymes.

It is now recognized that the pancreatic arterial glucose level is not the only determinant of insulin release but that hormone secretion is influenced by a variety of nutritional and hormonal factors. A number of amino acids are capable of either directly stimulating insulin release from the β cell or potentiating the effect of glucose on hormone secretion. Furthermore, the oral ingestion of protein and glucose provokes the secretion of enteric factors which themselves stimulate insulin release.[29, 30] Under normal circumstances, insulin secretion is primarily observed only during periods of nutrient ingestion; only minimal quantities need be secreted during fasting to prevent the development of unrestrained ketoacidosis. In all species thus far examined, plasma insulin falls to very low levels during caloric restriction; values below 5 to 10 μU per milliliter are routinely noted in the human being under these circumstances.[5, 31] Consequently, insulin levels great-

er than 5 to 10 μU per milliliter in associa- per 100 ml. are distinctly abnormal. The tion with blood glucose levels below 50 mg. peripheral plasma level of the hormone will be significantly lower than in the portal vein, reflecting both transhepatic removal (approximately 50 per cent of a physiologic load is removed in one transhepatic passage) and dilution in the total vascular space.[32] Nevertheless, in the few studies reported of simultaneous measurements of insulin in portal and peripheral venous blood, the peripheral values paralleled the concurrent portal ones. However, the possibility does exist that hypoglycemic syndromes associated with excessive insulin secretion may be associated with only minimal elevation of peripheral plasma insulin despite extremely high portal concentrations because of increased hepatic extraction as a secondary adaptation to excessive insulin release.

Opposed to the hypoglycemic effects of insulin are the actions of adrenocorticotropic hormone (ACTH), cortisol, glucagon, epinephrine, and growth hormone. The net effect of these hormones is to increase the ambient blood glucose level by (1) inhibiting glucose uptake by muscle (i.e., epinephrine, cortisol, and growth hormone), (2) increasing endogenous gluconeogenic amino acid supply by mobilization from muscle (i.e., cortisone), (3) activating lipolysis and providing increased free fatty acids as a source of energy and glycerol for gluconeogenesis (i.e., epinephrine, glucagon, growth hormone, ACTH, and cortisol), (4) inhibiting insulin secretion from the pancreas (i.e., epinephrine), (5) acute activation of glycogenolytic and gluconeogenic enzymes (i.e., epinephrine and glucagon)[33] and (6) chronic induction of gluconeogenic enzyme synthesis (e.g., glucagon and cortisol.[33]

DEFINITION, SIGNS, AND SYMPTOMS OF HYPOGLYCEMIA

Children are usually symptomatic when the true blood glucose reaches a concentration of approximately 40 mg. per 100 ml. Symptoms are frequently absent despite extremely low blood glucose levels in newborn infants. Cornblath and Schwarz[14] have suggested that blood sugar levels less than 30 mg. per 100 ml. in the full-term neonate and less than 20 mg. per 100 ml. in the premature and small-for-gestational age infant should define hypoglycemia in this age group. Criteria of normal blood glucose levels for the newborn infant will be discussed in greater detail in the section on neonatal hypoglycemia.

Two factors which are frequently overlooked when interpreting the glucose concentrations are the analytic method used and whether blood or serum (plasma) is being examined. Since the water content of whole blood is approximately 15 per cent less than serum and glucose is not completely equilibrated between red cell water and serum, serum or plasma glucose levels will be approximately 15 per cent higher than whole blood values. A large number of chemical and enzymatic methods are currently in use for the determination of glucose. The enzymatic methods using glucose oxidase[34] or a combination of hexokinase and glucose-6-phosphate dehydrogenase[35] specifically measure glucose. On the other hand, a variety of reducing methods are not as specific for glucose and therefore may occasionally give falsely elevated glucose levels in the newborn infant.[36]

The clinical symptomatology associated with a rapid and acute fall in blood glucose reflects primarily excessive epinephrine secretion (i.e., sweating, weakness, tachycardia, nervousness, and hunger). If the hypoglycemia is not relieved, manifestations of cerebral dysfunction such as headache, irritability, mental confusion, psychotic behavior, seizures, and coma become progressively more prominent. With frequent or prolonged episodes of hypoglycemia, permanent central nervous system dysfunction may result. As mentioned above, hypoglycemic symptoms in the neonatal period are less obvious and may be either completely overlooked or absent.

HYPOGLYCEMIC SYNDROMES

For the purpose of this review, we have arbitrarily divided the hypoglycemic syndromes into two main groups: (1) transient neonatal hypoglycemia and (2) hypoglycemia

Table II. Classification of hypoglycemia

I. Neonatal hypoglycemia
A. Hypoglycemia associated with the small-for-gestational age infant
B. Transient hyperinsulinemia of the newborn infant
1. Infant of the diabetic mother
2. Infant with erythroblastosis
II. Hypoglycemia of infancy and childhood
A. Hyperinsulinemia
1. β-cell hyperplasia
2. β-cell tumors
3. Nesidioblastosis
4. Functional β-cell secretory defects
B. Substrate limited
1. Ketotic hypoglycemia
2. Hypoglycemia associated with endocrine disorders
a. Panhypopituitarism
b. Isolated growth hormone deficiencies
c. ACTH deficiency
d. Addison's disease
e. Hypothyroidism
C. Hepatic enzyme deficiencies
1. Glycogen storage diseases
a. Glucose-6-phosphatase
b. Amylo-1, 6-glucosidase
c. Defects of the phosphorylase enzyme system
2. Disorders of gluconeogenesis
a. Fructose-1, 6-diphosphatase
b. Pyruvate carboxylase
3. Other enzyme defects
a. Glycogen synthetase
b. Galactose-1-phosphate uridyl transferase
c. Fructose-1-phosphate aldolase

of infancy and childhood. The vast majority of neonates developing hypoglycemia in the first 24 hours of life will have either a prenatal history (i.e., mothers with diabetes or toxemia) or physical findings (i.e., small-for-gestational age or prematurity) which identify them as high-risk infants. Although the hypoglycemia occurring in most newborn infants remits spontaneously within hours to days of diagnosis, it is important to recognize that chronic hypoglycemia in these infants can occur soon after birth and be due to well-defined hepatic enzyme defects, endocrine deficiencies, or persistent hyperinsulinism, disorders which will be considered under the discussion of hypoglycemia of infancy and childhood (to appear in Part II). Table II lists the syndromes which will be dealt with in more detail.

NEONATAL HYPOGLYCEMIA

General considerations. Glucose is rapidly transported across the placenta so that the fetal plasma glucose level closely approximates the maternal concentration.[37] Consequently, the fetus during gestation is not dependent on its own gluconeogenic capacity, since it is constantly being supplied by a glucose infusion from maternal sources. In this context, one would anticipate that the gluconeogenic mechanisms (e.g., hepatic gluconeogenic enzymes, transaminases, and protein catabolic systems) in placentates would not be fully developed until near or soon after parturition. Very little is known about the time of induction of the hepatic gluconeogenic enzymes in the human fetus, but inferences can be made from studies in various mammalian species. In vitro perfusions with radioactive labeled precursors[38] and in vitro studies with fetal liver slices[39-42] clearly demonstrate that in the fetus, gluconeogenesis is either absent or markedly depressed. Measurements of the levels of specific gluconeogenic enzymes have shown considerable species variation but, in general, confirm the conclusion that certain key rate-limiting enzyme activities are low near the time of parturition and do not reach full activity until several hours to days after delivery. For example, hepatic glucose-6-phosphatase activity in the fetal rat and pig increases considerably during the last few days of fetal life but then exhibits a further 2- to 3-fold increase in the first two days of life.[43, 44] Fructose-1,6-diphosphatase activity is nearly fully developed at parturition in the sheep,[42] guinea pig,[41] and rat[45, 46] but is very low in the fetal pig and does not increase until the second postnatal day.[44] Pyruvate carboxylase is present at birth in substantial amounts in all animals examined and would not appear to be rate limiting.[44, 46, 47] On the other hand, phosphoenolpyruvate carboxykinase is virtually absent in the neonatal rat but increases rapidly after delivery,[44-48] whereas this enzyme is relatively fully developed in the pig at the time of birth.[44] It seems obvious from these data, therefore, that detailed information concerning the maturation of the hepatic

gluconeogenic enzymes in the human being is essential if we are to understand fully the various pathogenic mechanisms responsible for the development of transient hypoglycemia of the newborn infant.

From the point of view of glucose homeostasis and energy requirements, it is rather surprising that in highly developed countries, the neonate upon delivery is placed in a position of being fully dependent upon his own resources whereas in less sophisticated societies he is supported by being put immediately to breast. The normal healthy newborn infant does have adequate stores of fat and glycogen to sustain a short period of caloric deprivation and appears capable of mobilizing these substrates as energy sources. For example, within a few hours after delivery, the plasma free fatty acids are elevated,[49] and glucagon evokes a glycemic response.[50, 51] However, glycogen stores are limited and within a short period of time the neonate becomes dependent upon gluconeogenesis as the sole mechanism for meeting the obligate glucose requirements of the central nervous system and other glucose-dependent tissues. Despite these considerations it is a rather common practice to withhold feeding of normal neonates for 12 hours, and even longer periods of caloric deprivation have been suggested in the past for low-birth-weight infants to avoid the problem of aspiration.[52]

Throughout gestation, the normal fetus is exposed to an ambient plasma glucose level similar to that of the mother. There is no a priori reason to believe that upon delivery, the glucose-dependent tissues of the neonate are more tolerant to low glucose supply than those of the adult. Indeed, the very opposite seems more likely, since many critical structures have yet to reach maturation. In this context, it is difficult to accept current definitions of clinically significant hypoglycemia, i.e., 2 values less than 30 mg. per 100 ml. in the full-term infant and 2 values less than 20 mg. per 100 ml. in the low-birth-weight infant.[14] The studies upon which these recommendations are based are limited in number, involved heterogeneous groups of patients, used different fasting-feeding schedules, and did not present long-term follow-up clinical information.[14, 50, 53-56] Brain damage has been reported in infants with blood glucose levels less than 30 mg. per 100 ml.[57] However, there have been no long-term, systematic prospective studies in which the incidence of clinically significant neurologic and psychologic damage has been assessed in relation to the blood sugar levels of the neonate in the early days of life. Although it is well documented that the nadir of blood glucose frequently occurs within 2 to 3 hours following birth, we feel that this should not be construed as being either the normal or desirable concentration for later hours of life. Until further studies relating to the effect of early feeding on the blood glucose concentration have been performed, the authors follow the policy of vigorously treating all newborn infants who have plasma glucose concentrations of less than 40 mg. per 100 ml.

The small-for-gestational age infant. Correlation between the weight and gestational age of infants and their fasting blood sugar levels three hours after delivery was recently reported by Lubchenco and Bard.[58] The highest risk for the development of blood sugar levels less than 30 mg. per 100 ml. was in the small-for-gestational age infants in whom the incidence of hypoglycemia also correlated with the degree of maturation, i.e., 18 per cent incidence in post-term, 25 per cent in term, and 67 per cent in premature infants. Birth weight alone may not always be an adequate criterion for identification of the gestationally malnourished infant; the weight/length ratio occasionally provides an additional useful identifying parameter.[59]

The factors predisposing the small-for-gestational age infant to the development of hypoglycemia have not been clarified. We have followed prospectively 7 normal weight and 10 small-for-gestational age neonates from birth through the first 24 hours of life with frequent sampling for determination of blood glucose, lactate, pyruvate, β-hydroxybutyrate, acetoacetate, and plasma alanine. None of the normal weight neonates ex-

hibited plasma glucose levels less than 55 mg. per 100 ml. during the first 12 hours of life at which time a feeding schedule was instituted. Approximately 50 per cent of the small-for-gestational age infants had plasma glucose levels less than 35 mg. per 100 ml. within 2 to 3 hours of delivery, and all had significantly higher blood lactate, pyruvate, and plasma alanine levels than the full-term neonates. This pattern was already discernible in cord blood and maintained through the first 24 hours of life despite the institution of a feeding regimen at the time hypoglycemia was first documented. This pattern of blood metabolites is highly suggestive of a maturation delay in the hepatic gluconeogenic enzymic apparatus. Of further interest is the finding that despite hypoglycemia, blood β-hydroxybutyrate and acetoacetate levels in the small-for-gestational age infants remained lower than in normal weight neonates suggesting inadequate fatty acid stores or defective fatty acid mobilization or a maturational delay in hepatic ketogenesis. Of concern is the fact that the supply of utilizable substrate for the central nervous system (i.e., glucose, ketone bodies) in the small-for-gestational age infant is deficient and may represent a significant risk factor in the production of irreversible brain damage.

Other factors associated with neonatal hypoglycemia. Hyperinsulinemia has been documented in infants of mothers with various forms of diabetes mellitus (i.e., chemical, clinically overt, and insulin-requiring).[60] Although there is technical difficulty in documenting hyperinsulinemia in the newborn infant of the insulin-requiring mother because of interference of insulin antibodies in the radioimmunoassay,[60] these infants on postmortem examination exhibit marked hyperplasia of the beta cell and a high content of insulin in the islets. Infants with erythroblastosis fetalis also have a high incidence of hypoglycemia which is secondary to hyperinsulinemia.[61] Beta cell hyperplasia also has been found at postmortem examination in these infants. In the offspring of diabetic mothers, beta cell hyperplasia is considered to be secondary to the chronic hyperglycemia resulting from the elevated maternal blood glucose level; no etiology is apparent in the erythroblastotic infant.

Hypoglycemia has also been reported in infants born to toxemic mothers[62] and in association with hypothermia in the newborn infant.[14] In the latter instance, cause and effect are not clear, since hypothermia is a common finding in adults with hypoglycemia. Hypoglycemia in the neonate in association with hypothermia may well be related to more rapid utilization of endogenous glycogen stores in the face of a decreased ability to perform gluconeogenesis. Infants have also been described with severe, unresponsive hypoglycemia in whom alpha cells were reported to be absent from the pancreas.[63] With the advent of the glucagon immunoassay, techniques are now available to document a deficiency of this glucoregulatory hormone.

Therapy. The time at which the neonate is begun on a feeding schedule varies from institution to institution. Most nurseries tend to have a fixed program in which the initial feeding consists of 5 per cent glucose at 4 to 12 hours after delivery in the normal neonate and even sooner in the premature or small-for-gestational age infant. Five per cent glucose (6.6 calories per ounce) is a poor nutritional substitute for human colostrum which contains 6.4 per cent lactose, 3 per cent lipid, 2 to 3 per cent protein, and 18 calories per ounce.[65] It has frequently been argued that 5 per cent glucose is safer than milk as an initial feeding in regard to the development of aspiration pneumonitis. However, studies in newborn rabbits revealed no pathologic differences 24 hours after the intratracheal instillation of either 5 per cent glucose or a formula feeding.[64] Furthermore, data on the relative frequency of aspiration pneumonitis in infants fed 5 per cent glucose or formula diets are not available.

It is the authors' current policy to monitor the blood glucose level of all high-risk infants (i.e., small-for-gestational age infants, premature infants, infants of diabetic mothers, etc.) at 1 to 2 hour intervals with Dextrostix (Ames). Since variable and inconsistent re-

sults are frequently observed with this method at low blood glucose concentrations, test results with Dextrostix are frequently compared with plasma glucose values determined by reliable laboratory methods. If the blood glucose level with this method is 45 mg. per 100 ml. or less, a blood specimen is obtained for measurement of glucose by the glucose oxidase method, and the infant is started immediately on a feeding of 5 per cent glucose followed subsequently at 2 to 3 hour intervals with standard formula feedings. Throughout this time, the blood glucose level is monitored before each feeding; in the large majority of instances, adequate glucose concentrations are maintained by this practice. If, however, the plasma glucose value remains below 40 mg. per 100 ml. by specific measurement, an intravenous infusion of 10 to 25 per cent glucose is begun. Specific rates of glucose administration have been reported[65a]; however, it is our opinion that the variability in requirements between patients is so great that the rate of administration needs to be individualized and the patient given an amount of glucose which will maintain his plasma glucose above 40 mg. per 100 ml. This approach to therapy requires frequent monitoring of the blood glucose and close observation of the volume of fluid being administered. On rare occasions, hypoglycemia persists despite this infusion and then cortisone acetate is administered intramuscularly at 8 hour intervals (total dose is 5 mg. per kilogram of body weight per day). On this regimen, the blood glucose level has been readily stabilized in the vast majority of infants. Usually, the intravenous infusion of glucose can be tapered after 48 hours and cortisone acetate therapy gradually eliminated during the subsequent 4 to 5 days. If hypoglycemia persists for more than 72 hours on this regimen, other causes for the disorder must be sought.

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THE EFFECTS OF EARLY AND LATE FEEDING OF INTRA-UTERINE FETALLY MALNOURISHED (IUM) INFANTS

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ABSTRACT. The effects of early versus late feeding were evaluated in 28 infants with intra-uterine fetal malnutrition (IUM). The criteria for IUM include: (1) birth weight below the 10th percentile of the Colorado's intra-uterine growth chart, (2) body length longer than expected for weight, and (3) signs of postmaturity described by Clifford. In 13 IUM infants whose birth weights exceeded 2,040 gm, the blood glucose levels, acid-base status, and calcium and magnesium values were comparable to those of 10 nonmalnourished control infants. Early (4 hours) or late (24 hours after birth) oral feeding did not alter their values during the first 48 hours of life. In 15 IUM infants who weighed less than 2,040 gm at birth, 3 of 9 late-fed infants (24 hours) developed symptomatic hypoglycemia, while none of 6 early-fed infants (4 hours) developed such difficulty. The blood glucose values at 48 and 72 hours of age and response to glucagon-epinephrine tolerance tests at 24 hours of life were significantly higher in the early-fed group. These observations suggest that the early feeding of infants with IUM, and birth weight below 2,040 gm may enhance glucose homeostasis in early neonatal life and prevent neonatal symptomatic hypoglycemia. *Pediatrics*, 42:261, 1968, NEWBORN INFANT, INFANT NUTRITION, MALNUTRITION, HYPOGLYCEMIA, FETAL MALNUTRITION.

RECENT STUDIES have shown that early feeding of low birth weight (LBW) infants may have beneficial effects on their glucose homeostasis and bilirubin metabolism.[1-4] LBW infants fed at 2 hours after birth have significantly higher serum glucose values and lower serum bilirubin levels during the first 24 hours and at 96 to 144 hours of age, respectively.[5] The early-fed babies also appeared to have stored a greater amount of liver glycogen reserve, as shown by a higher response to the glucagon-epinephrine tolerance test at 24 hours of age in comparison to those infants whose first feeding was delayed to 24 hours after birth. Infants with intra-uterine fetal malnutrition (IUM) may have a lower hepatic glycogen reserve at birth and potentially are more prone to develop symptomatic hypoglycemia during the neonatal period.[6,7] Recent surveys by Wybregt, *et al.*[7] and by Pildes, *et al.*[8] have demonstrated a high incidence of hypoglycemia in IUM infants during the early neonatal life. Since the symptomatic hypoglycemia is a consequence of disturbed glucose homeostasis resulting from inadequacy of exogenous glucose supply, glycogenolysis, and perhaps gluconeogenesis, it was the purpose of this study to determine whether early administration of feeding may favorably promote glucose homeostasis among the IUM infants as it did for the LBW nonmalnourished infants.

MATERIALS AND METHODS

Twenty-eight infants with signs of intra-uterine fetal malnutrition (IUM) admitted to the Michael Reese Hospital and Medical Center from October 1966 to May 1967

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This work was partially supported by The Children's Bureau Grant No. H-172 (CI) of the U. S. Department of Health, Education and Welfare, Washington, D.C., Infant's Aid Society of Chicago, and Kunstadter Research Fund, Michael Reese Hospital and Medical Center, Chicago, Illinois.

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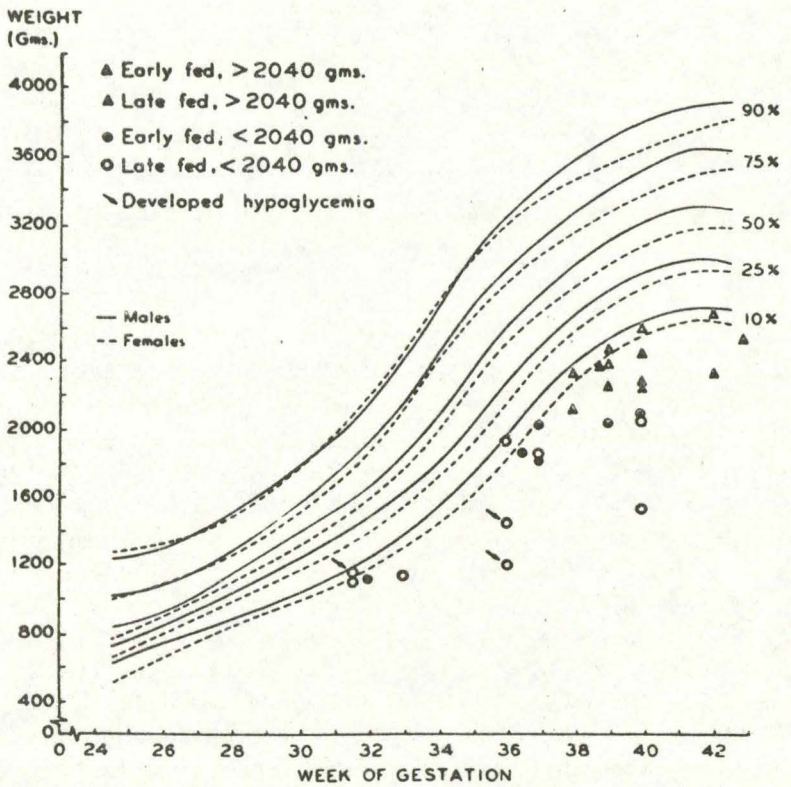

FIG. 1. Birth weights of study infants plotted against their gestational ages on the Colorado's growth chart.[9]

were the subjects of this study. Thirteen infants whose birth weight exceeded 2,040 gm were admitted to the full-term nursery, while 15 others whose birth weights were less than 2,040 gm were confined to the "premature" nursery. Our hospital policy specifies 2,040 gm (4 lb, 8 oz) as the weight limit for admitting infants to premature nursery. The criteria for IUM were: (1) birth weight lower than the 10th percentile of Colorado's intra-uterine growth chart[9] (Fig. 1); the calculation of the gestational age was based on the mother's last menstrual period; (2) body length longer than expected for weight, and (3) signs of postmaturity as described by Clifford.[10] All infants studied fulfilled these three criteria. In addition, 10 infants whose birth weights exceeded 2,040 gm, were appropriate for their gestational ages, and showed no signs of postmaturity[10] were used as control subjects. No control subjects were selected for the infants weighing less than 2,040 gm. The influence of early versus late feeding, particularly on the glucose homeostasis, of non-malnourished infants whose birth weights were less than 2,040 gm have been reported previously.[4] These data are cited as control values for the IUM infants weighing less than 2,040 gm in the present study. The clinical management, personnel, procedures, and conditions in the nursery were the same in both studies.

The birth weight, gestation, length, head circumference, and sex differences of the studied infants are listed in Table I.

The assignment of infants to either early or late-fed group depended upon the age when the infant was incorporated into the study group. If the subject was younger than 4 hours of age, he was included in the early-fed group; otherwise, he was assigned to the late-fed group. In the full-term nursery, five IUM infants (birth weight >2,040

gm) were fed a 20 calories per ounce formula* at 4 hours of age (early-fed group) and the subsequent feedings were given at 4-hour intervals. Eight of the IUM infants were first fed at 24 hours of age (late-fed group). Ten control infants were equally divided into two groups (early and late-fed groups) and were fed in the same fashion as in the IUM infant groups. The volume and caloric intake of the early-fed group during the first 24 hours of life averaged 41 ml/kg and 26.6 cal/kg, respectively, for the IUM group and 39.1 ml/kg and 25.9 cal/kg, respectively, for the control group (Table II). From 24 to 72 hours of age, the early and late-fed groups (both IUM and control groups) had similar volume and caloric intake. The infants were kept in an open crib and were dressed in a cotton shirt and diapered; one flannel blanket was wrapped around them. The room temperature was maintained at an average of 76°F and relative humidity was kept at 60%. None of these infants had difficulty during the study period and were discharged at 48 to 120 hours of age in good condition.

In the premature unit, the IUM infants were free of congenital anomalies and were in fair condition when admitted to the study. Six of these infants were given intravenous fluid (10% dextrose in water) at 80 ml/kg/24 hours (32 calories/kg/24 hours) beginning at 2 to 4 hours after birth. These are the early-fed infants. In nine other IUM babies, the feeding (orally) was started at 24 hours of age; the oral feedings for both early and late-fed groups were given at 3-hour intervals. The volume and total caloric intake for the early-fed group of infants during the first 24 hours of life averaged 78.7 ml/kg and 31.4 cal/kg, respectively (Table II). The volume and caloric intake of subsequent feedings were comparable for both early and late-fed groups of infants. The caloric intake during the first 5 days of life ranged from 30 to 78 cal/kg/24 hours. These infants were kept in incubators

* A proprietary formula (Similac) was used. The caloric distributions were: protein 11%, carbohydrate 42%, and fat 47%.

TABLE I

BIRTH WEIGHT, GESTATION, LENGTH, HEAD CIRCUMFERENCE, AND SEX OF 28 INTRAUTERINE MALNOURISHED (IUM) AND 10 CONTROL INFANTS

Data	*IUM*		*Control*
	<2,040 gm	*>2,040 gm*	*>2,040 gm*
Birth weight (gm)	1,630 ± 380	2,390 ± 270	2,860 ± 230
Gestation (wk)	36.0 ± 2.9	40.3 ± 1.9	39.2 ± 1.6
Length (cm)	43.6 ± 3.7	47.8 ± 2.1	49.6 ± 1.5
Head circumference (cm)	29.4 ± 2.0	32.7 ± 1.0	33.5 ± 0.3
Sex			
Male	2	6	2
female	13	7	8
Number of infants	15	13	10

Mean ± SD

at 50 to 60% humidity. Axillary temperatures were taken every half hour after admission until it became stabilized at 97°F to 98.6°F. Subsequently, the temperatures were taken every 8 hours.

Blood glucose, blood gases, and serum calcium and magnesium were determined at 24 and 48 hours of age in the >2,040 gm group and at 24, 48, 72, and 96 hours in the <2,040 gm groups of infants. Blood specimens for glucose were obtained by heel puncture and precipitated at cribside with barium hydroxide and zinc sulfate, and the filtrate was analyzed for glucose with a glucose oxidase method.[11] Capillary blood pH, pCO_2 and buffer base were determined by the micro-Astrup method.[12] Serum calcium

TABLE II

VOLUME AND CALORIC INTAKE PER KILOGRAM BODY WEIGHT OF EARLY-FED INFANTS DURING THE FIRST 24 HOURS

Data	*IUM*		*Control*
Birth weight (gm)	<2,040	>2,040	>2,040
Volume intake (ml/kg)	78.7	41.0	39.1
Caloric intake (cal/kg)	31.4	26.6	25.9

TABLE IV

CLINICAL SUMMARY OF THREE INTRA-UTERINE MALNOURISHED INFANTS* WHO DEVELOPED SYMPTOMATIC HYPOGLYCEMIA

Mother				*Infant*						
Case Number	*Age*	*History During Pregnancy*	*Gestation (wk)*	*Sex*	*Birth Weight (gm)*	*Length (cm)*	*Condition at Birth*	*First Symptoms and Age (hr)*	*Lowest Blood Sugar and Age (hr)*	*Treatment*
1	34	negative	36	F	1,420	45	good	Tremor—19	5–26	I.V. glucose ACTH
2	21	negative	36	F	1,200	42	first breath delayed	Tremor—21	19–21	I.V. glucose ACTH
3	24	chronic hypertension	31.5	M	1,190	38	fair	Apnea and cyanosis 20	8–25	I.V. glucose steroid

*All infants were Negro.

blath, *et al.*[6] and all three infants responded dramatically to intravenous administration of 50% glucose with relief of symptoms. A clinical summary of these three cases is presented in Table IV. All three infants were below the 10th percentile of Colorado's growth chart (Fig. 1). Two of the three infants showed signs of second stage, and one of third stage of postmaturity as described by Clifford.[10]

Figure 3 shows that early feeding of IUM infants weighing less than 2,040 gm produced a significantly higher blood glucose level at 48 and 72 hours of age (t test showed a P value of $<.05$ and $<.02$, respectively). Wu, *et al.*[4] demonstrated a similar

TABLE V

BLOOD pH, pCO_2, HCO_3, SERUM CALCIUM AND MAGNESIUM OF 15 INTRA-UTERINE MALNOURISHED INFANTS WEIGHING <2,040 GM

Data	*Early Fed*			*Late Fed*		
Age (hr)	*24*	*48*	*72*	*24*	*48*	*72*
pH	7.38 ± 0.12	7.38 ± .015	7.36 ± .010	7.36 ± .009	7.37 ± .015	7.40 ± .015
pCO_2 (mm Hg)	41.7 ± 4.1	42.5 ± 4.6	26.3 ± 4.0	40.9 ± 6.3	38.8 ± 4.2	32.0 ± 5.6
HCO_3 mEq/l	53.3 ± 7.4	58.6 ± 5.5	54.5 ± 6.9	53.1 ± 2.5	48.6 ± 3.0	53.4 ± 3.8
Serum calcium mg/100 ml	10.6 ± 1.3	9.2 ± 0.4	8.4 ± 0.4	9.2 ± 0.8	7.9 ± 0.8	8.4 ± 0.6
Serum magnesium (mg/100 ml)	1.8 ± 0.10	1.9 ± 0.14	2.1 ± 0.18	2.0 ± 0.09	2.1 ± 0.06	2.1 ± 0.06
Number of infants	6			9		

Mean ± S.E.M.

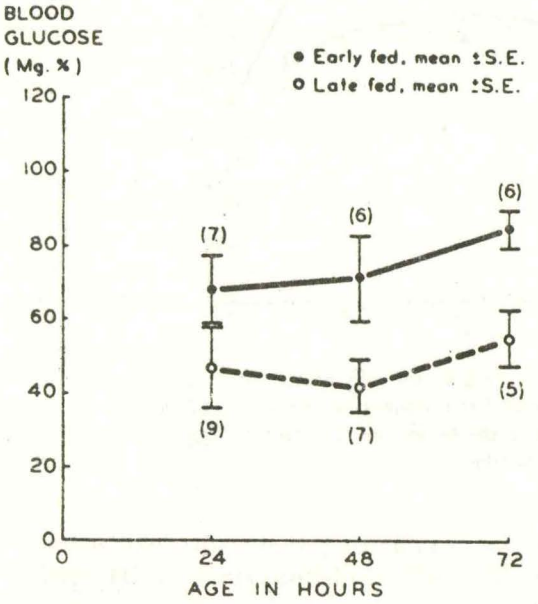

FIG. 3 Effect of early (4 hours) versus late feeding (24 hours) on the serum glucose values of intra-uterine malnourished infants weighing <2,040 gm at birth. P values at 48 and 72 hours of age are <.05 and <.02, respectively.

effect in infants with birth weight appropriate for their gestational age, with a significant difference in response apparent at 24 hours of age. The blood pH, pCO_2, BB, serum calcium and magnesium were not affected by the timing of first feeding (Table V).

The hyperglycemic response to glucagon-epinephrine challenge was higher in the early-fed IUM groups of infants as shown in Figure 4. The difference between early and late-fed groups was significant at 30 and 60 minutes after the glucagon-epinephrine administration ($p<.05$).

COMMENTS

This study shows that the metabolic state of the intra-uterine malnourished (IUM) infants during the early neonatal period may vary. The variation may be dependent on the duration and severity of the pathology that causes the intra-uterine fetal malnutrition. When the IUM infants were grouped into two weight categories, it became apparent that the larger IUM infants (birth weight >2,040 gm) did not manifest clinical and laboratory evidences of metabolic disturbance and that their glucose values, acid base status, serum calcium and magnesium level, and presumed liver glycogen stores were within the normal range. It

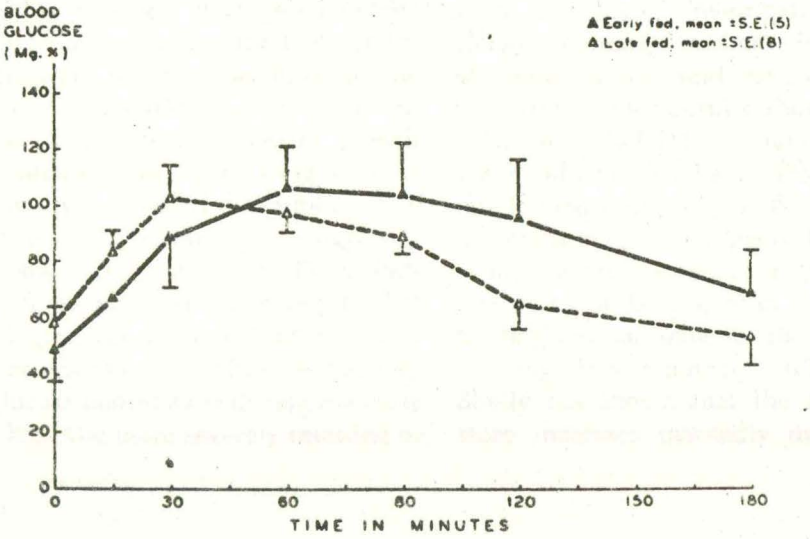

FIG. 2. Glucagon-epinephrine tolerance curves of five early-fed and 8 late-fed intra-uterine malnourished infants weighing >2,040 gm at birth; performed at 24 hours of age.

trimester of pregnancy.[14,15] In experimental animals, Emmanouilides, *et al.*[16] have shown that ligating one of the umbilical arteries during mid term of pregnancy in sheep could result in the birth of low birth weight, malnourished, newborn lambs, suggesting the possibility that the factors causing IUM most likely operate during the last trimester of pregnancy. It can be postulated from these two observations that, in IUM, a pathological event such as decreased uterine blood flow demonstrated by Emmanouilides and co-workers[16] could limit the provision of substrates necessary for the fetal hepatic glycogenesis, which normally occurs during the last trimester.[15] In normal infants, the hepatic glycogen level normally falls rapidly during the second to the third day of life.[15] It seems likely that in the IUM infants this rapid fall in liver glycogen coupled with decreased liver glycogen reserve, increased metabolic rate,[17] withholding of feeding, and perhaps some defect in adrenal medullary functions[18] could lead to the development of hypoglycemia.

In Beard and co-workers' study,[1] five of seven infants with birth weights below the 10th percentile of Lubchenco's curve, and whose feedings were withheld for 72 hours, had blood glucose levels of less than 25 mg/100 ml, although none developed symptoms referable to hypoglycemia. These findings are very similar to the ones found in our study.

In our smaller IUM babies (birth weight less than 2,040 gm), whose first feedings were withheld for 24 hours, the limited liver glycogen reserve was demonstrated by their reduced response to glucagon-epinephrine administration. Three of these infants had the typical symptomatic hypoglycemia described by Cornblath, *et al.*,[6] suggesting failure of adaptive mechanisms necessary to maintain a normal glucose value. In this type of infant, early provision of calories and carbohydrates improved blood glucose values and glucagon-epinephrine response, indicating that early feeding may enhance the infant's ability to maintain a normal glucose homeostasis and at the same time restore liver glycogen reserve sooner than if the initial feeding were delayed.

The effects of early or late feeding of low birth weight infants on glucose homeostasis have been described previously.[1-4] These studies concerned low birth weight infants appropriate for gestational age who presumably did not have IUM. The similarity of changes in carbohydrate metabolism induced by early feeding, particularly in the small infants who weighed less than 2,040 gm, suggest that the metabolic systems responsible for such activities are probably intact and similar in both non-malnourished and malnourished groups. Provision of a necessary substrate by early feeding may rapidly augment the insufficient hepatic reserve incurred during these infants' intrauterine existence.

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Biol. Neonat. *11*: 29–35 (1967)

From the Departments of Paediatrics and Biochemistry, United Oxford Hospitals

Plasma Glucose Levels in Infants Weighing 2,500 g and Less Fed Immediately after Birth with Breast Milk[1]

R. K. Ditchburn, R. H. Wilkinson, Pamela A. Davies and Patricia Ainsworth

There are now several reports of blood sugar levels during the first days of life in infants classified as premature [1, 2, 3, 4]. As Hjelm and Sjölin have pointed out [5], it is difficult to compare them or estimate their reliability, for earlier studies have measured total reducing substances or 'true sugar', while more recently the introduction of the enzymatic glucose-oxidase methods has made it possible to record glucose. There are certain precautions in technique necessary to avoid fallacious results [3, 6], and clinical details of infants tested should be known, as it is now apparent that sex, race and birthweight may variously affect blood sugar levels [3]. Correlations with precise food intake have been surprisingly few; indeed it is clear from many of the reports that the infants have been starved initially. It is the purpose of this paper to report blood sugar levels (estimated as plasma glucose) in infants fed immediately after birth and during the first 4 days of life with undiluted breast milk.

Method

Fifty-three infants weighing 2500 g or less at birth were studied. Thirteen infants weighed 2000 g or less, and 40 between 2001 and 2500 g. Twelve infants were born at gestations less than 34 weeks, and 41 at varying times thereafter. There were 28 males, and 25 females. Only one of the infants was a Negro. Eighteen were more than 2 standard deviations below the mean birthweight for their gestation (using standards of the National Birthday Trust's Perinatal Mortality Survey of 1958). They were all fed undiluted breast milk whenever possible, though a few had a half cream dried milk towards the end of the 4 day period. In the first 24 h of life they were given 60 ml/kg body weight, on the 2nd

[1] A shortened version of this paper was read by one of us (Pamela A. Davies) at a meeting in Kyoto, 1965, following the XI. International Congress of Pediatrics.

day 90 ml/kg body weight, on the 3rd day 120 ml/kg body weight, and on the 4th day 150 ml/kg body weight. These totals were sometimes exceeded slightly on the 3rd and 4th days in infants small for their gestation. The technique of feeding has been described previously [7].

Whenever possible cord blood was collected at delivery. Estimations were made at approximately 24, 36, 48, 60, 72 and 96 h after birth, using capillary blood from the heel. Specimens were always collected just before a feed was due. Intervals between feeding varied according to the clinical condition and size of the infant, from 1 to 4 h. Blood was collected into a tube containing fluoride, and centrifuged immediately for 5 min. It was then stored at a temperature of 4°C until estimations were made by the glucose oxidase method in an Auto Analyzer [8]. In the early part of the study some of the cord blood samples were left for some hours before they were centrifuged and put in the refrigerator.

Results

Levels of plasma glucose of 53 infants at intervals after birth are shown in Fig. 1. The line joining the means is also drawn in all the remaining figures. Female infants have higher mean levels than males during the period tested (Fig. 2), and infants weighing 2001–2500 g have higher mean levels than those weighing 2000 g and less (Fig. 3). None of these differences are statistically significant. Infants whose birth weight was more than two standard deviations below the mean

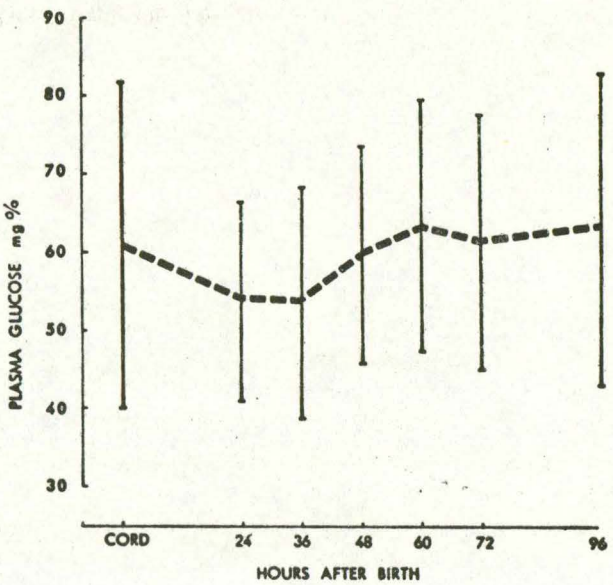

Fig. 1. Mean levels and standard deviations (53).

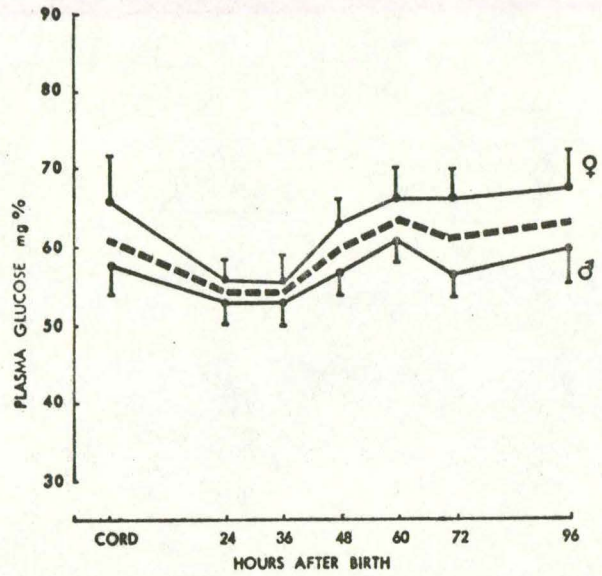

Fig. 2. Mean levels and standard error in males (28) and females (25).

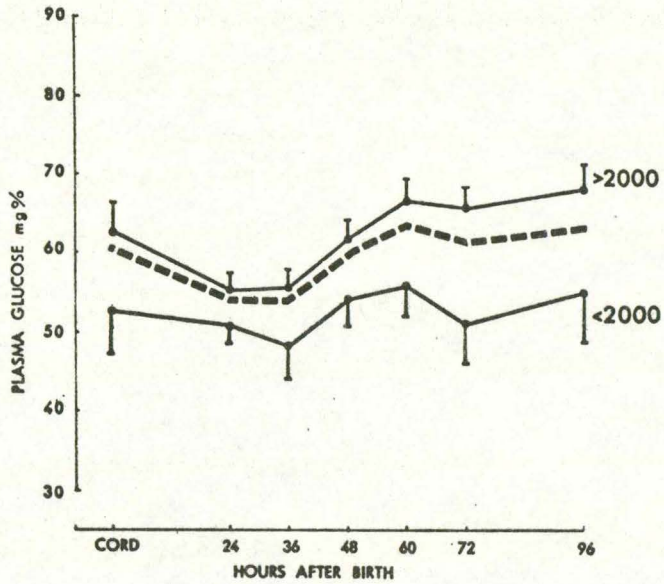

Fig. 3. Mean levels and standard error in infants above (40) and below (13) 2000 g.

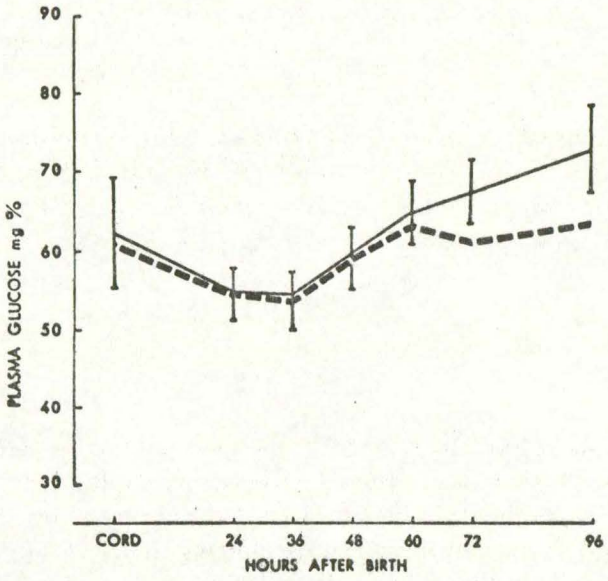

Fig. 4. Mean levels in infants with birth weight more than two standard deviations below mean for gestation (18).

for their gestation show a mean curve very similar to that of the group as a whole, with slightly higher values from 60 h onwards (Fig. 4). The mean levels for cord blood cannot unfortunately be regarded as accurate, as some of the specimens were left at room temperature for varying periods after collection.

Discussion

The reliability of various methods of determining glucose in newborn infants has recently been assessed by HJELM and SJÖLIN. Certain precautions must be observed to avoid falsely high or falsely low readings. In a series of preliminary experiments it was found that whole blood collected into fluoride tubes and centrifuged immediately yielded plasma in sufficient quantities for the specific enzymatic glucose method. The levels of glucose remained constant within the experimental error when the plasma was analysed at varying intervals up to 24 h, providing it was stored at 4°C. The glucose oxidase method removes the fluoride from the plasma as magnesium fluoride

before dialysis. Immediately after this removal, the dialysate reacts with the enzyme dye mixture. We estimated glucose in plasma rather than whole blood in order to eliminate the risk of error from glycolysis and remove the effect of haematocrit variation. Our results would read approximately 10–20 mg% higher than a whole blood sample, and must be interpreted accordingly. It has been known for some time that blood sugar levels in the early neonatal period are lower than those in older children and adults. They may fall very low in the first 24 h of life [9]. In our investigation the lowest mean value after this period found in 53 infants was 54.1 mg%, and occurred at 36 h following delivery. The apparent lower mean values in male infants and in those of lower birth weight and maturity, confirm the similar findings by CORNBLATH *et al.* [3].

It was not until 1959 that abnormal neurological behaviour after the first 24 h of life was correlated in certain infants with persistently low blood sugar levels (below 20 mg%) and the symptoms relieved by the administration of intravenous glucose [10]. This and subsequent reports by CORNBLATH and his colleagues have given much impetus to the study of symptomatic hypoglycaemia in the neonatal period. Among infants classified as premature (2500 g or less at birth) there are many who are abnormally small for the period of gestation and it is generally agreed that they are at greatest risk [10, 11, 12]. Symptomatic hypoglycaemia is an important condition, for it is now clear that a substantial number of the affected infants, some despite apparently adequate treatment, later show severe mental retardation [11, 12]. SMALLPEICE and DAVIES [7] have suggested that this condition is largely avoided by the immediate, liberal and frequent feeding of breast milk. The plasma glucose levels shown here for infants more than two standard deviations below mean birth weight for their gestation support this view (Fig. 4). It is also reinforced by the fact that for the past three years no infant with symptomatic hypoglycaemia has been seen in a much larger group of infants on the same feeding regime as that described here. Truly immature infants, of whom there are relatively few in this study, have mean levels lower than the group as whole. Nevertheless over the same period of time, careful follow up of a larger group of such infants does not show any seriously retarded [13].

Although in the established case of symptomatic hypoglycaemia intravenous glucose has a dramatic therapeutic effect, it is clear that low glucose levels alone are not responsible for symptoms, for

certain infants with levels below 20 mg% may be asymptomatic and develop normally. Other biochemical abnormalities, of which a low lactate level may be only one of many [14, 15], probably coexist when symptoms occur. It seems likely therefore, that breast milk exerts its beneficial effect in other ways than providing the necessary glucose.

Summary

Plasma glucose levels (at intervals from 24 h until the 4th day) were estimated by an Auto Analyser glucose oxidase method in 53 infants classified as premature by birthweight. All were fed immediately after birth with undiluted breast milk whenever possible, at a rate of 60 ml/kg body weight in the first 24 h, increasing to 150 ml/kg body weight by the 4th day.

The lowest mean plasma glucose level, 54.1 mg% occurred at 36 h of age. Persistently low levels were not seen in any infant. Male infants and infants of low birth weight had mean levels lower than those for the group as a whole.

Mean plasma glucose levels of infants of birth weight more than two standard deviations below the mean for gestation did not differ from those of the group taken as a whole.

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OXYGEN THERAPY, CLYSIS

8. OXYGEN USAGE: For years we have lived under the impression that if an infant appeared blue, he always needed more oxygen. This may be true for the mature infant, but unfortunately, this is not true for the immature infant. Many immature babies are quite cyanotic and have PO_2's in the clearly toxic range. Conversely, we also realize that an immature infant in oxygen concentrations approaching room air can develop retrolental fibroplasia. The upshot of all this is that the small hosptial can be held culpable unless they can adequately demonstrate that they can follow blood PO_2 levels accurately. Few small hospitals have accurate micro blood gases available, and for this reason we feel that an immature baby, who requires oxygen, should be referred at the earliest possible convenience. We would like to stress that referrals should be early, for indeed, if delay occurs the opportunity to offer this child a reasonable chance at a normal life is frequently lost. The correction of acidosis, hypoglycemia, etc., must occur soon or irreparable damage is done. Too many times people look upon referrals as a defeat, and we encourage you to think of this in different terms. If we look upon the final outcome of the infant, then an appropriate referral becomes a victory for all concerned.

but high humidities are not necessary for body temperature maintenance when the principal heat protection is provided from radiant sources rather than from warming of the air in the incubator.

OXYGEN THERAPY

Need for Oxygen

When a newborn infant needs extra oxygen, it must be administered with great care because there is a causal relationship between a higher than normal (60 to 100 mm Hg) oxygen tension in arterial blood and retrolental fibroplasia (retinopathy of prematurity). When the normal oxygen tension is exceeded, there is an increased risk of retrolental fibroplasia. The upper limit of arterial oxygen tension and its duration which are safe for these infants is not known. It is probable that even concentrations of 40% oxygen in inspired air (formerly considered safe) could be dangerous for some infants.

An inspired oxygen concentration of 40% may be insufficient for infants with cardiorespiratory disease to raise the oxygen tension of arterial blood to a normal level. In such instances, an inspired oxygen concentration of 60%, 80%, or higher may be necessary. However, it is difficult to judge by clinical signs the concentration of inspired oxygen necessary to maintain effective oxygenation of tissues in these infants. An infant may have peripheral cyanosis and yet may have a normal or even an elevated arterial oxygen tension. Therefore, arterial blood gas measurements are extremely important for regulation of the concentration of inspired oxygen when an oxygen-enriched environment is considered necessary.

Recommendations

1. A normal newborn infant has an oxygen tension in arterial blood of 60 to 100 mm Hg. It is recommended that, when newborn infants breathe oxygen-enriched mixtures, the

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oxygen tension of arterial blood be kept close to this normal range.

2. Inspired oxygen may be needed in relatively high concentrations to maintain the arterial oxygen tension in the normal range.

3. If blood gas measurements are not available, a mature infant who is not apneic but has generalized cyanosis may be given oxygen in a concentration just high enough to abolish the cyanosis. However, the infant born before 34 weeks' gestation or weighing less than 2,000 gm (4 lb, 7 oz) who requires an inspired oxygen concentration greater than 40% for more than brief periods should be treated, where feasible, in a hospital at which the inspired oxygen concentration can be regulated on the basis of blood gas measurements.*

4. The ideal sampling sites for arterial oxygen tension studies are the radial or temporal arteries. In most circumstances, however, in hospitals where well established experience has reduced the technical hazards, a sample from the descending aorta through an indwelling umbilical arterial catheter is satisfactory.

5. Equipment for the regulation of oxygen concentration (as provided by some incubators and respirators) and devices for mixing oxygen and room air may not function properly; therefore, it is essential that, when an infant is placed in an oxygen-enriched environment, the concentration of oxygen be measured with an oxygen analyzer at least every 2 hours. The performance of the oxygen analyzer must be checked daily by calibration with room air and 100% oxygen.

6. Mixtures of oxygen and room air may be delivered to an infant by endotracheal tubes, masks, funnels, hoods, or incubators. Regardless of the method used, the mixture should be warmed and humidified.

7. The condition of infants requiring oxygen may improve rapidly. Under these circumstances, the inspired oxygen concentration should be lowered carefully in decrements that

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*The Committee recognizes that, at the present time, this represents an optimal standard of care; and, it may well be impossible to arrange for such transfer because of lack of facilities and transport problems. The Committee hopes that, by making this recommendation, all concerned in the delivery of health care to the newborn infant will work toward making this standard a reality.

maintain the oxygen tension of arterial blood in the normal range.

8. It should be appreciated that oxygen is toxic to organs other than the retina (e.g., lungs), which may be damaged even if the foregoing criteria are adhered to. To avoid prolonged hyperoxic exposure of the lungs, if very high ambient concentrations of oxygen are required to maintain a normal arterial oxygen tension, a reasonable compromise may be to lower the oxygen concentration progressively after the first 1 or 2 days, even though this may result in a somewhat lower arterial oxygen tension than normal.

9. A person experienced in recognizing retrolental fibroplasia (retinopathy of prematurity) should examine the eyes of all infants born at less than 36 weeks' gestation or weighing less than 2,000 gms (4 lb, 7 oz) who have received oxygen therapy. This examination should be made at discharge from the nursery and again at 3 to 6 months of age. If there are no fundal abnormalities on discharge from the hospital, no further eye examination is necessary.

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RETROLENTAL FIBROPLASIA IN A CYANOTIC INFANT

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ABSTRACT. Proliferative retrolental fibroplasia was documented by ophthalmoscopy and histopathological study in a 940-gm birth weight infant with severe cyanotic congenital heart disease who died at the age of 11 weeks. Arterial oxygen tensions usually considered to be pathologic were not noted in this infant and would not appear to have been possible in view of the cardiac anomalies found during life and at autopsy. These observations indicate that retrolental fibroplasia may occur in immature infants in the absence of oxygen abuse.

Pediatrics, 50:765, 1972, RETROLENTAL FIBROPLASIA, PREMATURITY, OXYGEN THERAPY.

THE causative relationship of oxygen therapy to retrolental fibroplasia has been recognized generally since the publication of the results of the cooperative study on retrolental fibroplasia in 1956.[1] The sporadic occurrence of retrolental fibroplasia in premature infants without oxygen therapy and, less frequently, in term infants has been mentioned previously but infrequently reported.[2,3]

This report describes clinically diagnosed and histologically proved retrolental fibroplasia in a child with cyanotic congenital heart disease in whom significant pathologic elevation of the arterial Po_2 would not appear to have been possible.

CASE REPORT

A 940-gm Caucasian male infant with breech presentation had an Apgar rating of 1 at one minute and 6 at five minutes and required resuscitation. Because of cyanosis and substernal retractions, he was given oxygen by free flow over the face at 4 liters/min for one hour and 3 liters/min until transfer. On admission to the University of Washington Neonatal Intensive Care Unit at the age of 4 hours, he had clinical and radiological evidence of mild hyaline membrane disease. Gestational age was estimated by physical characteristics to be 31 weeks. An umbilical arterial catheter was inserted and 30% oxygen was administered via an oxygen hood. Initial blood gases were Po_2, 43 mm Hg; Pco_2, 37 mm Hg; pH, 7.28. The inspired oxygen concentration was increased gradually from 30% to 60% during the next eight hours but the Po_2 did not rise above 94 mm Hg (Table I). By 12 hours of age, the chest radiograph showed partial clearing of the lungs. Although congenital heart disease was suspected, there was no radiographic evidence of cardiac enlargement. The oxygen concentration was reduced gradually to 40% by 24 hours of age and by 44 hours the infant was breathing room air (Table I). Respiratory distress was mild with considerable improvement by the third day of life when the arterial catheter was removed.

On the third day, he was noted to have a grade 2/6 systolic murmur along the left sternal border. Cyanosis was noted on day 4. By the 11th day of life he had regained his birth weight and was progressing satisfactorily, but cyanosis increased on day 12. Thirty per cent oxygen was given from day 15 to day 17. The arterial Po_2 was 46 mm in 30% oxygen. Enlargement of the liver, tachypnea, and mild cardiomegaly were present by day 30. By the third week of life, the diagnosis of tetralogy of Fallot was made on the basis of mild cyanosis, a grade 2 systolic murmur at the base of the heart and single second heart sound; the electrocardiogram showed right ventricular hypertrophy, while radiographs of the chest recorded diminished pulmonary vascular markings and a heart normal in

Abbreviations

F_IO_2: Fraction of inspired oxygen
Pao_2: Arterial oxygen pressure
Pco_2: Carbon dioxide pressure
Po_2: Oxygen pressure

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TABLE I

SERIAL ARTERIAL OXYGEN TENSION VALUES AND FRACTION OF INSPIRED OXYGEN

Age	F_IO_2	PaO_2 (*mm Hg*)
4 hours	.3–.35	43
5 hours	.4	41
6 hours	.5	50
8 hours	.5	55
12 hours	.6	92
16 hours	.5	94
20 hours	.4	65
24 hours	.4	64
28 hours	.4	61
32 hours	.4	67
35 hours	.35	109
36 hours	.28	70
40 hours	.28	85
44 hours	.21	77
56 hours	.21	69
82 hours	.21	70
15 days	.26	46
18 days	.23	54
11 weeks	1.0	38
11 weeks	1.0	38
11 weeks	1.0	34

overall size but with a suggestion of right ventricular enlargement; the aorta descended on the right. He was discharged at 6 weeks of age weighing 1,820 gm.

Binocular indirect ophthalmoscopy was performed through dilated pupils at weekly intervals beginning at day 12 until discharge and again at the age of 10 weeks. Dilatation and tortuosity of the retinal vessels at the posterior pole and intraretinal proliferation of new retinal vessels in localized areas of the temporal periphery (stage 1 proliferative retrolental fibroplasia) was noted in each eye on day 19. Progressive increase in the vessel proliferation to involve the entire temporal retinal periphery in each eye occurred during the ensuing weeks, and proliferation of new vessels into the vitreous (stage 2 proliferative retrolental fibroplasia) was noted on day 33. Ophthalmoscopy was performed last on day 75 when the characteristics of stage 2 proliferative retrolental fibroplasia were noted again.

TABLE II

CARDIAC CATHETERIZATION DATA

Catheter Position	*Saturation*	*Pressure*
Right Atrium*	28%	Mean = 6–9
Right Ventricle*	22%	63/13
Aorta (ascending)*	29%	60/31
Aorta (ascending)†	48%	52/28

* Infant crying.
† Infant quiet.

The patient was readmitted at 11 weeks of age because of extreme cyanosis, grunting respiration, and two hypoxic episodes on the day of admission. A cardiac catheterization was performed. Pressures and saturations recorded are shown in Table II. Biplane angiocardiography with injection of contrast material into the right ventricle confirmed the clinical diagnosis of severe tetralogy of Fallot with probable pulmonary atresia. The aorta was immediately opacified but no pulmonary outflow tract was seen. A patent ductus arteriosus arose from the left subclavian artery, and the right and left pulmonary arteries filled via this channel. There was marked overriding of the aorta with a right-sided aortic arch and a heavily trabeculated hypertrophied right ventricle with a hypoplastic outflow tract without apparent continuity with the main pulmonary artery. The cardiac catheterization-angiocardiographic diagnosis was: (1) tetralogy of Fallot with markedly hypoplastic or atretic right ventricular outflow tract; (2) pulmonary blood flow via a patent ductus arteriosus arising from the left subclavian artery; and (3) right aortic arch. Because of the severe progressive hypoxia, a Waterston anastomosis between the ascending aorta and the right pulmonary artery was performed on the day following cardiac catheterization, but cyanosis and cardiac failure persisted and death occurred 48 hours after surgery.

PATHOLOGY

A complete autopsy examination confirmed the clinically diagnosed disorders of the cardiovascular system and eyes. The origin of the aorta overrode a ventricular septal defect and arched to the right. The right ventricular chamber was markedly enlarged. The pulmonary outflow tract was extremely small with a rudimentary bicuspid pulmonary valve which had an opening less than 2 mm in diameter. A short left innominate artery bifurcated into a left carotid and a left subclavian which communicated via a patent ductus arteriosus with the hypoplastic pulmonary arteries and the pulmonary outflow tract. The ductus arteriosus was occluded by a 0.3 cm thrombotic plug near the origin of the pulmonary arteries. The surgical anastomosis between the right lateral aspect of the aorta and the right pulmonary artery contained a thrombus.

The eyes were received in 10% formaldehyde solution (Formalin), opened horizontally, and studied under the dissecting microscope. Tufts of white tissue projected

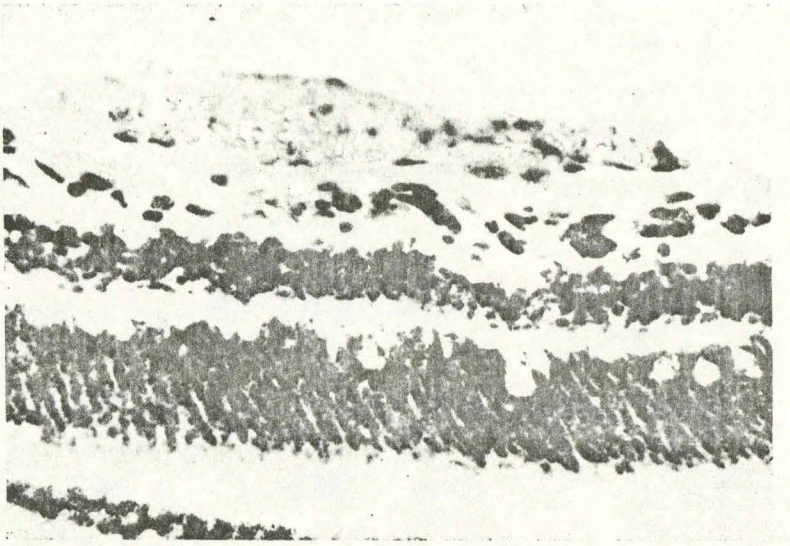

FIG. 1. Surface proliferation of peripheral retinal vessel (hematoxylin-eosin, ×160).

into the vitreous cavity from the termination of the visible retinal vessels along the temporal equator in each eye. The eyes were embedded in paraffin, sectioned, and stained with hematoxylin-eosin or PAS-hematoxylin. Microscopic examination revealed abnormalities limited to the temporal periphery of the retina in each eye. Retinal vessels had left their normal position within the retina to lie on the surface of the retina (Fig. 1) and to enter the vitreous cavity (Fig. 2). The pathologic diagnosis was retrolental fibroplasia, proliferative stage 2, both eyes.

DISCUSSION

The case reported documents the occurrence of retrolental fibroplasia in a child ap-

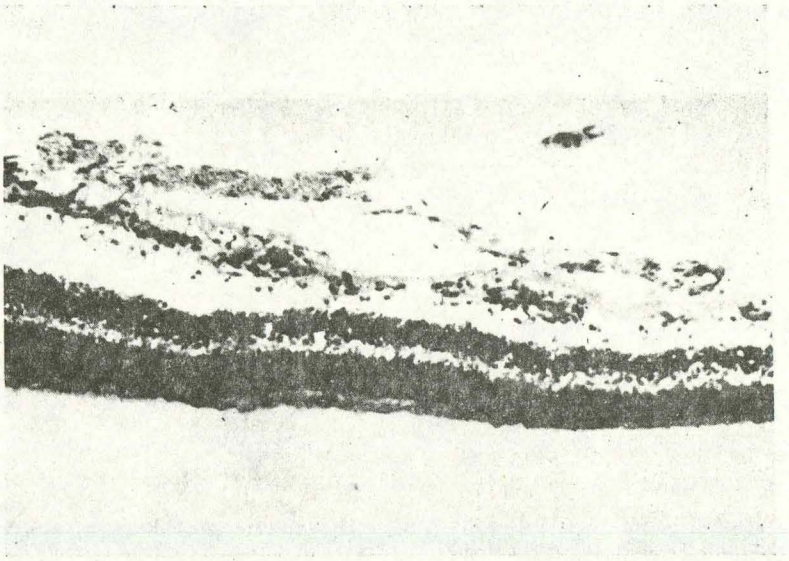

FIG. 2. Intravitreal proliferation of peripheral retinal vessels (hematoxylin-eosin, ×152).

parently incapable of transmitting blood with a high arterial oxygen tension to the retina. All arterial blood samples during the first three days of life were obtained from the descending thoracic aorta. The aortic oxygen tension must have been similar to that in the retinal vessels, since any shunt occurring through the ductus arteriosus had to be in a left-to-right direction due to the pressure-flow gradient created by the severely hypoplastic pulmonary artery and the rudimentary pulmonary valve. Although the oxygen tension during the first four hours of life was not known, the method of oxygen administration (free flow), the low Po_2 values obtained during the next several hours, and the existing anatomic defects indicate that a sustained Po_2 elevation could not have occurred.

Following the establishment of the etiologic relationship of oxygen to retrolental fibroplasia, oxygen therapy in most premature nurseries was restricted to a maximum of 40% in the inspired air irrespective of clinical demands. Increased mortality among premature infants was observed during those years of restricted oxygen use.[4] The cooperative study of retrolental fibroplasia[1] showed that the incidence of retrolental fibroplasia was directly proportional to the duration of time spent by the infant in an oxygen rich environment but was not affected significantly by changes in inspired oxygen concentration below 50%. More recently, it has been recognized that the concentration of oxygen in the inspired air is unimportant if circumstances exist which prevent elevation of the Po_2 in the arterial blood perfusing the retina, and a more flexible use of oxygen based upon clinical need has been advocated.[5] While arterial blood gas monitoring provides the best indication of need for oxygen and effectiveness of oxygen therapy, critical levels for arterial Po_2 which are likely to be associated with retrolental fibroplasia have not been established.

Zacharias[6] has emphasized the risks of marked elevation of the Pao_2 which may occur due to continued oxygen therapy following recovery from episodic attacks of cyanosis or apnea. Such infants easily are capable of pathologic hyperoxygenation in contrast to the infant reported here.

The cooperative study[1] also showed that the incidence of retrolental fibroplasia was inversely proportional to birth weight. Although there is no doubt that oxygen abuse is associated with an increased incidence of retrolental fibroplasia, we believe that certain low birth weight infants will develop retrolental fibroplasia in the total absence of supplemental oxygen. The prognosis for survival among low birth weight infants is improving,[7,8] and occasional cases of retrolental fibroplasia will occur in spite of careful oxygen monitoring.

SUMMARY

Retrolental fibroplasia was noted at 19 days of age in both eyes of a 940-gm birth weight infant who died at the age of 11 weeks following surgery for tetralogy of Fallot. Autopsy confirmed both severe cyanotic congenital heart disease and retrolental fibroplasia, proliferative stage 2. The occurrence of retrolental fibroplasia in a cyanotic child indicates that the disorder may occur in low birth weight infants in the absence of oxygen abuse.

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9. CLYSIS: The use of clysis is generally reserved for those infants who are not able to tolerate oral feedings. In general, they are very sick infants with poor peripheral circulations. Since the absorption of subcutaneous fluids is dependent upon an intact peripheral circulation; we feel the use of this modality of fluid therapy, is rarely, if ever indicated.

NEWBORN RESUSCITATION

10. RESUSCITATION IN THE DELIVERY ROOM AND NURSERY:

A. Minimal equipment available (resuscitation tray)

1. Laryngoscope with an infant size blade. Extra batteries - bulbs
2. Suction - DeLee traps, catheters, and mechanical suction
3. Oxygen supply - humidified and warmed
4. Infant size plastic airways
5. Endotracheal tubes, sizes 8 - 14 Fr. (or 2.5 mm to 4.0 mm ID)
6. Some type of positive pressure apparatus with an infant size bag (500 cc) Infant Ambu, Hope Resuscitator, etc.
7. Feeding tubes size 5 and 8 Fr. for passage into the stomach for aspiration and checking nares for choanal atresia.

B. Minimal equipment available (umbilical catheters)

1. Solution for skin disinfection (Betadine)
2. Sterile gloves
3. Sterile saline
4. 4 by 4 sterile gauze
5. Instrument set: Kelly clamp or mosquito hemostat, scapel blade No. 11 or 15, and holder, probe, forceps (ophthalmologic) with teeth, scissors, curved needle and silk suture, No. 3 or 4, needle holder;
6. Polyvinyl catheter, No. $3\frac{1}{2}$ or 5 Fr. arterial preferably with radiopaque marker (Argyle)
7. Syringe, 5 to 10 ml.
8. Sterile towels or circumcision drape

C. Personnel available who can bag breath an infant

D. Personnel available who can intubate an infant

E. Personnel available who can insert an umbilical catheter

F. Medications available - Sodium Bicarbonate, Adrenalin - Aqueous 1:1,000, $D_{50}W$, Naloxone or other narcotic antagonist

G. Adequate suction

10.A. OUTLINE FOR RESUSCITATION:

1. Heart rate is the most important parameter

2. Always insure a clear airway (suction!!)

I. Heart rate is between 120 and 180 but is falling - oxygen by face mask. If heart rate continues to fall and respiratory effort gets weaker - BAG BREATH THE INFANT!

II. Heart rate has been 100 - 120 but now falls below 100; always bag breath with oxygen but as heart rate continues to fall always INTUBATE!

III. Heart rate less than 100, initially, intubate (may try short course of bag breathing, but be ready to intubate immediately)

IV. Heart rate less than 40 - with no improvement after intubation and ventilation - institute cardiac massage

V. Additional measures:

1. Keep the infant warm - (chilling $\longrightarrow$ acidosis)

2. Correct acidosis - any infant requiring resuscitation can be safely assumed to be acidotic. Give 3 meq. of Sodium Bicarbonate per kilogram of body weight diluted with an equal volume of D_5W or $D_{10}W$ - give per umbilical vein catheter over 2 - 4 minute period. This mat be repeated up to 3 times. Call the pediatrician for further advice prior to transport.
We strongly advise that physicians caring for newborns be able to insert an umbilical venous catheter on short notice. This is frequently the only vessel available for sodium bicarbonate therapy and is, indeed, one of the few life saving measures instituted in the distressed newborn. We recognize that the catheter frequently is placed in or near the liver and that the solutions infused are relatively hypertonic and probably do lend to a certain amount of liver necrosis. However, the child can repair his damaged liver but can not repair his damaged brain if the sodium bicarbonate is not given. When the catheter has been placed and the sodium bicarbonate given, infuse $D_{10}W$ at a rate of 80 - 100 cc. per kilogram of body weight per 24 hours to prevent hypoglycemia.

3. Consult a newborn referral center for advice on possible referral of any infant that requires resuscitation.

UMBILICAL VEIN CANNULATION

Incidations:

1. "Parental and/or blood infusions, when peripheral veins are difficult to cannulate. (Especially when hypertonic solutions are given)
2. Exchange transfusions" [1]

Materials:

The following equipment and materials are necessary for catheter placement -

1. "Solution for skin disinfection, povidone-iodine (Betadine)
2. Sterile gloves
3. Sterile saline
4. 4 x 4 sterile gauzes
5. Instrument set:

    a. Kelly clamp or mosquito hemostat
    b. Scapel blade No. 11 or 15; and holder
    c. Probe
    d. Forceps with teeth (ophthalmologic)
    e. Polyvinyl catheter No. 3 1/2 or 5 Fr. arterial preferably with radiopaque marker (Argyle)
    f. syringe, 5 to 10 ml.
    g. sterile towel or circumcision drape" [2]

Insertion procedure:

The entire procedure should be done in the incubator or under a radiant heater to avoid chilling the infant;[3] if he is cyanotic or in respiratory distress, a plastic oxygen hood (Sierracin or Ohio Company) can be placed over his head to increase oxygen concentration.[4]

When not precluded by the emergency (i.e., acute asphyxia), the following protocol should be followed. The operator carefully scrubs hands and arms to the elbows and puts on sterile gloves. After carefully preparing the umbilical stump and surrounding abdominal wall with an antiseptic solution, sterile towels are placed around the stump and a "circumcision drape" placed with the hole over the stump.[5]

Sterile saline is rinsed through the polyvinyl catheter to prevent introduction of air. The umbilical stump is amputated close to the abdomen with a scalpel (a scissors should not be used since it tends to pinch and distort the anatomy of the cord). The vein is probed, this is the thin-walled, collapsible vessel usually at the 12 o'clock position. Any visible clots should be removed with forceps.

The venous wall may be grasped by the forceps with teeth (or the Kelly clamp may be attached to give more leverage).[6] The catheter is then inserted

and gently advanced. Obstruction at the level of the abdominal wall may be relieved by gentle traction on the umbilical cord stump accompanied by steady but gentle pressure for about 30 seconds. If an umbilical vein catheterization is performed, the next site of obstruction is the portal system (the catheter meets resistance several centimeters before the distance marked on the catheter is reached). The catheter should be withdrawn several centimeters, gently rotated, and reinserted in an attempt to get the tip through the ductus venosus into the inferior vena cava. Occasionally, it will not be possible to get the catheter into the inferior vena cava for anatomical reasons, and vigorous attempts to advance the catheter are to be avoided.[7]

Recommendations:

The position of the catheter must be identified by X-ray immediately after insertion. If the X-ray after umbilical vessel cathetrization indicates that the catheter has been inserted too far, it may be gently withdrawn an estimated amount for appropriate placement. If the catheter is not in far enough, it must be completely withdrawn and a new sterile one inserted after appropriately preparing the area again with antiseptic solutions, and so forth.[8]

Complications:

The catheter is a foreign body; its introduction into the blood vessel also introduces bacteria into a sterile area.

A thrombus may form around the catheter site.

Introduction of the catheter may tear the vein and, if advanced to the right atrium, may tear the atrial wall.

Hypersomolar solution introduced into the catheter in the liver area may enter the liver vasculature and cause necrosis of tissue.[9]

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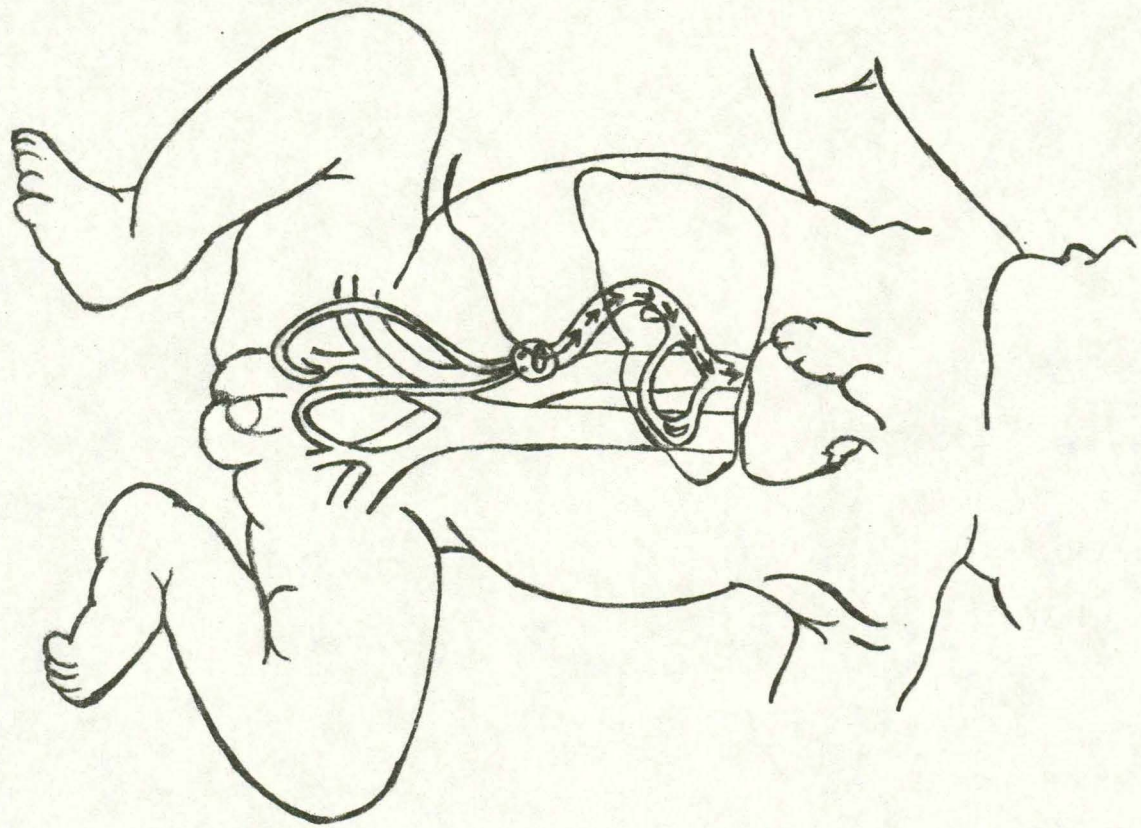

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7. Klaus, Fanaroff, Care of the High-Risk Neonate, p. 16.

8. Ibid., p. 16.

9. Pierog, Approach to the Medical Care of the Sick Newborn, p. 261.

CORD CARE

11. CORD CARE: In the past, no single method of cord care emerged as superior. However, recent work by pilder, et. al., Journal of Pediatrics, Vol. 82: 987 - 990, June 1973, has demonstrated the apparent superiority of a triple dye preparation. This preparation contains: brilliant green, gypsom violet, and proflavine semasulfate solution, and can be obtained from Kerr Chemical Company and/or Xttrium Laboratory in Chicago, Illinois.

Effect of triple dye on staphylococcal colonization in the newborn infant

The effectiveness of triple dye, hexachlorophene, or liquid soap bathing in the reduction of staphylococcal colonization rate was evaluated in a study of 1,117 infants. Cord colonization rate was 10.5 per cent in the triple dye group, 41.1 per cent in the hexachlorophene group, and 71.5 per cent in the control group. These differences are significant ($p < 0.001$). Nasal colonization rate was similar in the triple dye (12.4 per cent) and hexachlorophene groups (15.8 per cent), and both were significantly ($p < 0.001$) lower than the rate in the control group (48.3 per cent). After the study was terminated, triple dye was applied to the cords of all infants admitted to the nursery. In 1,147 infants cultured during the following six months, the staphylococcal cord colonization rate was 1.8 per cent and the nasal colonization was 5.2 per cent. Triple dye was considered an effective agent in maintaining low staphylococcal colonization rates in newborn nurseries.

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TOTAL body bathing of newborn infants with 3 per cent hexachlorophene has been associated with a lowered colonization rate of coagulase-positive *Staphylococcus aureus* and a decreased incidence of skin infection caused by this bacterium.[1-5] The safety of 3 per cent hexachlorophene has recently been questioned,[6-9] and the routine prophylactic use of hexachlorophene for total body bathing of neonates is currently not recommended.[10-11]

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Within a month following the discontinuance of hexachlorophene bathing, the rate of staphylococcal colonization rose quickly in our nursery and in nurseries throughout the country.[12] An increased incidence of staphylococcal disease has also been reported.[13] Since the maintenance of a low colonization rate has been considered of value in the prevention of staphylococcal disease,[2-5, 14] alternative measures to the use of hexachlorophene should be sought.

The purpose of this controlled study was to evaluate the effectiveness of triple dye as compared to hexachlorophene or castile soap (control) bathing in reducing the rates of staphylococcal colonization in the large nursery of a general hospital. Triple dye, recom-

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Table I. Dates, location, and numbers of infants in each study group

Dates	*Triple dye*	*Hexachlorophene*	*Control*
2/21 - 3/17	WD 50 (150)		WD 51 (109)
3/20 - 4/7	WD 50 (112)	WD 51 (98)	
4/12 - 5/19	WD 51 (127)	WD 50 (160)	
5/22 - 6/30	WD 51 (142)	WD 50 (126)	WD 54 (98)
Total	531	379	207
7/5 - 1/5	All wards (1,147)		

WD = ward.

mended by Jellard[15] in 1957, is composed of brilliant green 2.29 Gm., proflavine hemisulfate 1.14 Gm., crystal violet 2.29 Gm., and water q.s.a.d. 1,000 ml.[15]

METHODS AND MATERIALS

The nursery for healthy infants at Cook County Hospital consists of five wards located on the same floor. The first two wards (50 and 51) have 30 to 40 crib spaces each; the remaining three wards have 15 to 25 crib spaces. Infants in two of the wards (52 and 53) were not included in the study because they were delivered by cesarean section or because the mothers may have had complications related to labor or delivery. A total of 93 nursing personnel administer to these areas and although an attempt was made to maintain the same personnel in each unit, daily changes in assignment because of illness or vacations were frequently necessary. Medical students and house staff rotate through all of these units.

The infants were assigned to one of three groups (triple dye, hexachlorophene, or control) according to the schedule shown in Table I. It was decided that approximately 100 infants would be included in each group before the therapeutic measures were to be interchanged. A control group from two separate wards was included at the beginning and end of the study to rule out naturally occurring changes in the rate of colonization.

All infants were bathed shortly after admission and daily thereafter. The hexachlorophene group of infants was bathed with undiluted 3 per cent hexachlorophene which was applied with cotton balls and rinsed off immediately with tap water. Careful attention was given to the base of the cord. The control group was bathed with liquid castile soap using the same technique. The third group had triple dye applied to the cord and to about an inch of the surrounding skin at the time the infant was given his first bath with castile soap.

When the study was terminated, the decision was made to use triple dye in all subsequent infants admitted to any of the five wards, and cultures continued to be taken for the next six months in the three wards included in the study.

Cultures were taken from the base of the umbilical stump and from the anterior nares of the infants on the third day of life. Infants were discharged thereafter. All cultures were done by one individual. The culture swab was inoculated into trypticase soy broth and then streaked on mannitol salt agar. The plates were examined at 24 and 48 hours; mannitol-fermenting colonies were selected for coagulase testing in rabbit plasma.

RESULTS

The results of cultures of the umbilical cord are shown in Fig. 1. Fifty-six of the 531 infants (10.5 per cent) who received a single application of triple dye to the cord were colonized with coagulase-positive *S. aureus*. This figure was significantly lower ($p < 0.001$) than the colonization rate (41.1 per cent) observed in infants who were bathed with hexachlorophene (156 of 379). The colonization rates in the above two groups were significantly lower ($p < 0.001$) than that of the control group of infants who were bathed only with castile soap (148 of 207, 71.5 per cent).

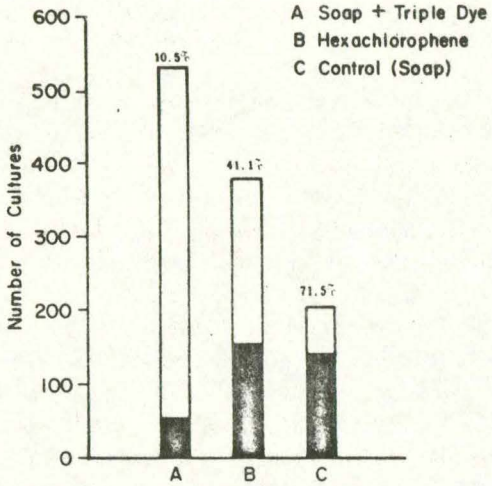

Fig. 1. Cord colonization rate. Percentage of colonization on the cord (indicated at top of bar) was significantly lower ($p < 0.001$) in Group A than in Groups B or C. The percentage of colonization in Group B was significantly lower ($p < 0.001$) than that in Group C.

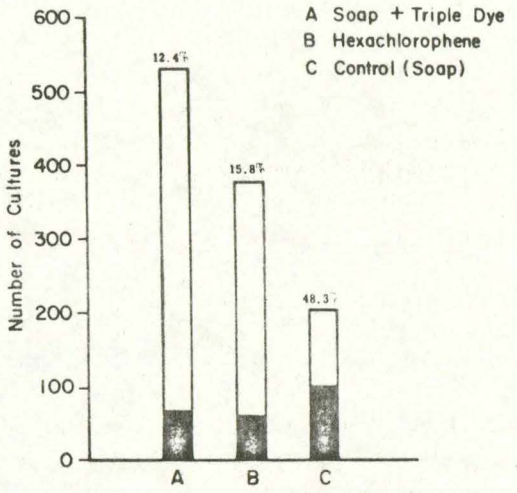

Fig. 2. Nasal colonization rate. Percentage of nasal colonization (indicated at top of bar) was significantly lower ($p < 0.001$) in Groups A and B than in Group C.

The nasal colonization rate is given in Fig. 2. Sixty-six (12.4 per cent) of the 531 infants who were treated with triple dye were colonized as compared with 60 (15.8 per cent) of the 379 who were bathed with hexachlorophene. This difference was not significant. However, the nasal colonization rate of the control infants (100 of 207, 48.3 per cent) was significantly higher ($p < 0.001$) than that of either the triple dye or the hexachlorophene group of infants.

After triple dye was applied to all the infants admitted to any of the wards, the colonization rate declined even further. The nasal colonization was 5.2 per cent and cord colonization, 1.8 per cent in 1,147 infants cultured during the ensuing six months.

DISCUSSION

The single application of triple dye to the cord of newborn infants at the time of admission to the newborn nursery effectively decreased the rate of staphylococcal colonization. Triple dye was recommended by Jellard[15] as a means of lowering the reservoir of Staphylococcus in the umbilical stump, and thus to reduce the frequency of spread of organisms from this area to the nose and to other sites by the nursing personnel or by the infant himself. Jellard applied triple dye to the cord stump and to about an inch of surrounding skin on a daily basis until separation of the cord took place. In the present study, a single application was sufficient to maintain a low rate of staphylococcal colonization on the third day of life.

Triple dye continued to be effective during the 6 month period following the termination of the study. In fact, the colonization rate dropped significantly ($p < 0.01$) even in the unit previously receiving triple dye. Since personnel from this unit were not completely restricted to that area, it is likely that the higher rate of colonization observed during the first period of study was influenced by those from surrounding areas.

Our findings are similar to those reported by Hardyment and associates.[16] On the other hand, it has been claimed that triple dye is less effective than bathing with hexachlorophene in preventing staphylococcal colonization.[3] However, to our knowledge, there have been no controlled studies to compare the two methods. With the introduction of 3 per cent hexachlorophene in 1952[1] and its widespread use after 1960, the use of triple dye diminished. The purple dye tended to stain diapers, making its use undesirable. Since

disposable diapers are currently used in most nurseries, staining no longer poses an important problem.

The rate (41.1 per cent) of colonization of the umbilical stump by infants bathed with hexachlorophene in this study was higher than those reported in some studies[3, 5] but similar to those reported by Gezon and associates[4] and Shaffer and associates.[17] The differences may be attributed to variations in nursery technique. Gluck and Wood[3] recommended that a sterile cotton-tipped applicator be used to cleanse the trough created by the skin-cord margin. Others have recommended that hexachlorophene be allowed to dry on the skin.[14] In our nursery, the solution was rinsed off immediately and, although special attention was paid to the umbilical stump, the technique was not carried out meticulously as suggested by Gluck and Wood.

The possibility that triple dye might simply inhibit bacterial multiplication as long as it is present on the cord rather than prevent acquisition of the organism cannot be completely ruled out since follow-up cultures were not taken after discharge. A study of this problem would be difficult to design since one would have to determine which organisms had been acquired in the hospital and which at home.

The possible absorption and toxic properties of triple dye have not been evaluated. Since it is applied only once to a relatively avascular area which dries quickly, we believe, significant absorption is unlikely. Triple dye may be considered as a possible alternative to hexachlorophene for the maintenance of low staphylococcal colonization rates in newborn nurseries.

The authors are grateful to Mrs. Loretta Boxx for technical assistance, Mrs. Lucy Bates, Nursing Supervisor, and to the nursing staff for their interest and diligent attention to the protocol.

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PHOTOTHERAPY

12. PHOTOTHERAPY: We have recently written a short paper on phototherapy and include it here to give you general guidelines on the care of the jaundiced infant.

GUIDELINES FOR PHOTOTHERAPY

Precautions:

Be sure of the diagnosis before initiating phototherapy -

> "In the use of any new type of therapy there are problems. One must be aware of these limitations if the therapy is to be used effectively. The diagnosis of some neonatal diseases can be obscured or delayed because visible jaundice is suppressed. Jaundice has traditionally been an important early sign for the suspicion of such common disease states as sepsis and blood group incompatibility. It is also useful in the detection of some rare conditions associated with mild hemolysis. When phototherapy is employed, the degree of visible skin jaundice is decreased. The skin is decolorized before serum levels are affected, and one can have infants under phototherapy with serum bilirubin levels of 10 to 12 mg. per 100 ml. who appear clinically nonjaundiced. It is, therefore, important to establish the etiology of the jaundice before treatment with light is instituted. A simple approach is to require that all infants have serum bilirubin with a direct-reacting fraction determined, a blood smear, Coombs' test, and culture, along with any other appropriate blood test indicated by history, before receiving phototherapy."[1]

Indications:

When to start phototherapy -

Premature infant - 8 to 10 mgm %
Full-term infant - 12 to 15 mgm %

When to stop phototherapy -

Premature infant - 8 or less mgm %
Full-term infant - 10 to 12 mgm %

As to when to start the lights, the faster the bilirubin is rising the sooner the bililight is applied. You do not wait until the highest value is reached before starting the light. Always remember to keep the infant in the hospital for 24 hours after the use of the light, and reevaluate the serum bilirubin to be sure that there is no rebound once the bililights have been discontinued.

Equipment:

Types of light source available -

"The most effective light conditions for treating jaundice in newborn infants have not, as yet, been defined. Nearly all studies describe the light used only in terms of foot-candles. This supplies only an expression of the sensation of brightness produced by the light. More meaningful would be to describe the light in terms of the radiant energy in that portion of the spectrum (blue) which is important in the photodestruction of bilirubin.

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1. "Neonatal Jaundice and Phototherapy," Lucey, Jerold, MD: Pediatric Clinics of North America, Vol. 19, No. 4, November 1972, pgs. 827-835.

Equipment (continued)

1. Fluorescent lights such as Cool White, Daylight, Vita-lite and Blue have all been used successfully with levels of intensity ranging from 100 to 500 foot-candles. Some studies using natural light of greater intensity have also been done. There is no proof that high intensities (over 1000 foot-candles) are more effective or needed in hyperbilirubinemia of prematurity.
2. Blue lights are more effective in vitro, in vivo, in man. The unresolved question is whether exposure of infants to monochromatic light will cause any adverse effects. This type of lighting constitutes a considerable environmental change for the newborn infant and must be approached cautiously."[2]

Distance from the light -

A. Isolette - "if the light hood is placed too close to the top of the incubator,,it can cause the temperature to rise inside the incubator. Other factors effecting this are ambient air temperature and air circulation in the nursery. Adjusting the hood so it is 3" to 4" above the incubator normally avoids heat build-up."[3]

"Infants treated with phototherapy in Isolettes (Air-Shields) receive more irradiance than infants in open bassinets at the same distance and with the same light source. The beveled Plexiglas canopy of the Isolette may create a focusing effect, thereby concentrating a greater energy flux at the center of the bassinet."[4]

B. Open crib - be sure that the infant is kept warm. That is why it is generally recommended that the isolette be used for infants under phototherapy.

"The distance from the light source to the infant in the crib is generally 18 inches."[5]

Eye Cover - "it is recommended that infants being treated with phototherapy have their eyes covered by light-tight bandages, such as the Olympic Bili-Mask, a sterile, disposable, light-weight eye cover adjustable to fit all infants. Bili-Masks are available from the Olympic Surgical Company (Cat. No 52400 ... Box 12 Bili-Masks). Any eye cover should be removed at regular intervals to check the infant's eyes for possible infection, unrelated to phototherapy."[6]

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2. Ibid, pg. 833-834

3. Olympic Bililite Operating Instructions, pg. 2

4. "Phototherapy for Neonatal Hyperbilirubinemia - A Dose, Response Relationship," - Mim, LeRoy, M.D., The Journal of Pediatrics, October, 1973, pgs.658-662.

5. "Phototherapy of Jaundice in the Newborn Infant-Effect of Various Light Intensities", Sisson, Thomas, M.D., The Journal of Pediatrics, July 1972 pg. 35-38

6. Olympic Bili-Lite Operating Instructions, pgs. 1-2

Change of light source - "The radiant energy of fluorescent bulbs decreases rapidly after 200 hours of use. To achieve the maximum effect from phototherapy, fluorescent bulbs should be replaced after 200 hours."[7]

"At Temple University Hospital we noted unexpected treatment failures with blue fluorescent lamps used over an extended burning time (more than 250 hours). An investigation of the energy output of these lamps showed a surprisingly rapid loss of emission from the phosphors, because of internal overheating."[8]

Problems:

1. Loose stools - "The stools of infants receiving phototherapy are often greenish, dark brown, and loose. This change in color is caused by the increased stool content of bilirubin photodegradation products. In situations where this has been studied carefully it has not been noted to result in more frequent stools, or in significant water loss."[9]

2. Rash - " A transient rash, lasting a few hours, occurs in some infants receiving phototherapy. It is identical to the so-called flea bite dermatitis of newborn infants. A similar rash has also been noted in jaundiced infants not receiving phototherapy. No sequelae have been noted."[10]

3. Bronzing Discoloration - "Occurs in infants with liver disease who are treated with light. Infants with an elevated direct-reaching serum bilirubin can develop a muddy, green, or bronze skin color when exposed to any light."[11]

4. Increase water loss - need to incrase intake when under the lights - "Preliminary studies suggest that infants receiving phototherapy may have increased insensible water loss, peripheral skin blood flow, and heat loss. If these studies are confirmed, some adjustments in thermal and water balance during phototherapy will be indicated."[12]

5. Loss of visible icterus with increased need to follow serum bilirubin levels - "Whenever light is used in the presence of known hemolysis serum bilirubin levels must be followed very carefully, as visual judgment of jaundice is unreliable under such conditions and rapid rises in serum bilirubin level can occur unexpectedly."[13]

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7. Olympic Bili-Lite Operating Instructions, Pgs. 1-2

8. "Phototherapy of Jaundice in the Newborn Infant-Effect of Various Light Intensities": Sisson, Thomas, M.D., The Journal of Pediatrics, July, 1972 pg. 35

9. "Neonatal Jaundice and Phototherapy", Lucey, Jerold, M.D.: Pediatric Clinics of North America, Vol. 19, No. 4, Nov., 1972, pgs. 830-832.

10. Ibid, pg. 830-832
11. Ibid,
12. Ibid
13. Ibid

Problems: (continued)

6. Eyes must be covered - "All human clinical studies reported to date have been done on infants whose eyes were shielded in some fashion. There is no evidence on which to confirm or deny the possibility that infants' eyes might be damaged if thery were exposed to the amounts of light used in phototherapy."[14]

7. Adequate skin surface must be exposed - make sure that the diaper is off when the infant is under the light.

8. A definite dose-response relationship has been established. For maximum effectiveness, the baby should be in the center of the light source within either the bassinet or isolette.

"The recording sensor was placed alternately in each of six areas of the bassinet pad to record light radiation. Maximum irradiance occurred at the center of the bassinet."[15]

9. The phototherapy lights must be off during the time that the bilirubin is being drawn on the infant.

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14. "Neonatal Jaundice and Phototherapy", Lucey, Jerold, M.D. : Pediatric Clinics of North America, Vol. 19, No. 4, Nov., 1972, pgs. 830-832.

15. "Phototherapy for Neonatal Hyperbilirubinemia-A Dose, Response relationship", Mims, LeRoy, M.D., The Journal of Pediatrics, October, 1973, pg. 659.

PHOTOTHERAPY WARNING

The appearance of erythema on the skin of two infants exposed to fluorescent lights as treatment for hyperbilirubinemia has come to the attention of the Food and Drug Administration. On site investigation of the incident by personnel of the FDA Bureau of Radiological Health indicated that the clinical determination of erythema was consistent with the measured ultraviolet exposure levels. The occurence indicates an urgent need to alert physicians and hospitals to the possibility of injury to the exposed infant from certain exposure conditions which may be used in phototherapy.

Hazardous levels of ultraviolet radiation, which are not effective in phototherapy, and extremely intense visible radiations can be present in the output of fluorescent lamps. The agency strongly recommends that any institution, or physician, using phototherapy in the treatment of hyperbilirubinemia immediately take the following precautions:

1. Shield fluorescent lamps with ultraviolet absorbing filter materials made from selected plastics or ultraviolet absorbing glass. If such filtering materials are not presently between the infant and the fluorescent source, they should be installed immediately.

2. They eyes of newborn infants should be protected from the intense visibile light from any phototherapy source by means of a suitable opaque blindfold. A simple bandage has been reported to be effective.

Communications should be directed to the Direct, Bureau of Radiological Health, Food and Drug Administration, 5600 Fisher Lane, Rockville, Maryland 20852.

Robert L. Elder, Sc. D.
Deputy Director
Bureau of Radiological Health
DHEW

The concerns raised by Dr. Elder have prompted the following response from the Academy's Committee on Fetus and Newborn .....

The recent warning[1] issued by the Bureau of Radiological Health relating to the use of fluorescent light for treatment of hyperbilirubinemia must be put in proper perspective with respect to present day practices. Phototherapy is perhaps the most widely used therapeutic treatment for newborn infants in this country. Its use has spread rapidly from university medical centers to hospitals with rather small delivery services. There are no formal, published guidelines on the precise way of administering phototherapy. However, there is a body of data on studies which show that fluorescent light will reduce the level of unconjugated serum bilirubin; and, most of these studies have been done with a relatively standard geometry. The use of certain standards will automatically prevent the ultraviolet radiation which probably caused the reported erythema of the infant's skin. [1]

The usual mode of administering phototherapy is to use Cool-White or Daylight fluorescent bulbs in a commercial fixture or in a homemade model. Use of these fixtures over an infant in a closed incubator automatically sets the light to patient distance and thus the maximum light intensity with standard bulbs is predetermined. Most commercial fixtures come equipped with a sheet of plastic, usually Plexiglass G, in the light path; and it is absolutely imperative that any homemade fixture incorporate such a plastic filter. Plexiglass G will block the ultraviolet light in the erythema waveband which was implicated in the recent incident[1] (0% transmission for wavelengths shorter than 335 nm.) The use of a closed incubator is not absolutely essential; however, the plastic or glass top of an incubator provides the additional light filtration needed if the light fixture's plastic sheet is inadvertently omitted.

Instances in which this rigid prescription is not followed have been noted. Other types of fluorescent fixutres are suspended over or placed adjacent to an open bassinet. The light level reaching the infant is either guessed at by visual comparison with a commercial installation or a hand-held photographic light meter is used to determine the light intensity reaching the infant. Both of these practices can lead to problems. In the first method the eye is a poor judge of absolute light intensities, in the second method a standard photographic light meter is extremely sensitive to light in the yellow and green portions of the visible spectrum and extremely insensitive to light in the "phototherapy effective band" of 420 to 480 nm. Thus, neither mode of measurement can tell you whether the infant is receiving the same intensity of "blue"light as he would receive under a standard phototherapy fixture.

One final not relates to the use of "selected plastics or ultraviolet absorbing glass." The commonly available plastics and glasses all absorb ultraviolet in the region of interest; only specially manufactured materials can transmit any radiation in the ultraviolet region.

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1. Elder, R.L.: News release, Bureau of Radiological Health, Department of Health, Education and Welfare, October 26, 1973.

Neonatal Jaundice and Phototherapy

*Jerold F. Lucey, M.D.**

There is a growing body of evidence indicating that bilirubin is toxic for human brain cells in some infants at serum levels below the traditional figure of 20 mg. per 100 ml.[1, 11, 19, 43, 82, 111] It now appears that a spectrum of brain injury, from defects in cognitive function to death from kernicterus, exists. It is known that factors such as asphyxia, acidosis, hypothermia, hypoglycemia, hypoproteinemia, sepsis, certain drugs, and extreme prematurity, when they occur either alone or in combination, can increase the susceptibility of infants to this brain damage.[1, 70] The clinician, therefore, faces a severe dilemma when there is no precise threshold at which to act and when he is required to assay degrees of susceptibility in individual infants. He is often understandably reluctant to recommend exchange transfusions for seriously ill infants with low levels of serum bilirubin, and yet he is now aware that these infants probably are at an increased risk of brain damage at such levels. The ready availability of a simple therapy, such as phototherapy, that is effective in lowering or preventing serum bilirubin concentrations from rising makes it an attractive therapy. Its simplicity has, however, led to a casual approach in its use which should not be encouraged.

This article is a review of some of the indications for the uses of phototherapy. With any new therapy there are initially limitations in our knowledge of its use and unresolved questions arise. The problems and questions which arise in regard to phototherapy will first be discussed. The present indications will also be listed.

QUESTIONS

Is Phototherapy Effective in Lowering Serum Bilirubin? Many carefully controlled studies have now been published, and all have found that phototherapy is effective in lowering serum bilirubin levels.[16, 18, 35, 39,

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Studies cited in this review were aided by United Cerebral Palsy, Easter Seal Foundation, and National Institutes of Health Grant PHS 1 RO 1 HD05561 01.

[42, 71, 80, 98] It has been used with particularly good results in the treatment of hyperbilirubinemia of premature infants. In this situation, one can achieve 30 to 50 per cent lower average serum bilirubin concentrations in light-treated infants as compared to controls.[67] In an average low birth weight infant nursery this means that instead of having a 20 per cent incidence of serum bilirubin levels of over 15 mg. per 100 ml., one can have an incidence of approximately 2 per cent.[67] If one accepts the present evidence that bilirubin can be neurotoxic at concentrations above 15 mg. per 100 ml., then the avoidance of such levels would seem to be a worthwhile goal.

Are There Any Neurotoxic Effects from the Products of Photodecomposition? The early fears that the photodecomposition products of bilirubin might be retained or might be neurotoxic have not been confirmed. A convincing body of experimental animal,[6, 21, 42, 44] in vitro,[37, 52, 53, 102, 104] and human clinical evidence[36, 47] exists which is very reassuring.

In the human infant receiving phototherapy, bilirubin undergoes decomposition to a series of derivatives that exhibit progressively less yellow color and are water soluble. These derivatives are not retained in the body, but are rapidly excreted in the bile and urine.[85, 86, 97] It is particularly reassuring that a few infants with congenital hyperbilirubinemia (Crigler-Najjar disease) have been treated for nearly 3 years with phototherapy with good results.[36, 47] If neurotoxicity were going to occur, one would certainly expect it to be apparent in this disease with prolonged therapy. Clinical observation and studies (some of which have been controlled) in university centers of over 7000 infants have also failed to demonstrate any neurotoxic effects.[65] A survey of 11 leading university centers using phototherapy in July 1971 also failed to reveal any serious side-effects (Table 1).

One study done in vitro under highly abnormal conditions suggested that the serum albumin-binding capacity might be decreased by the use of light.[81] The relevance of this finding has been questioned[49, 97] and it has not been confirmed in vivo.[53]

PROBLEMS

In the use of any new type of therapy there are problems. One must be aware of these limitations if the therapy is to be used effectively.

The Diagnosis of Some Neonatal Diseases can be Obscured or Delayed Because Visible Jaundice is Suppressed. Jaundice has traditionally been an important early sign for the suspicion of such common disease states as sepsis and blood group incompatibility. It is also useful in the detection of some rare conditions associated with mild hemolysis. When phototherapy is employed, the degree of visible skin jaundice is decreased. The skin is decolorized before serum levels are affected, and one can have infants under phototherapy with serum bilirubin levels of 10 to 12 mg. per 100 ml. who appear clinically nonjaundiced. It is, therefore, important to establish the etiology of the jaundice before treat-

Table 1. *Unpublished Survey of Clinical Experience with Phototherapy in University Centers in the United States, July 1971*

OBSERVER	UNIVERSITY	YEARS EXPERIENCE	NO. OF INFANTS				COMPLICATIONS	FOLLOW-UP IN PROGRESS
			Premature	Full Term	Rh	ABO		
Pildes	University of Illinois	2½	80	150	15	50	Diarrhea, rashes, early skin pigment changes, slow weight gain	No
Klaus	Case Western Reserve University	3½	300	200	40	60	Bronze infants (4)	No
Hodgman and Wu	University of Southern California	3	400	250	50	100	Loose stools, rashes, slow weight gain	Yes
Giunta	Brown University	3½	181	256	69	60	Rash (12)	Planned
Blumley	Duke University	3	30	150	10	20	Lethargy, bronzing, diarrhea, burns (1)	Yes
Stahlman	Vanderbilt University	2	128	147	18	7	Loose stools	No
Lucey	University of Vermont	5	400	100	30	50	Rashes, loose stools	Yes
Fox	Mt. Sinai School of Medicine	3	400	900	–	–	Delayed detection eye infection (2)	Yes
Sisson	Temple University	3½	250	200	40	200	Skin rash transient, occasional loose stools, rare-increased hemolysis suspected	Yes
Ferreiro	University of Chile	5	1200	1000	50	80	Rashes, loose stools	Yes
Brown	University of Georgia	3	26	24	2	10	–	Yes
Kevy	Harvard University	3	50	25	40	40	? Infants sluggish	No
Cochrane	Harvard University	3	600	–	–	–	Rashes, loose stools	No
Blackburn	Yale University	3	280	–	–	–	Rashes, loose stools	No

ment with light is instituted. A simple approach is to require that all infants have serum bilirubin with a direct-reacting fraction determined, a blood smear, Coombs' test, and culture, along with any other appropriate blood test indicated by history, before receiving phototherapy.

If this routine is followed, very few of these conditions will be missed and valuable time will not be lost. Jaundice is not actually a very early or an invariably present sign in infection. The liberal use of early blood cultures when sepsis is suspected is certainly to be preferred to awaiting the development of obvious jaundice.

Infants on Phototherapy Have Loose, Greenish Stools. The stools of infants receiving phototherapy are often greenish, dark brown, and loose. This change in color is caused by the increased stool content of bilirubin photodegradation products. In situations where this has been studied carefully it has not been noted to result in more frequent stools, or in significant water loss.[114]

Some Infants Receiving Phototherapy have Transient Skin Rashes. A transient rash, lasting a few hours, occurs in some infants receiving phototherapy. It is identical to the so-called flea bite dermatitis of newborn infants. A similar rash has also been noted in jaundiced infants *not* receiving phototherapy. No sequelae have been noted.

A Transient and Benign Bronze Discoloration of the Skin Occurs in Infants with Liver Disease Who are Treated with Light. Infants with an elevated direct-reacting serum bilirubin can develop a muddy, green, or bronze skin color when exposed to any light. Kopelman[50] has called attention to this and has expressed concern. It has not been noted in over 400 infants with normal neonatal hyperbilirubinemia whom we have treated. It is apparently not a harmful complication. The pigments produced in the skin in this condition are probably similar to those produced in patients with biliary atresia and hepatitis when they are exposed to natural sunlight.

The use of phototherapy in liver disease or in infants with an elevated direct-reacting bilirubin does not, however, appear to be either effective or helpful and, therefore, is not recommended.

The Effectiveness of Light is Difficult to Predict in Rh Disease and ABO Incompatibility. The effectiveness of light therapy in an individual case is very difficult to predict. Generally, one can expect that light will be effective in the milder cases of erythroblastosis, but exceptions do occur. The reasons for therapeutic failures are not understood but probably rapid hemolysis is the most important factor in failures. It may also be that the amount of light needs to be increased in such cases or that there are other factors in the sera or skin which interfere with the effect of light.

Proof that phototherapy is effective in hemolytic disease is difficult to assemble, as truly comparable control groups are impossible to collect. In our own experience (Table 2) we have found that we have decreased our percentage of exchange transfusions in infants with positive Coombs' tests from 25 per cent to 10 per cent. Kaplan[46] and Sisson[109] have reported similar clinical experiences in ABO incompatibility. It also appears that the number of repeat exchange transfusions can be decreased by pho-

Table 2. *Phototherapy and Hemolytic Disease*

	1966	1967	1968	1969	1970	1971
No. of infants with positive Coombs' test	24	28	27	32	20	30
Per cent treated with light	8	54	74	81	90	90
Per cent receiving exchange transfusion	25	18	11	12	15	10

totherapy. While still experimental in this situation, phototherapy appears to be a valuable adjunct to therapy, but certainly not a replacement. Recently, sensible guidelines have been suggested as to the indications for phototherapy in this situation.[74]

Whenever light is used in the presence of known hemolysis serum bilirubin levels *must* be followed very carefully, as visual judgment of jaundice is unreliable under such conditions and rapid rises in serum bilirubin level can occur unexpectedly.

Late Anemia May Occur in Infants with Coombs' Positive Red Blood Cells Who Have Received Phototherapy and Have Not Had Exchange Transfusions. If light therapy has been successfully employed and an exchange transfusion avoided, one must remember that the survival time of the infants' Coombs-positive cells is short and anemia usually will occur in 1 to 8 weeks after birth. It is, therefore, necessary to carry out careful follow-up examinations with frequent hemoglobin determinations, and transfusions for this late anemia may be necessary. It is not known as yet whether light per se affects red blood cell survival in vivo. In vitro studies, done with nonphysiologic amounts of light indicate some damage to the red blood cell membrane.[50] In vivo studies and clinical observations have not confirmed this finding.[9]

Phototherapy May Affect the Growth of Infants, Particularly Head Growth. In a 2 year follow-up of 30 infants from an original study of 98 infants,[40] it was found that 10 of 14 light-treated infants had head circumferences two standard deviations below normal as compared to 5 of 16 controls. The authors have repeated this study on another 97 infants and now report that the weight, length, and head circumference were the same in light-treated and control groups at 30 days of age.[117] The findings of other groups are in agreement with this finding, and no significant differences have been found.[45, 67, 80, 84, 89, 95] We have recently completed a follow-up study of 72 infants (39 light-treated, 33 controls) at 4 to 6 years of age and have not found any significant differences between these two groups. The original study of Ballowitz[4, 5] suggesting growth retardation in Gunn rats treated with phototherapy has also been retracted by the author.[6]

Phototherapy Might Cause Eye Damage. All human clinical studies reported to date have been done on infants whose eyes were shielded in some fashion. There is no evidence on which to confirm or deny the possibility that infants' eyes *might* be damaged if they were exposed to the amounts of light used in phototherapy.

The applicability of animal studies in this situation is difficult to assess. Several animal species are notoriously susceptible to eye damage from small amounts of light,[27, 107] and when continuous exposure and

atropine is used to dilate the pupil, any relevance to the human situation becomes rather remote.

This will be a difficult area to investigate, but in the interim some form of intermittent eye shielding certainly seems worthwhile. These shields may be removed frequently when the infant is not under therapy to allow for visual stimulation or detection of infection.

Light May Affect Other Components in the Blood. Very few studies of the effects of light on substances other than bilirubin have been done. We have not found any effects on serum amino acids in infants receiving phototherapy. We have also not detected any unusual effects in infants receiving antibiotics (penicillin, ampicillin, kanamycin). Blackburn has not detected any effects on the red blood cells in vivo.[9]

In sick and cyanotic infants in whom unusual intravenous solutions such as vitamins, intravenous fat or protein hydrolysates plus antibiotics and other medications, are being used, we must be careful to observe for unusual effects.

It seems quite probable that light will have some effect upon riboflavin and perhaps other components of blood. This is a promising area for future research.

New Metabolic Effects of Phototherapy. Preliminary studies suggest that infants receiving phototherapy may have increased insensible water loss, peripheral skin blood flow, and heat loss.[116, 118] If these studies are confirmed, some adjustments in thermal and water balance during phototherapy will be indicated.

No effect upon cortisol, growth hormone levels,[93] or urinary 17 ketosteroid excretion[84] in infants receiving phototherapy have been noted. Uric acid levels have not been affected.[93]

INDICATIONS

HYPERBILIRUBINEMIA OF PREMATURITY. The main indication for phototherapy is for the modification of hyperbilirubinemia of prematurity. With the use of phototherapy one may avoid potentially dangerous serum concentrations of bilirubin. Proof that there is a decrease in brain damage with this treatment is not available. Such studies are in progress but it will be several years before definitive results can be expected. In the initial studies of its effectiveness, all low birth weight infants were treated.[71, 98] Later studies have indicated that this is no longer necessary[34, 101] and that essentially the same results may be obtained by treating only those infants whose serum bilirubins rise to 10 mg. per 100 ml. The premature infant who is highly susceptible to kernicterus[70] (Table 3) requires special consideration, as such infants may develop kernicterus at very low concentrations of serum bilirubin (10 to 15 mg. per 100 ml.).[48] If these infants are to be treated experimentally with phototherapy, they should be treated shortly after birth. No proof that this, or any other form of therapy (exchange transfusion or phenobarbital), is effective in such cases has been published.

MILD HEMOLYTIC DISEASE. Phototherapy is a useful adjunct in the

Table 3. *Factors Identifying the "Highly Susceptible to Kernicterus" Low Birth Weight Infant*

Birth weight of less than 1500 gm.
Hypothermia
Asphyxia (severe prenatal or postnatal)
Acidosis
Hypoalbuminemia
Sepsis
Meningitis
Drugs (which affect albumin bilirubin binding)
Serum bilirubin above 10 mg. per 100 ml.

treatment of mild hemolytic disease resulting from either Rh incompatibility or major blood group incompatibility.[46, 109] It cannot be used as a replacement for exchange transfusion when the serum bilirubin exceeds 20 mg. per 100 ml.

CONGENITAL DEFECTS IN BILIRUBIN METABOLISM. Phototherapy is a useful adjunct in the long-term treatment of the Crigler-Najjar Syndrome.[36, 47] No experience with other congenital defects of bilirubin metabolism have been reported.

BILIARY ATRESIA. One can produce a lowering of total serum bilirubin levels in some infants with biliary atresia. It is not a very pronounced effect and no clinical benefits have been noted in the few infants we have treated.

JAUNDICE OF UNKNOWN ETIOLOGY. The use of light in situations where the etiology of the jaundice is obscure is impossible to evaluate. Light should be used in these situations only after a diagnostic work-up has been carried out.

The incidence of brain damage from idiopathic hyperbilirubinemia in full-term infants is so low, and the condition so rare in our experience, that this should be an unusual indication for its use.

HOW MUCH AND WHAT TYPE OF LIGHT

The most effective light conditions for treating jaundice in newborn infants have not, as yet, been defined. It will take several years before this can be established. The problems involved are highly complex and many answers will require long-term follow-up studies. What can be given at this time are suggestions as to the general quality and quantity of light that has already been shown to be effective. This may not necessarily be the best, nor the safest, as some totally unexpected long-term effects could become apparent. This seems unlikely.

Thorington et al.[112] have recently reviewed the studies published and pointed out that much of the data, when viewed by a photobiologist or lighting engineer, are not reported in sufficient detail to allow precise analysis. Nearly all studies describe the light used only in terms of footcandles. This supplies only an expression of the *sensation* of brightness produced by the light. More meaningful would be to describe the light in

terms of the radiant energy in that portion of the spectrum (blue) which is important in the photodestruction of bilirubin. In vitro and animal studies[108, 110] now indicate that this is in the 440 to 470 mμ range. The term for this is flux—quantity of total radiant power or energy in watts per square centimeter. It is unfortunate that there was no simple way of directly measuring flux. Simple, but expensive, spectroradiometers are now available that can accomplish this. In the clinical studies reported the conditions have varied widely with respect to the dose and spectral distribution of the light. The following broad generalizations appear valid:

1. Fluorescent lights such as Cool White, Daylight, Vita-lite and Blue have all been used successfully with levels of intensity ranging from 100 to 500 foot-candles. Some studies using natural light of greater intensity have also been done. There is no proof that high intensities (over 1000 foot-candles) are more effective or needed in hyperbilirubinemia of prematurity.

2. Blue lights are more effective in vitro, in vivo, in rat studies (Hewitt et al., unpublished study), and in man. The unresolved question is whether exposure of infants to monochromatic light will cause any adverse effects. This type of lighting constitutes a considerable environmental change for the newborn infant and must be approached cautiously. We have, to date, extensive experience only with infants raised under broad-spectrum light during the last 30 years since fluorescent lighting was introduced into wide usage. It should be remembered that physiologic jaundice may, in fact, be a disease "aggravated" by bad illumination in our present nurseries.[66]

If one wants to use the minimal amount of radiant energy to produce an effect on bilirubin, then he will choose blue light. If one is concerned about other possible effects of monochromatic light[27] then one will continue using broad-spectrum light. A possible solution to this dilemma is offered by the recent exciting studies of Ferreiro et al. (personal communication, 1972). His group has shown that 48 hours of early phototherapy on the second and third days after birth is as effective as the traditional 144 hours of continuous therapy. These studies suggest that in addition to the photodestruction of bilirubin in peripheral tissues, there may be an additional mechanism that improves bilirubin excretion which is activated by early, intense exposure of short duration. If these studies are confirmed, then considerable less exposure to light will be required to avoid hyperbilirubinemia of prematurity than has been employed in the past.

CHANGING OF BULBS. The spectral output of all fluorescent lamps does deteriorate with time. It has therefore been suggested that fluorescent lamps be changed every 200 to 400 hours[42, 110] in order to insure maximum effectiveness. However, if the lamps are run under proper conditions (not allowed to overheat) this precaution is not necessary. Most fluorescent bulbs will, under normal conditions, not lose significant radiant power in the blue range during 2000 hours of operation.

INTERMITTENT VERSUS CONTINUOUS EXPOSURE. At the present time in many newborn nurseries and in nearly all intensive care nurseries, the environmental lighting is not varied during a 24 hour cycle.

No studies have demonstrated the presence of circadian rhythms in premature infants in the first week of life, but little attention has, in fact, been paid to the light conditions.

Intermittent light therapy is effective in treating hyperbilirubinemia.[121] It is nearly as effective as continuous light (Ferreiro, personal communication, 1972). When intermittent light therapy is employed, one probably should monitor serum bilirubin levels more carefully than under continuous therapy. If one is concerned about the remote possibility of eye damage and changes in circadian rhythms, then intermittent therapy offers an attractive therapeutic alternative that seems quite reasonable.

Studies designed to better define the minimal amount of light needed to reduce serum bilirubin levels are needed. It is now obvious that the originally arbitrarily chosen light conditions often supply more light than is needed.

In conditions in which rapid hemolysis is occurring and phototherapy is being used, rapid rebounds can occur when phototherapy is discontinued. Intermittent therapy is therefore not indicated when treating hemolytic disease.

INFANTS IN WHOM PHOTOTHERAPY MAY NOT BE EFFECTIVE. Certain infants appear not to respond to phototherapy. This includes not only some infants with hemolytic disease,[88] but also infants with liver disease or breast milk jaundice, and American Indians. The reasons for therapeutic failure in these infants are not understood. Whenever one encounters therapeutic "failures" the light source should, of course, be checked. The presence of clothing, opaque incubators, or failure to turn the infant frequently all obviously decrease the effectiveness of light.

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HIGH RISK NEWBORNS, GESTATIONAL AGE ASSES

13. HIGH RISK INFANTS - physical findings

Apgar score below 5
Active resuscitation required
Chilled baby (Temperature below 97° R)
Abdominal distention
Meconium stained
Jaundiced
Single umbilical artery
Seizures (twitching, eye-rolling)
Low birth weight for gestational age
Fever or hypothermia
Depression
Absense of femoral pulse
Scaphoid (empty) abdomen
Excessive mucus
Temperature instability
Consistent rapid respiratory rate - tachypnea (60+)
Episodes of apnea or bradycardia
Unusual change in feeding behavior, poor suck
Frequent regurgitation and/or vomiting
Excessive weight loss or failure to gain
Diarrhea or blood in the stool
Hyperirritability, hyperactivity
Marked pallor or plethora
Cyanosis or "dusky" episodes
Unusual positioning, rigidity, or hypotonia
Reddened cord stump, weeping or foul smelling cord
Petechiae or excessive bruising
Persistent tachycardia
Lethargy (especially note a change)
Grunting respirations
Nasal flaring
Retractions
Difficult breathing from any cause
Failure to pass stool within 24 hours
Failure to urinate within 24 hours

We feel that the items on the above list deserve special attention and should form the basis for inservice programs in the obstetrical and newborn departments of each hospital. The Perinatal Program is always happy to furnish educational materials to implement such inservice programs.

14. GESTATIONAL AGE ASSESSMENT: "MATURITY" : For years we have looked only at the baby's weight as an indication of his maturity. We now recognize that the length of gestation is a much more critical factor. We are also aware that the amount of growth that has occurred for the period of time in utero is very important. Unfortunately, the calculation of gestational age by using the date of the last menstrual period is not always accurate. In fact, these calculations are frequently off by a month or more. For this reason, a physical assessment of the newborn must be carried out to verify the gestational age. Nurses are quite capable of performing this assessment.

Both weight and gestational age are important in the classification of infants at birth to anticipate morbidity and mortality and the optimum care necessary to reduce these problems. An accurate weight on admission to the nursery is necessary. A careful menstrual history is important for estimating gestational age, but should not replace a clinical estimation of gestational age as part of the physical examination, particularily when the history is inexact or a discrepancy between birth weight and gestational age exists. The following can be considered for evaluating the newborn:

A. The following formula is used for estimation of maternal due date, last menstral period date - subtract 3 months and add 7 days - this determines the estimated due date.

e.g. - December 10th = first day of last menstral period
12th months - 3 months = 9th month
7 + 10 = 17 ∴ Estimated due date = September 17th

B. Physical examination:

a. Breast tissue -

1. Under 1-2 mm in diameter - 35-36 weeks

2. 4+ mm - 36-39 weeks
3. 7+ mm - 39-44 weeks

b. Foot creases

1. Preterm infant - more turgid and may have only fine wrinkles
2. Mature infant is well and deeply creased (involving heel creases 29 weeks and above)

c. Testes and labia

1. Testes - undescended - to 30 weeks
2. Testes - high in the canal - few rugae - 30-36 weeks
3. Testes - lower - more rugae - 36-39 weeks
4. Testes - descended, pendulous scrotum, rugae complete 39-44 weeks

1. Labia - majora widely separated - prominent clitoris to 36 weeks
2. Labia - majora nearly cover labia minora - 36-39 weeks
3. Labia - minora and clitoris covered - 39-44 weeks

d. Neuro - muscular tone

1. Heel to ear
   a. No resistance - to 30 weeks
   b. Slight resistance - 30 to 34 weeks
   c. Difficult - 34 - 36 weeks
   d. Impossible 39-44 weeks

2. Scarf sign
   a. No resistance - to 30 weeks
   b. Minimal resistance - 34-36 weeks
   c. Fair resistance - 36-38 weeks
   d. Difficult 38 - 44 weeks

3. Suck evaluation

4. Grasp

5. Moro

It becomes clear that to identify the low birth weight infant of 2,500 gms. or less at birth as the only infant at risk is in error. It is important to keep in mind that there are babies that weigh more than 2,500 gms. and are actually premature or immature, and babies that weigh less than 2,500 gms. which are at full term, but are under grown or undernourished in utero, and are at increased risk for hypoglycemia.[6,7]

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Neurological Evaluation of the Maturity of Newborn Infants

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Cerebral maturation during the last three months of fetal life brings about constant modification of muscle tone and of certain reflexes. This has enabled a scheme to be devised, whereby the neurological maturity of the premature infant at different ages can be assessed. Saint-Anne Dargassies (1955) defined this neurological progression by analysing a group of 100 prematures of known gestational age, and the longitudinal evolution of healthy prematures, born at 28 weeks' gestational age and studied up to 40 weeks' gestational age. The clinical results have been compared with the electroencephalographic (Dreyfus-Brisac, Flescher, and Plassart, 1962) and anatomical (Larroche, 1962) stages of development of the brain. In applying this maturation scheme to 'small-for-dates' babies it has been concluded that brain development during fetal life progresses independently of unfavourable gestational circumstances. Chronic fetal stress is reflected mainly in the birthweight and to a lesser degree in the body length at birth. The brain, however, from the point of view of anatomy and physiology, evolves more in proportion to the gestational age (Gesell and Amatruda, 1945; Bergström, Gunther, Olow, and Söderling, 1955; Saint-Anne Dargassies, 1955).

The original observations on which this paper is based are those of Minkowski, Larroche, Vignaud, Dreyfus-Brisac, and Saint-Anne Dargassies (1966). This paper presents a practical method for applying clinically the principles described by these authors. Butler and Bonham (1963) estimated that a third of infants weighing less than 2500 g. have a gestational age greater than 38 weeks. The small-for-dates baby is liable to develop serious metabolic disturbance shortly after birth; for this reason it is imperative that the assessment of gestational age be made early. Occasionally the initial neurological evaluation of maturation is confused by signs of neurological disorders. But, as a rule, neurological examination during the first days of life can provide data that are both precise and easy to evaluate. Physical criteria, such as the quality of the hair, the skin, and the plantar creases, can provide additional clinical evidence of maturity (Usher, McLean, and Scott, 1966; Mitchell and Farr, 1965; Farr, Mitchell, Neligan, and Parkin, 1966; Farr, Kerridge, and Mitchell, 1966).

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General Principles

Saint-Anne Dargassies (1955) has applied to the premature baby the method of neurological examination described by Thomas (Thomas and Saint-Anne Dargassies, 1952; Thomas, Chesni, and Saint-Anne Dargassies, 1960). Appreciation of muscle tone is a fundamental feature in this examination, and includes study of the resting posture or attitude, 'passive tone', and 'active tone'. 'Passive tone' is appreciated by the physician applying certain movements to the infant who remains passive and at rest, while, for instance, the amplitude of passive movements of a single joint is measured. In contrast, 'active tone' is studied with the infant in an active situation, the physician noting, for instance, the righting reaction of the trunk when the infant is placed vertically.

Only those parts of the examination that are required to appreciate the infant's maturity are given in the Figures. The following notes are intended to supplement and clarify the tests set out in Fig. 1, 2, and 3. Gestational ages are calculated from the first day of the mother's last menstrual period.

Passive Tone (Fig. 1)

Lower limb.

Technique for the heel-to-ear manœuvre. With the baby lying flat on the table and keeping the *pelvis flat on the table*, lift the legs as far as possible and then attempt to touch the head with the feet. Observe the distance between feet and head (Fig. 1 (2)).

Popliteal angle measurement. Maintaining the pelvis *flat* on the table, flex the thigh at the hip to achieve a

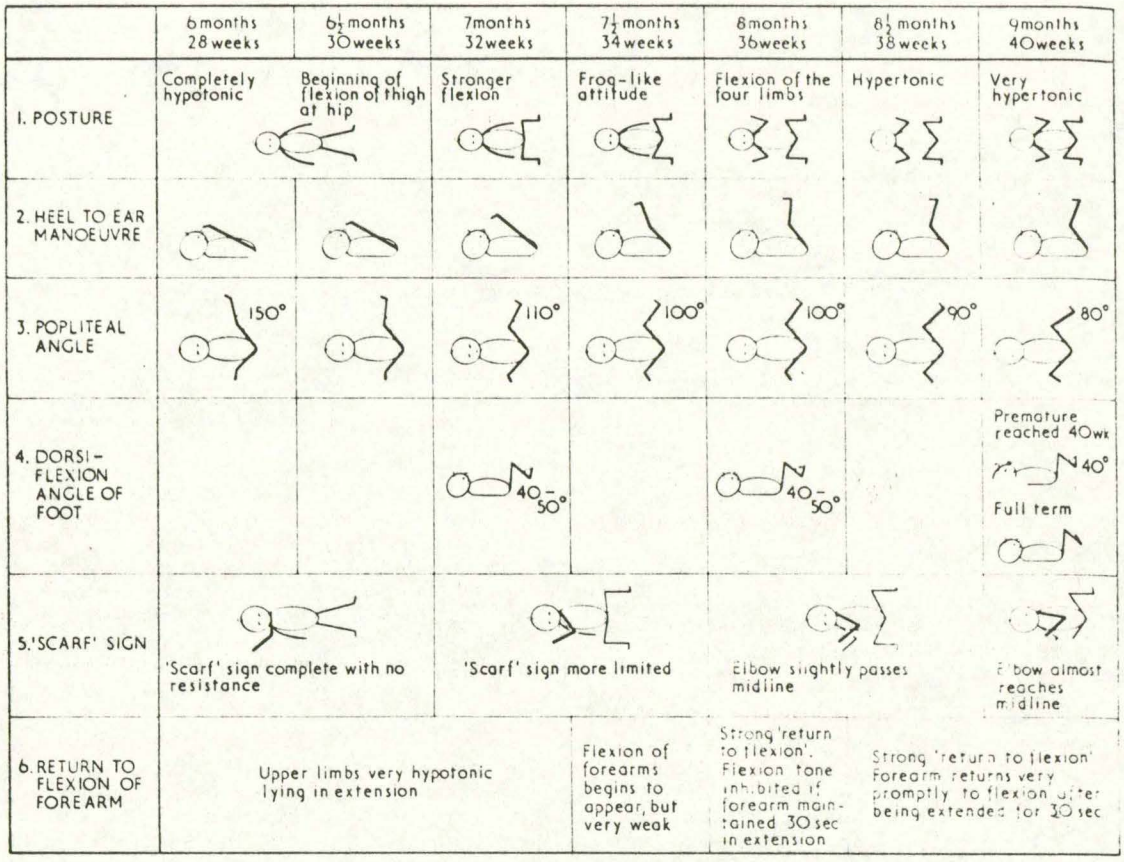

FIG. 1.—*Passive tone. Increase of tone with maturity illustrated by means of 6 clinical tests.*

knee-chest position. Holding the thigh in the knee-chest position, lift the lower segment of the leg and observe the angle formed with the thigh, which is the popliteal angle (Fig. 1 (3)).

Angle of dorsi-flexion of the foot. In a full-term newborn at birth the foot can be fully dorsi-flexed. In a premature baby, only partial dorsi-flexion can be achieved. The angle of dorsi-flexion of the foot decreases during gestation, this explains the difference of position in automatic walking: a premature who has reached 40 weeks walks in a toe-heel progression or on tip-toes; a full-term 40 weeks' newborn walks in a heel-toe progression using the whole sole of the foot for support (Fig. 1 (4)).

Upper limb

'Scarf' sign ('signe du foulard', indicating that the arm encircles the neck like a scarf). Take the infant's hand and try to put it around the neck and as far posteriorly as possible over the opposite shoulder: in the full-term baby the muscle tone resists this manœuvre. In the premature baby, the hypotonicity allows the elbow to be moved to the opposite shoulder (Fig. 1 (5)).

Return to position of flexion. In the mature baby, when the forearm is released after full extension at the elbow, it returns rapidly to a position of flexion. Maintain such extension for 30 seconds and observe the promptness of the return to flexion (Fig. 1 (6)).

Active Tone (Fig. 2)

Righting reaction of lower extremities and trunk. With the baby in the standing position, assess the support of body weight and the righting of the trunk (Fig. 2 (1 and 2)).

Righting reaction of the head

Neck extensors. With the baby sitting, and the head hanging down on the chest, move the trunk slowly backward and observe the reaction of the head; this allows the tone of the extensor muscles on the back of the neck to be tested (Fig. 2 (3)).

Neck flexors With the baby lying on the table, grasp

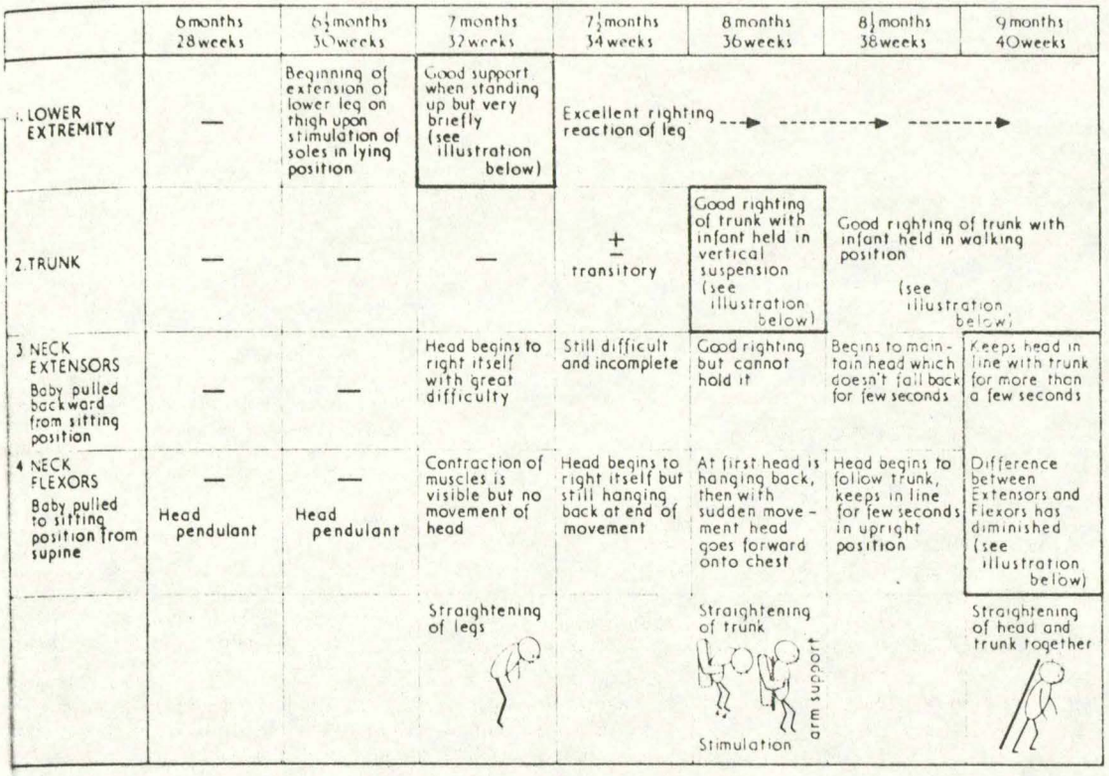

FIG. 2.—*Active tone. Increase of tone with maturity illustrated by means of 4 tests of righting reactions.*

the hands (or the shoulders if a very small premature) and pull him slowly to the sitting position, observing the position of the head in relation to the trunk. This manoeuvre the tone of the flexor muscles on the front of the neck to be checked (Fig. 2 (4)).

The righting of the head on the trunk is observed first in the sitting position, then in the lying position. In a full-term baby, the difference between extensors and flexors of the neck has diminished; he will be able to keep his head from falling back for at least a few seconds.

Reflexes (Fig. 3)

Observation of the sucking and rooting reflexes, grasp reflex, and automatic walking requires no comment (Fig. 3 (1, 2, 3, and 6)), so that only two of the items set out in Fig. 3 require explanation.

Moro reflex (Fig. 3 (4)). A gentle technique is to be used with premature babies: lift the baby a few centimetres off the bed by holding both hands and suddenly let go. A complete reaction has three components: (i) Abduction and extension of the arms; (ii) opening of the hands; (iii) crying.

Crossed-extension reflex (Fig. 3 (5)). Rub the sole of one foot (left) while the same leg is held in extension and observe the response in the opposite (right) leg. The complete response has three components: (i) Extension of the right leg, after a rapid flexion or 'retreating'; (ii) adduction of the right leg, the right foot going toward the left foot (this adduction component only appears at 32 weeks); (iii) fanning of the toes.

Discussion

Passive tone (Fig. 1). This is responsible for the progressive development of the predominantly flexor posture of the newborn infant at term (Fig. 1 (1)). Muscle tone is completely flaccid at 28 weeks, increases first in the distal segments, to proceed in a caudocephalic direction. Flexor hypertonicity is generalized at term. The measurement of different limb-angles gives an objective measurement of passive tone; all these angles diminish as the muscle tone increases. The foot-leg angle seems to indicate relaxation of the passive tone of the posterior muscles of the leg. There is no satisfactory explanation of the difference in the foot-leg angles observed in the neonate born at 40 weeks' gestation and the premature having reached the gestational age of 40 weeks.

	6 months 28 weeks	6½ months 30 weeks	7 months 32 weeks	7½ months 34 weeks	8 months 36 weeks	8½ months 38 weeks	9 months 40 weeks
1. SUCKING REFLEX	Weak and not really synchronized with deglutition		Stronger and synchronized with deglutition	Perfect ---→	---→	---→	
2. ROOTING REFLEX	Long latency period. Response is slow and imperfect		Complete and more rapid. Hand-to-mouth attraction established	Brisk Complete --→ Durable	---→	---→	
3. GRASP REFLEX	Finger grasp is good and reaction spreads up whole upper limb but not strong enough to lift infant up off bed		Stronger	Stronger	The reaction of upper limb is strong enough to lift infant up off bed ---→	---→	
4. MORO REFLEX	Weak, obtained just once, and not elicited every time		Complete reflex → ---→		---→	---→	
5. CROSSED EXTENSION	Flexion and extension in a random pattern, purposeless reaction		Extension but no adduction	Still incomplete	Good response with :- 1. Extension 2. Adduction ---→ 3. Fanning of the toes	---→	
6. AUTOMATIC WALKING	—	—	Begins tip-toeing with good support on sole and a righting reaction of legs for a few seconds	Pretty good Very fast Tip-toeing		• A premature who has reached 40 weeks. Walks in a toe-heel progression or tip-toes • A full-term new born of 40 weeks Walks in a heel-toe progression on whole sole of foot	

FIG. 3.—*Reflex. Development of reflex activity with maturity, illustrated for sucking, rooting, grasp, Moro, crossed extension, and automatic walking reflexes.*

Active tone (Fig. 2). This is evaluated through the righting reactions, investigated segment by segment. At first only the righting of the lower extremities exists, and this is seen when the infant is held upright. Later the infant is able to sustain the weight of his body, and righting of the trunk occurs. Finally, the righting of the head becomes possible, by action of the neck extensors when the baby is inclined backwards from a sitting position; then, by action of the neck flexors, when the baby is pulled to sitting position from supine. The equality of flexor and extensor muscle tone in the neck in the neonate at term allows the head to be maintained momentarily in the line of the trunk. Finally, active tone is responsible for the quality of the primary reactions (or reflexes) (Fig. 3). At 28 weeks these reflexes are present but weak and difficult to elicit several times in succession. With increasing age, they become progressively stronger.

Difficulties in appreciating muscle tone. Robinson (1966) in his recent article on assessment of gestational age, states, 'the methods so far proposed for 'dating' babies by neurological examination have been insufficiently precise, or required too much experience in assessment of muscle tone, to be practicable for general use'. He has, accordingly, rejected muscle tone as an indicator of maturity, and instead has depended upon the presence or absence of certain reflexes, in particular, the pupillary reflex. It remains our contention that appreciation of muscle tone, following the scheme outlined above, should enable a paediatrician, after several months of practice, to differentiate short gestation from small-for-dates infants.

Optimal conditions for the examination. The examination immediately after birth should be followed by a second examination 2 or 3 days later, as the tone changes in the days that follow birth. The examination should be made when the infant is as wide awake as possible, for if the infant is sleepy the tone is much more relaxed and the primary reactions slow or absent. The best time is about an hour before feeding, when the infant is neither too sleepy as after a feed, nor too agitated while awaiting the next feed.

Summary

Neurological examination of the newborn infant is described, based on the evaluation of passive

tone, active tone, and primary reflexes. Gestational age may thereby be assessed at birth, enabling short gestation infants to be distinguished from those that are small-for-dates.

I am deeply indebted to Dr. Saint-Anne Dargassies for the neurological teaching she gave me, and to Dr. M. Klaus for helpful criticism. This report was supported in part by U.S. Public Health Service Research Grant MO1 FR 81-04.

An educational film demonstrating this technique of neurological examination has been made by Minkowski (1965): 'Developpement du système nerveux central de la période fetale au terme'. Copies are available at 'Service du Film de Recherche Scientifique', 96 boulevard Raspail—Paris 6e.

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SPECIAL ARTICLE

Clinical assessment of gestational age in the newborn infant

A scoring system for gestational age, based on 10 neurologic and 11 "external" criteria, has been applied to 167 newborn infants. The "external" score gave a better correlation with gestation than did the neurologic score, but the combined total score was better than either alone. The correlation coefficient for the total score against gestation was 0.93. The error of prediction of a single score was 1.02 weeks and of the average of two independent assessments was 0.7 weeks. The method gives consistent results within the first 5 days and is equally reliable in the first 24 hours of life. This scoring system is more objective and reproducible than trying to guess gestational age on the presence or absence of individual signs.

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IN RECENT years there has been increasing interest in the assessment of gestational age in the newborn infant and in differentiating the short-gestation from the small-for-date infant. A number of clinical parameters have been used. These have fallen into two broad groups—a series of neurologic signs, dependent mainly on postures and primitive reflexes, and a series of superficial or external characteristics.

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THE NEUROLOGIC ASSESSMENT

The original impetus for the neurologic assessment came from the classical work of the French school under André Thomas and subsequently Madame Saint-Anne Dargassies.[1] Various criteria, based mainly on tone and primitive reflexes, were assessed and a

gestational age was established at which each particular clinical sign appeared. Koenigsberger[2] and Amiel-Tison[3] have recently reviewed the criteria used.

Robinson[4] selected 20 criteria from the Prechtl[5] schema for detection of neurologic abnormality in the newborn infant and applied these to the assessment of infants of varying gestational age. He concluded that the 5 most useful tests of gestational age were the pupillary reflex, which is consistently absent under 29 weeks and present after 31 weeks, the glabellar tap, which is absent before 32 weeks and present after 34 weeks, the neck-righting reflex, which appears between 34 and 37 weeks, the response of the neck flexors to traction on the hands, which is positive after 33 weeks, and the head turning to light, which appears between 32 and 36 weeks.

EXTERNAL CHARACTERISTICS

Farr and associates[6] reviewed a number of external characteristics which might be useful in the assessment of gestational age and developed a system of scoring each criterion. Farr and associates[7] subsequently analyzed the value of 11 of these criteria in the assessment of gestational age. In a series of 272 infants, they obtained a correlation coefficient between score and gestation of 0.75 for boys and 0.77 for girls and found that the best regression formula for the prediction of gestational age was $1.1201T - 0.0170T^2$ with 95 per cent confidence limits of ± 2.4 weeks. The characteristics they measured were skin texture, skin color, skin opacity, edema, lanugo, ear form, ear firmness, genitals, breast size, nipple formation, and plantar skin creases.

MATERIAL AND METHODS

Pilot study. We initially did a pilot study of all the neurologic criteria, as defined by Koenigsberger,[2] Amiel-Tison,[3] and Robinson,[4] in a series of 133 infants. We found that there was a wide overlap of gestational age at which an individual neurologic sign

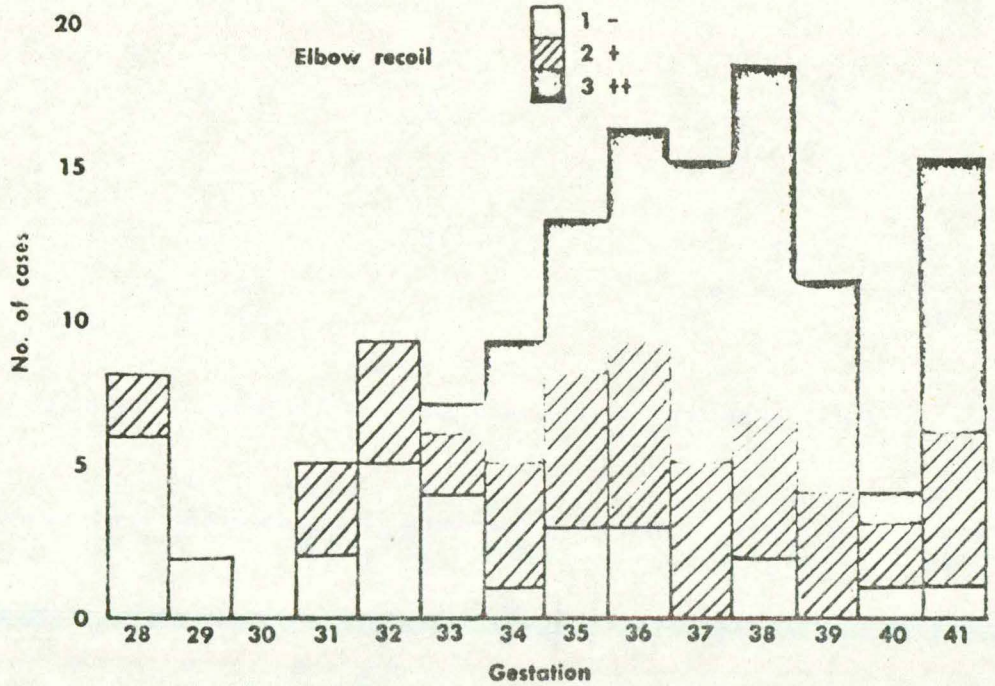


Fig. 1. Histogram showing wide range of gestational age at which a particular neurologic criterion (elbow recoil) may be fully or partially developed.

ight be present or absent and that it was ry difficult to predict gestation objectively on the basis of individual criteria (Fig. 1). Moreover, some signs were difficult to elicit. These included the pupillary reflex, for which it was often difficult to get the eyes adequately open and to see the pupil against the dark iris. The neck-righting reflex was also difficult to elicit and was frequently absent, even in full-term infants. The glabellar tap was consistently present in all the infants over 30 weeks' gestation and thus of little value within the range covering the majority of infants for assessment.

Selection of criteria. A series of neurologic criteria were selected on the basis of being easily definable and reproducible by different observers and least influenced by the "state" of the baby or the presence of neurologic abnormality (Table I). Because of the difficulty of trying to give an estimate of gestational age based on the presence or absence of a particular neurologic sign, as done by previous authors, we decided instead to score each neurologic sign along lines used by Farr and associates[6] for external characteristics (Table II).

Scoring system. In each instance, 0 was the lowest score and compatible with the posture or state of the reflex in the immature infant. We did not selectively load any particular sign but divided each into the number of grades that could be readily defined (Figs. 2 to 6). In parallel with this series of selected neurologic criteria, we also used the criteria for external characteristics as defined by Farr and associates[6]; the same scores were used with the exception that we divided nipple formation into 4 instead of 3 grades (Table III). If the score differed on the two sides, the mean was taken.

Case material. Newborn infants on the obstetric landings and in the Special Care Unit and Premature Nursery of the Jessop Hospital for Women were studied. The infants were unselected. The only ones excluded were those too ill to be examined or those with an absent Moro response.

All of the assessments in this report were made by one observer (L. M. S. D.). At the time of the examination, the expected date of delivery was not known to the observer. After the assessment, the mother was personally interviewed in every instance, and details were obtained of the last menstrual period. We included for subsequent analysis all infants of mothers who were certain of the date of their last menstrual period, had a regular 28 day (± 2 days) cycle, and had no bleeding subsequent to the last menstrual period. We excluded all cases in which the mother had been on oral contraceptives during the 12 months prior to conception. We did not exclude cases in which the uterine size was considered during pregnancy to be incompatible with the duration, as Farr and associates[7] had, as

Table I. Neurologic criteria

Criterion	*Score*
Posture	0 - 4
Square window	0 - 4
Dorsiflexion of Foot	0 - 4
Arm recoil	0 - 2
Leg recoil	0 - 2
Popliteal angle	0 - 5
Heel to ear	0 - 4
Scarf sign	0 - 3
Head lag	**0 - 3**
Ventral suspension	**0 - 4**
Total	**0 - 35**

Table II. External criteria

	Score
Edema	0 - 2
Skin texture	0 - 4
Skin color	0 - 3
Skin opacity	0 - 4
Lanugo	0 - 4
Plantar creases	0 - 4
Nipple formation	0 - 3
Breast size	0 - 3
Ear form	0 - 3
Ear firmness	**0 - 3**
Genitals	**0 - 2**
Total	**0 - 35**

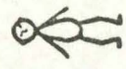
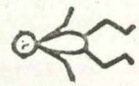
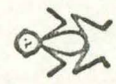
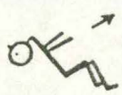
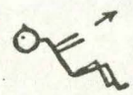
NEUROLOGICAL SIGN	SCORE					
	0	1	2	3	4	5
POSTURE						
SQUARE WINDOW	 90°	 60°	 45°	 30°	0°	
ANKLE DORSIFLEXION	 90°	 75°	 45°	 20°	 0°	
ARM RECOIL	 180°	 90–180°	 <90°			
LEG RECOIL	 180°	 90–180°	 <90°			
POPLITEAL ANGLE	 180	 160°	 130°	 110°	 90°	 <90°
HEEL TO EAR						
SCARF SIGN						
HEAD LAG						
VENTRAL SUSPENSION						

Fig. 2. Scoring system for neurologic criteria. For legend see opposite page.

SOME NOTES ON TECHNIQUES OF ASSESSMENT OF NEUROLOGIC CRITERIA

POSTURE: Observed with infant quiet and in supine position. Score 0: Arms and legs extended; 1: beginning of flexion of hips and knees, arms extended; 2: stronger flexion of legs, arms extended; 3: arms slightly flexed, legs flexed and abducted; 4: full flexion of arms and legs.

SQUARE WINDOW: The hand is flexed on the forearm between the thumb and index finger of the examiner (Fig. 3). Enough pressure is applied to get as full a flexion as possible, and the angle between the hypothenar eminence and the ventral aspect of the forearm is measured and graded according to diagram. (Care is taken not to rotate the infant's wrist while doing this maneuver.)

ANKLE DORSIFLEXION: The foot is dorsiflexed onto the anterior aspect of the leg, with the examiner's thumb on the sole of the foot and other fingers behind the leg (Fig. 4). Enough pressure is applied to get as full flexion as possible, and the angle between the dorsum of the foot and the anterior aspect of the leg is measured.

ARM RECOIL: With the infant in the supine position the forearms are first flexed for 5 seconds, then fully extended by pulling on the hands, and then released. The sign is fully positive if the arms return briskly to full flexion (Score 2). If the arms return to incomplete flexion or the response is sluggish it is graded as Score 1. If they remain extended or are only followed by random movements the score is 0.

LEG RECOIL: With the infant supine, the hips and knees are fully flexed for 5 seconds, then extended by traction on the feet, and released. A maximal response is one of full flexion of the hips and knees (Score 2). A partial flexion scores 1, and minimal or no movement scores 0.

POPLITEAL ANGLE: With the infant supine and his pelvis flat on the examining couch, the thigh is held in the knee-chest position by the examiner's left index finger and thumb supporting the knee. The leg is then extended by gentle pressure from the examiner's right index finger behind the ankle and the popliteal angle is measured (Fig. 5).

HEEL TO EAR MANEUVER: With the baby supine, draw the baby's foot as near to the head as it will go without forcing it. Observe the distance between the foot and the head as well as the degree of extension at the knee. Grade according to diagram. Note that the knee is left free and may draw down alongside the abdomen (Fig. 6).

SCARF SIGN: With the baby supine, take the infant's hand and try to put it around the neck and as far posteriorly as possible around the opposite shoulder. Assist this maneuver by lifting the elbow across the body. See how far the elbow will go across and grade according to illustrations. Score 0: Elbow reaches opposite axillary line; 1: Elbow between midline and opposite axillary line; 2: Elbow reaches midline; 3: Elbow will not reach midline.

HEAD LAG: With the baby lying supine, grasp the hands (or the arms if a very small infant) and pull him slowly towards the sitting position. Observe the position of the head in relation to the trunk and grade accordingly. In a small infant the head may initially be supported by one hand. Score 0: Complete lag; 1: Partial head control; 2: Able to maintain head in line with body; 3: Brings head anterior to body.

VENTRAL SUSPENSION: The infant is suspended in the prone position, with examiner's hand under the infant's chest (one hand in a small infant, two in a large infant). Observe the degree of extension of the back and the amount of flexion of the arms and legs. Also note the relation of the head to the trunk. Grade according to diagrams.

If score differs on the two sides, take the mean.

we considered it would eliminate some of the small-for-date infants, who form an integral part of the study.

All assessments were made within 5 days of delivery; in a large proportion the first assessment was made within 24 hours. In many infants multiple assessments were made. The series comprises 167 infants.

RESULTS

Fig. 7 shows the distribution of total score against gestation in the 167 infants. Only the first assessment in each infant was included in this analysis. The correlation coefficient of the total score against gestation was 0.93.

The regression formula for the total score *(x)* against gestation *(y)* is:

$$y = 0.2642x + 24.595.$$

The best regression line for the data is a linear one (Fig. 8). The error of prediction of a single score based on this data is 1.02 weeks and the 95 per cent confidence limits ± 2 weeks. If two independent assessments are done on the same infant, the error of prediction of the average of the 2 readings is 0.7 weeks and the 95 per cent confidence limits 1.4 weeks.

The correlation coefficient of the external characteristics against gestation was 0.91 and of the neurologic criteria 0.89. The corresponding 95 per cent confidence limits on the single scoring by the superficial characteristics were 2.4 weeks and of the neurologic criteria 2.6 weeks.

An analysis of multiple assessments done in 70 of these infants showed that the score was not influenced by the state of the baby and that it was as reliable during the first 24 hours as during the subsequent 4 days.

After completion of the survey, the scores obtained independently by 3 pediatricians

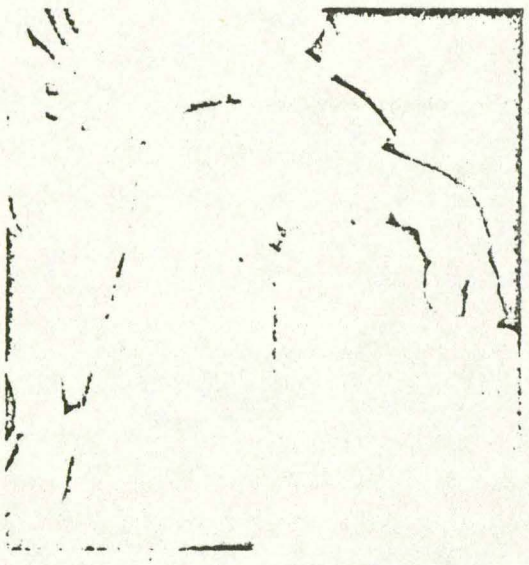


Fig. 3. Technique for square window.

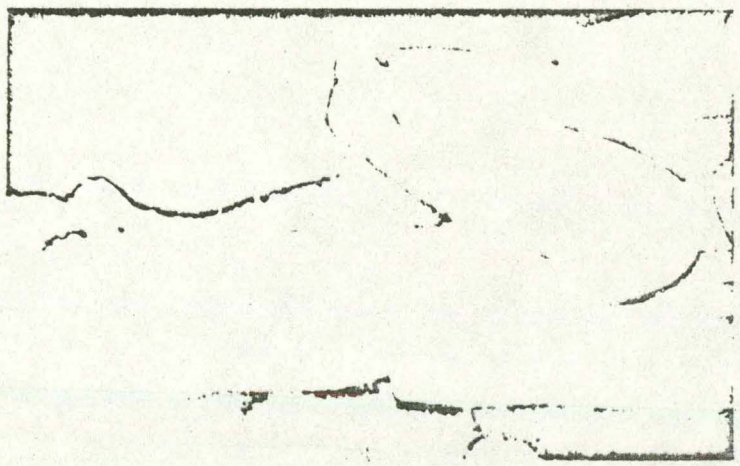


Fig. 4. Technique for dorsiflexion of foot.

Table III. Scoring system for external criteria

External sign	Score*				
	0	*1*	*2*	*3*	*4*
Edema	Obvious edema of hands and feet; pitting over tibia	No obvious edema of hands and feet; pitting over tibia	No edema		
Skin texture	Very thin, gelatinous	Thin and smooth	Smooth; medium thickness. Rash or superficial peeling	Slight thickening. Superficial cracking and peeling especially of hands and feet	Thick and parchment-like: superficial or deep cracking
Skin color	Dark red	Uniformly pink	Pale pink; variable over body	Pale; only pink over ears, lips, palms, or soles	
Skin opacity (trunk)	Numerous veins and venules clearly seen, especially over abdomen	Veins and tributaries seen	A few large vessels clearly seen over abdomen	A few large vessels seen indistinctly over abdomen	No blood vessels seen
Lanugo (over back)	No lanugo	Abundant; long and thick over whole back	Hair thinning especially over lower back	Small amount of lanugo and bald areas	At least ½ of back devoid of lanugo
Plantar creases	No skin creases	Faint red marks over anterior half of sole	Definite red marks over > anterior ½; indentations over < anterior ⅓	Indentations over > anterior ⅓	Definite deep indentations over > anterior ⅓
Nipple formation	Nipple barely visible; no areola	Nipple well defined; areola smooth and flat, diameter < 0.75 cm.	Areola stippled, edge not raised, diameter < 0.75 cm.	Areola stippled, edge raised, diameter > 0.75 cm.	
Breast size	No breast tissue palpable	Breast tissue on one or both sides, < 0.5 cm. diameter	Breast tissue both sides; one or both 0.5 - 1.0 cm.	Breast tissue both sides; one or both > 1 cm.	
Ear form	Pinna flat and shapeless, little or no incurving of edge	Incurving of part of edge of pinna	Partial incurving whole of upper pinna	Well-defined incurving whole of upper pinna	
Ear firmness	Pinna soft, easily folded, no recoil	Pinna soft, easily folded, slow recoil	Cartilage to edge of pinna, but soft in places, ready recoil	Pinna firm, cartilage to edge; instant recoil	
Genitals Male	Neither testis in scrotum	At least one testis high in scrotum	At least one testis right down		
Female (with hips ½ abducted)	Labia majora widely separated, labia minora protruding	Labia majora almost cover labia minora	Labia majora completely cover labia minora		

Adapted from Farr and associates, Develop. Med. Child Neurol. 8:507, 1966.

*If score differs on two sides, take the mean.

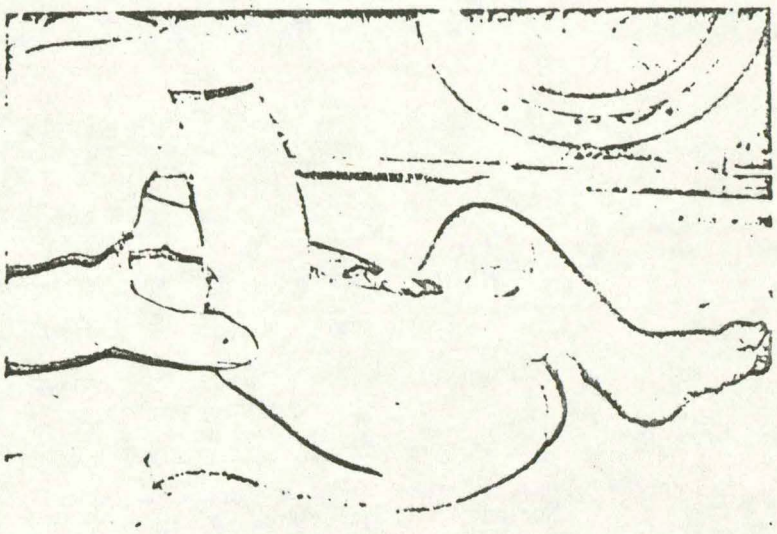


Fig. 5. Technique for popliteal angle.

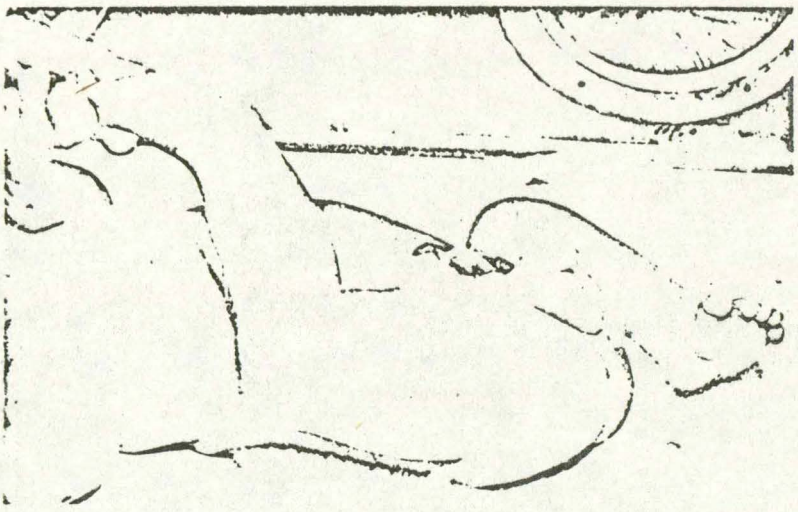


Fig. 6. Technique for heel to ear maneuver.

(A, B, and C) were compared with those obtained by L. M. S. D. in the same infants. The 3 series comprised 9, 10, and 130 infants, respectively; in each case the pediatrician practiced the scoring system on a number of infants before doing the comparative study. The Student's t test of the difference in scores between those of L. M. S. D. and each of the observers showed no significance.

The scores obtained by 3 nurses (D, E, and F) were then compared with those obtained by L. M. S. D. on the same infants. The 3 series comprised 11, 7, and 11 infants, respectively. None of the nurses had any previous experience at all with the method. The Student's t test showed no significant difference in scores between observers D and F and L. M. S. D. but did show a difference with observer E, who con-

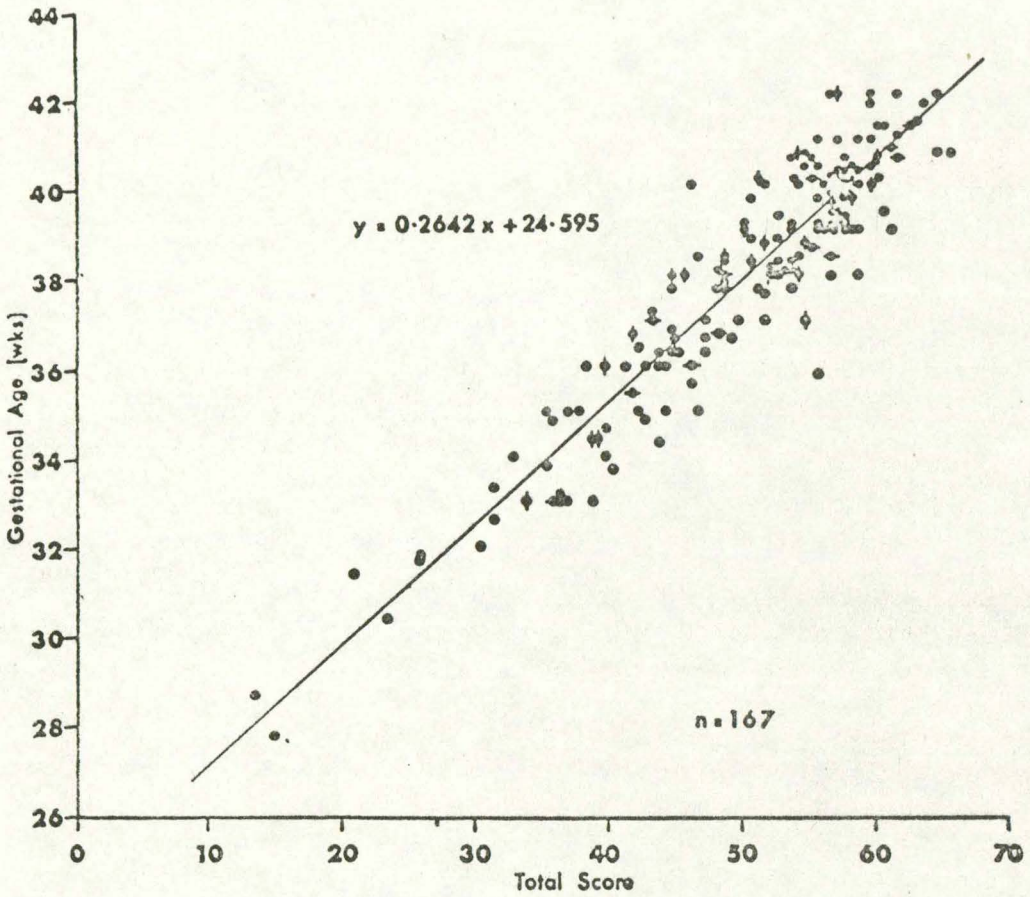


Fig. 7. Distribution of total score against gestational age in 167 infants. The best regression line is a straight line. Filled circle with vertical line through it = small-for-date infants with weight under the tenth percentile for gestational age (No. = 23); filled circle with horizontal line through it = large-for-date infants, with weight above the ninetieth percentile for gestational age (No. = 14); filled circle = appropriate weight for dates with weight between the tenth and ninetieth percentile (No. = 130).

sistently scored 5 points higher for each infant than did L. M. S. D.

DISCUSSION

The scoring system we have used has proved to be a reliable technique for assessment of gestational age in the newborn infant. The criteria used are easily defined and the scoring system can be readily learned by doctors and nurses. With a little practice, the whole procedure can be completed in about 10 minutes.

The system as a whole is much more objective and reliable than the method of trying to base gestation on the presence or absence of individual criteria.

Analysis of our data has shown that the external characteristics scored collectively give a better index than the neurologic criteria. However, the total score, using both groups of parameters, gives a better result than either alone.

The greater accuracy using the total score (with 95 per cent confidence limits of 2.0 weeks) compared with the superficial criteria (95 per cent confidence limits 2.4 weeks) is of the same order as that attained by Farr and associates[7] when comparing their superficial criteria (95 per cent confidence limits 2.4 weeks) with prediction of

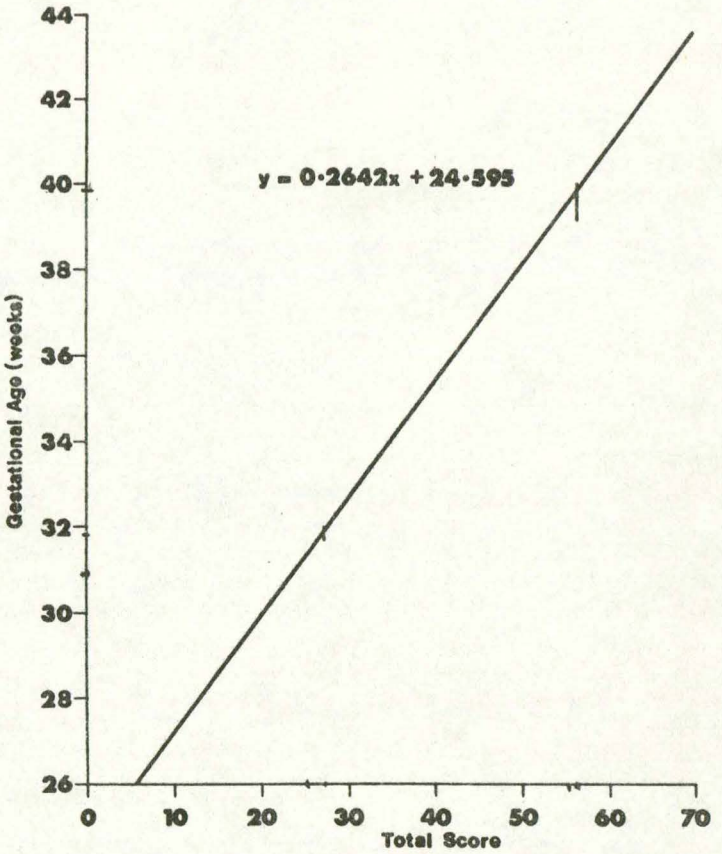


Fig. 8. Graph for reading gestational age from total score.

gestation by birth weight (95 per cent confidence limits 3.0 weeks).

We are grateful to Prof. R. S. Illingworth, Dr. A. Moosa, and Prof. J. Knowelden for help and advice, Dr. J. A. Black for access to infants under his care, Miss M. Flavin and nursing staff for their assistance and collaboration, Mr. A. S. Foster for the illustrations, and Mr. A. T. Tunstill for the photography.

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PHYSICAL FINDINGS	EST GA	WEEKS GESTATION																			
		24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
EXAM FIRST HOURS																						
VERNIX		Appears								Covers Body							Decreases in Amount		No Vernix			
BREAST TISSUE		None											1-2 MM		4MM		7 MM or More					
NIPPLES		Barely Visible								Well Defined Flat Areola					Well Defined, Raised Areola							
SOLE CREASES		None								1, Anterior Transverse		2, Anterior Transverse			Anterior 2/3 Sole		Creases Involving Heel					
EAR CARTILAGE		Pinna Soft, Stays Folded										Returns Slowly From Folding			Thin Cartilage Springs Back		Firm, Remains Erect From Head					
EAR FORM		Flat, Shapeless										Beginning Incurving of Periphery			Partial Incurving Upper Pinna			Well Defined Incurving All of Upper Pinna				
GENITALIA - TESTES & SCROTUM		Undescended						Testes High in Canal, Few Rugae						Testes Lower More Rugae			Testes Descended, Pendulous Scrotum, Rugae Complete					
LABIA & CLITORIS		Labia Majora Widely Separated, Prominent Clitoris												Labia Majora Nearly Cover Labia Minora			Labia Minora & Clitoris Covered					
HAIR (Appears on Head @ 20 wks)		Eyebrows & Lashes						Fine, Woolly Hair									Hair Silky, Single Strands					
LANUGO (Appears @ 20 wks)		Lanugo over Entire Body				Vanishes From Face					Slight Lanugo over Shoulders						No Lanugo					
SKIN TEXTURE		Thin										Smooth, Medium Thickness							Desquamation			
SKIN COLOR & OPACITY		Translucent, Plethoric. Numerous Venules (Abdomen)													Pink, Few Large Vessels Overall		Pale Pink, No Vessels Seen					
SKULL FIRMNESS		Soft to 1 inch From Anterior Fontanelle											Springy at Edges Of Fontanelle. Center Firm			Bones Hard. Sutures Easily Displaced		Bones Hard, Cannot be Displaced				
POSTURE - RESTING		Lateral Decubitus				Hypotonia		Slight Increase in Tone, Lower Extremity				Frog-Like			Total Flexion							
RECOIL		Absent						Slight, Lower Extremities				None Upper Ext Good Lower Ext			Slow Upper Ext		Good Upper Ext					
LATER EXAM																						
TONE - HEEL TO EAR		No Resistance						Slight Resistance				Difficult		Almost Impossible			Impossible					
TONE - SCARF MANEUVER		No Resistance										Minimal Resistance		Fair Resistance			Difficult					
TONE - NECK EXTENSORS		Absent						Slight				Fair		Good								
TONE - NECK FLEXORS		Absent										Minimal		Fair								
REFLEXES - MORO		Barely Apparent				Complete, Exhaustible				Good, Complete		No Abduction		Complete with Abduction								
REFLEXES - PUPILS TO LIGHT		React																				
REFLEXES - GRASP		Feeble				Fair				Solid, Involves Arms				May Pick Infant Up								
REFLEXES - ROOTING		Minimal c Reinforcement				Good c Reinforcement				Good												
REFLEXES - CROSSED EXTENSION		Slight Withdrawal						Withdrawal				Withdrawal & Extension					Withdrawal, Extension & Abduction					
REFLEXES - AUTOMATIC WALK		Absent										Minimal					Fair, Toes		Good, Heels			
REFLEXES - TRUNK ELEVATION		Absent										Slight					Good					
REFLEXES - GLABELLAR TAP		Absent						Appears						Present								
REFLEXES - HEAD TURNS TO LIGHT		Absent								Appears				Present								
CLINICAL ESTIMATE, GA*																						
CALCULATED GA																						
		24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44

EKS GESTATION

NURS 209 2/71 IOWA METHODIST HOSPITAL - NICU

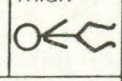
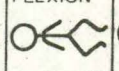
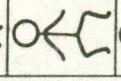
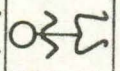
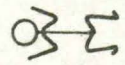
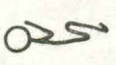
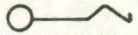
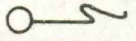
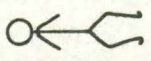
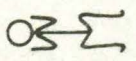
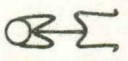
UNIVERSITY OF COLORADO MEDICAL CENTER
NEWBORN AND PREMATURE CENTER

CLINICAL ESTIMATION OF GESTATIONAL AGE

CLINICAL ESTIMATION OF GESTATIONAL AGE

AN APPROXIMATION BASED ON PUBLISHED DATA

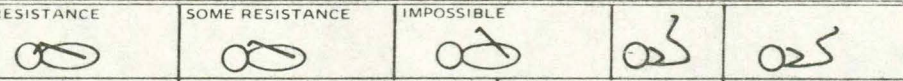
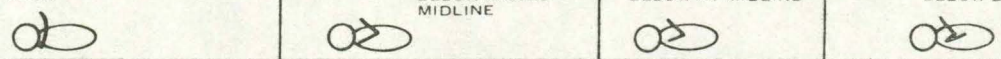
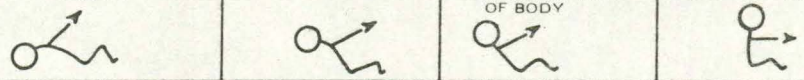
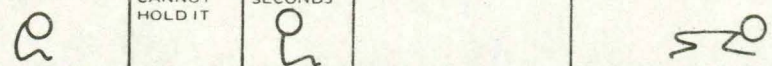
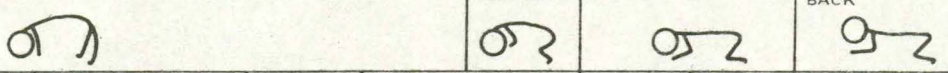
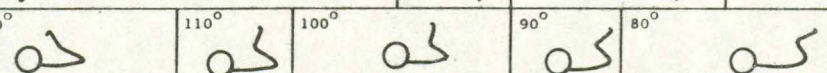
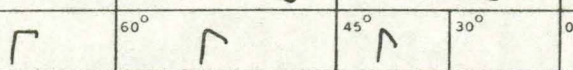
EXAMINATION FIRST HOURS

PHYSICAL FINDINGS	WEEKS GESTATION																												
	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
VERNIX	APPEARS				COVERS BODY, THICK LAYER														ON BACK, SCALP, IN CREASES		SCANT, IN CREASES		NO VERNIX						
BREAST TISSUE AND AREOLA	AREOLA & NIPPLE BARELY VISIBLE NO PALPABLE BREAST TISSUE														AREOLA RAISED		1-2 MM NODULE		3-5 MM	5-6 MM	7-10 MM			?12 MM					
EAR FORM	FLAT, SHAPELESS														BEGINNING INCURVING SUPERIOR		INCURVING UPPER 2/3 PINNAE				WELL DEFINED INCURVING TO LOBE								
EAR CARTILAGE	PINNA SOFT, STAYS FOLDED												CARTILAGE SCANT RETURNS SLOWLY FROM FOLDING				THIN CARTILAGE SPRINGS BACK FROM FOLDING				PINNA FIRM, REMAINS ERECT FROM HEAD								
SOLE CREASES	SMOOTH SOLES & CREASES												1-2 ANTERIOR CREASES		2-3 ANTERIOR CREASES		CREASES ANTERIOR 2/3 SOLE		CREASES INVOLVING HEEL				DEEPER CREASES OVER ENTIRE SOLE					
SKIN THICKNESS & APPEARANCE	THIN, TRANSLUCENT SKIN, PLETHORIC, VENULES OVER ABDOMEN EDEMA												SMOOTH THICKER NO EDEMA				PINK		FEW VESSELS		SOME DESQUAMATION PALE PINK		THICK, PALE, DESQUAMATION OVER ENTIRE BODY					
NAIL PLATES	APPEAR												NAILS TO FINGER TIPS										NAILS EXTEND WELL BEYOND FINGER TIPS					
HAIR	APPEARS ON HEAD				EYE BROWS & LASHES				FINE, WOOLLY, BUNCHES OUT FROM HEAD										SILKY, SINGLE STRANDS LAYS FLAT				?RECEDING HAIRLINE OR LOSS OF BABY HAIR SHORT, FINE UNDERNEATH					
LANUGO	APPEARS				COVERS ENTIRE BODY												VANISHES FROM FACE				PRESENT ON SHOULDERS		NO LANUGO						
GENITALIA TESTES									TESTES PALPABLE IN INGUINAL CANAL								IN UPPER SCROTUM				IN LOWER SCROTUM								
SCROTUM									FEW RUGAE								RUGAE, ANTERIOR PORTION				RUGAE COVER		PENDULOUS						
LABIA & CLITORIS											PROMINENT CLITORIS LABIA MAJORA SMALL WIDELY SEPARATED						LABIA MAJORA LARGER NEARLY COVERED CLITORIS				LABIA MINORA & CLITORIS COVERED								
SKULL FIRMNESS	BONES ARE SOFT								SOFT TO 1" FROM ANTERIOR FONTANELLE								SPONGY AT EDGES OF FONTANELLE CENTER FIRM				BONES HARD SUTURES EASILY DISPLACED				BONES HARD, CANNOT BE DISPLACED				
POSTURE RESTING	HYPOTONIC LATERAL DECUBITUS 								HYPOTONIC 				BEGINNING FLEXION THIGH 		STRONGER HIP FLEXION 		FROG-LIKE 		FLEXION ALL LIMBS 		HYPERTONIC 			VERY HYPERTONIC 					
RECOIL - LEG	NO RECOIL 														PARTIAL RECOIL 						PROMPT RECOIL 								
ARM	NO RECOIL 																		PROMPT RECOIL MAY BE INHIBITED 				PROMPT RECOIL AFTER 30' INHIBITION 								
	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48

CLINICAL ESTIMATION OF GESTATIONAL AGE

AN APPROXIMATION BASED ON PUBLISHED DATA

CONFIRMATORY NEUROLOGIC EXAMINATION TO BE DONE AFTER 24 HOURS

PHYSICAL FINDINGS		WEEKS GESTATION: 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48
TONE	HEEL TO EAR	NO RESISTANCE (26–29) · SOME RESISTANCE (30–33) · IMPOSSIBLE (34–37) · (38–39) · (40–42) 
	SCARF SIGN	NO RESISTANCE (20–30) · ELBOW PASSES MIDLINE (30–34) · ELBOW AT MIDLINE (34–38) · ELBOW DOES NOT REACH MIDLINE (38–48) 
	NECK FLEXORS (HEAD LAG)	ABSENT (30–34) · (34–38) · HEAD IN PLANE OF BODY (38–40) · HOLDS HEAD (40–48) 
	NECK EXTENSORS	HEAD BEGINS TO RIGHT ITSELF FROM FLEXED POSITION (32–36) · GOOD RIGHTING CANNOT HOLD IT (36–38) · HOLDS HEAD FEW SECONDS (38–40) · KEEPS HEAD IN LINE ⊂ TRUNK > 40° (40–44) · TURNS HEAD FROM SIDE TO SIDE (44–48) 
	BODY EXTENSORS	STRAIGHTENING OF LEGS (32–36) · STRAIGHTENING OF TRUNK (36–40) · STRAIGHTENING OF HEAD & TRUNK TOGETHER (40–48) 
	VERTICAL POSITIONS	WHEN HELD UNDER ARMS, BODY SLIPS THROUGH HANDS (26–34) · ARMS HOLD BABY LEGS EXTENDED (34–36) · LEGS FLEXED GOOD SUPPORT ⊂ ARMS (36–48)
	HORIZONTAL POSITIONS	HYPOTONIC ARMS & LEGS STRAIGHT (26–36) · ARMS AND LEGS FLEXED (36–38) · HEAD & BACK EVEN FLEXED EXTREMITIES (38–42) · HEAD ABOVE BACK (42–48) 
FLEXION ANGLES	POPLITEAL	NO RESISTANCE (20–28) · 150° (28–30) · 110° (30–32) · 100° (32–34) · 90° (34–38) · 80° (38–48) 
	ANKLE	45° (32–36) · 20° (36–38) · 0 (38–40) · A PRE-TERM WHO HAS REACHED 40 WEEKS STILL HAS A 40° ANGLE (40–48) 
	WRIST (SQUARE WINDOW)	90° (28–30) · 60° (30–32) · 45° (32–36) · 30° (36–38) · 0 (38–40) 
REFLEXES	SUCKING	WEAK NOT SYNCHRONIZED ⊂ SWALLOWING (26–32) · STRONGER SYNCHRONIZED (32–34) · GOOD (34–36) · GOOD HAND TO MOUTH (36–38) · PERFECT (38–48)
	ROOTING	LONG LATENCY PERIOD SLOW, IMPERFECT (26–30) · HAND TO MOUTH (30–34) · BRISK, COMPLETE, DURABLE (34–38) · COMPLETE (38–48)
	GRASP	FINGER GRASP IS GOOD STRENGTH IS POOR (26–32) · STRONGER (32–38) · CAN LIFT BABY OFF BED INVOLVES ARMS (38–42) · (42–46) · HANDS OPEN (46–48)
	MORO	BARELY APPARENT (20–26) · WEAK NOT ELICITED EVERY TIME (26–32) · STRONGER (32–34) · COMPLETE ⊂ ARM EXTENSION OPEN FINGERS, CRY (34–38) · ARM ADDUCTION ADDED (38–42) · (42–46) · ?BEGINS TO LOSE MORO (46–48)
	CROSSED EXTENSION	FLEXION & EXTENSION IN A RANDOM, PURPOSELESS PATTERN (26–32) · EXTENSION BUT NO ADDUCTION (32–34) · STILL INCOMPLETE (34–38) · EXTENSION ADDUCTION FANNING OF TOES (38–40) · COMPLETE (40–48)
	AUTOMATIC WALK	MINIMAL (30–32) · BEGINS TIPTOEING GOOD SUPPORT ON SOLE (32–36) · FAST TIPTOEING (36–38) · HEEL TO PROGRESSION WHOLE SOLE OF FOOT (38–42) · A PRE-TERM WHO HAS REACHED 40 WEEKS WALKS ON TOES (42–46) · ?BEGINS TO LOSE AUTOMATIC WALK (46–48)
		20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48

PONDERAL INDEX

The weight-length ratio aids in calling attention to the small for dates infant. The ratio increases with fetal age, i.e., the baby becomes heavier for his length as he approaches full-term. In intrauterine growth retardation, the weight - length ratio decreases, since the rate of gain in weight is affected more than length. The weight-length ratio is calculated using the following formula:

$$\frac{100 \times \text{weight in grams}}{(\text{length in cm})^3} = \text{Ponderal Index (P.I.)}$$

The formula for the PI is based on a computation developed in 1905 by Rohrer, a German anthropologist. Recently, Lubchenco[1] and Miller[2] have revived interest in the PI. When assessing small-for-dates babies, it serves as a predictive tool. A Low PI has been particularly associated with hypoglycemia, and pulmonary hemorrhage. (There is no apparent explanation for the association with pulmonary hemmorrhage.)

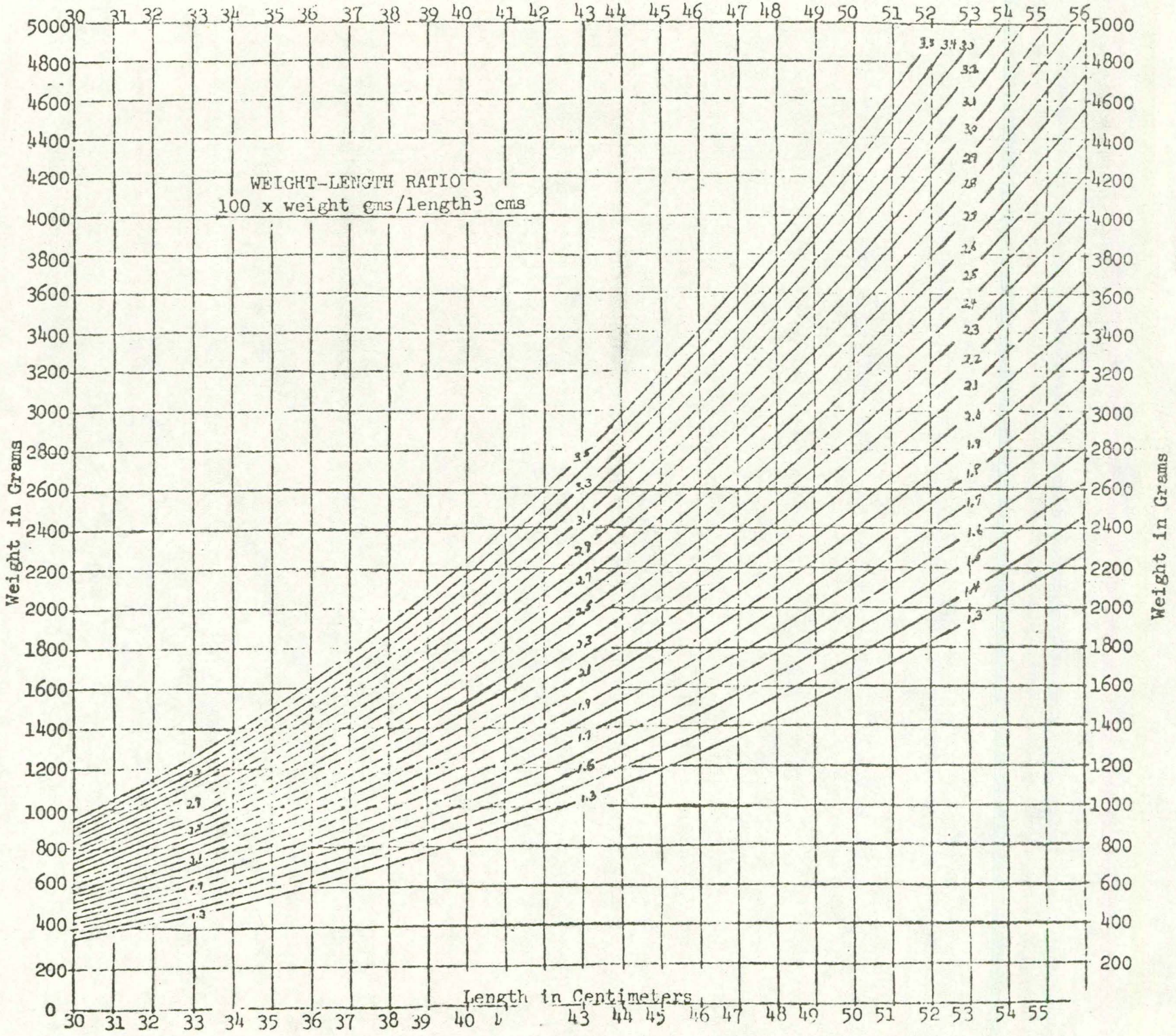
For this assessment to be accurate, it is necessary to have an accurate assessment of the gestational age. In an attempt to arrive at a reasonable assessment of GA, a physical exam based on neurological and physical development is coupled with the mother's history of the expected day of confinement and a reasonable gestational age is arrived at. It should be pointed out that using EDC's alone is not reliable since many times the dates are off by a month or two. By doing a careful physical assessment, these discrepancies can be made apparent.

In the past, maturity of infants was judged on the basis of body weight alone; in other words, if a baby weighed more than 2,500 gms. he was considered mature and concern was not expressed. However, if he was less than this amount, he was considered to be an immature or premature baby. We feel that it is far more productive and practical to assess gestational age and also the amount of growth for dates in arriving at a reasonable prediction of the newborn infant's maturity.

We realize that there are no specific conditions that can be predicted on the basis of a given ponderal index. However, the fact that a number of infants with low PI's have been shown to have hypoglycemia, alone, makes this a valuable tool. Unfortunately, hypoglycemia does not always manifest itself with obvious signs and symptoms. Increasing the index of suspicion by a predictive tool such as the PI should help to prevent the neurological sequelae of prolonged, untitled, hypoglycemia.

prepared by:

Herman A. Hein, M.D.


WEIGHT-LENGTH RATIO
100 x weight gms/length3 cms
Weight in Grams
Length in Centimeters
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600 2800 3000 3200 3400 3600 3800 4000 4200 4400 4600 4800 5000

8/72

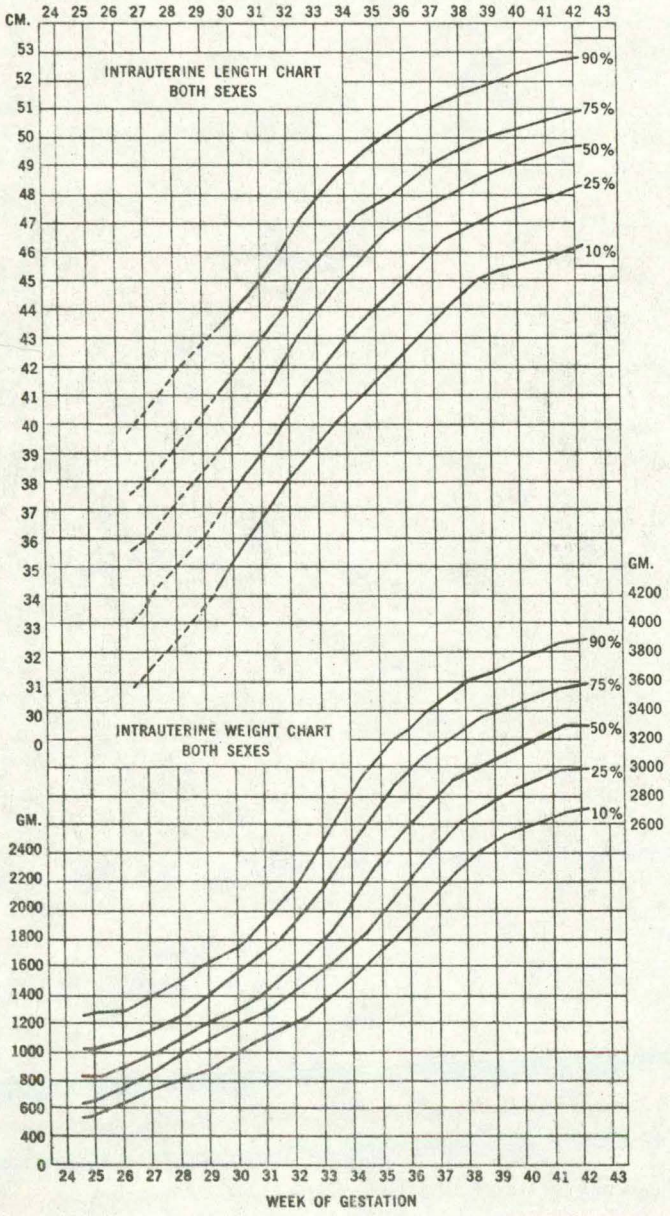
Colorado Intrauterine Growth Charts

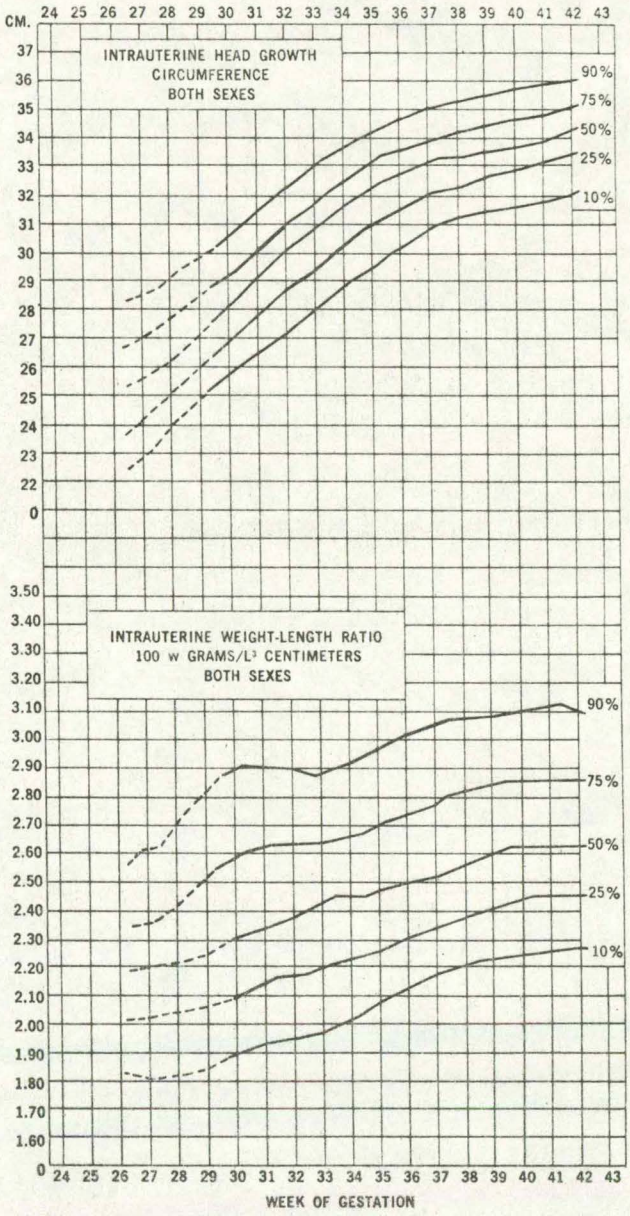
Name

Birth date

Hospital number

Date





From Lubchenco, L.O., et al.: Pediatrics 37:403, 1966.
Additional copies available from Ross Laboratories, Columbus, Ohio 43216

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46901/NOVEMBER, 1971

LITHO IN USA

Classification of Newborns

University of Colorado Medical Center

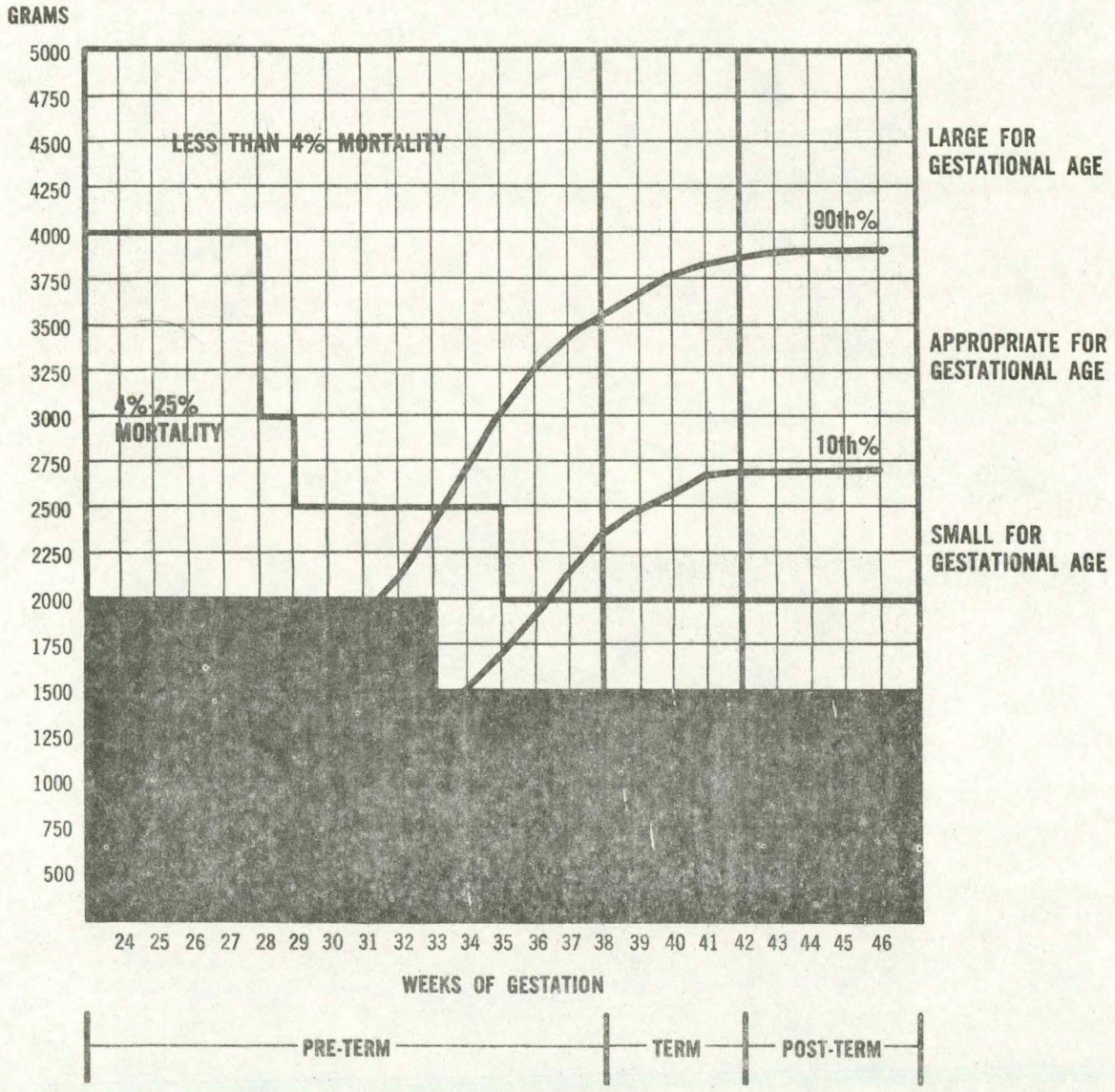
Name _____

Birth Date _____

Hospital Number _____

Estimated Gestational Age _____

Physician _____



Classification of Newborns by Birthweight and Gestational Age and by Neonatal Mortality Risk

From: Battaglia, F.C., and Lubchenco, L.O: J. Pediat. 71:161, 1967. The C. V. Mosby Company, St. Louis, Missouri.
Additional Copies available from Ross Laboratories, Columbus, Ohio 43216.

46900/NOVEMBER, 1971

LITHO IN U.S.A.

ARTICLES

INTRAUTERINE GROWTH IN LENGTH AND HEAD CIRCUMFERENCE AS ESTIMATED FROM LIVE BIRTHS AT GESTATIONAL AGES FROM 26 TO 42 WEEKS

Lula O. Lubchenco, M.D., Charlotte Hansman, M.D., *and* Edith Boyd, M.D.

Premature and Newborn Center and Child Research Council, University of Colorado Medical Center, Denver

INTRAUTERINE growth in weight as estimated from live births at gestational ages 24 to 42 weeks has been published in a previous paper.[1] It is the purpose of this communication to present the equivalent percentile patterns of intrauterine growth in length and head circumference as determined from the same sample of infants. Percentile charts have been constructed for length, head circumference, and weight-length ratio in order to visualize growth in several dimensions as an aid in detecting conditions which affect fetal growth.

The relationship of weight to length and head circumference should be of value in determining aberrations of fetal growth.

These charts are estimates of intrauterine growth, based on measurements of infants born alive at various gestational ages, as determined from the onset of the mother's last menstrual period. It is recognized that premature birth itself is unnatural and presents an indeterminable bias in the data. Since the growth of fetuses in utero cannot be measured, the data are presented with reservations; therefore, the charts of intrauterine growth in length, head circumference, weight, and weight-length ratio are only approximate definitions of the group pattern of fetal growth with gestational age.

CLINICAL MATERIAL AND METHODS

All liveborn infants admitted to Colorado General Hospital Full-Term and Premature Infant Nurseries from July, 1948, to January, 1961, are included in the sample. Data from the records of infants over 36 weeks gestation admitted after 1955 were not used because of the large numbers already tabulated in these groups of longer gestation.

Excluded from the total sample of 7,827 babies were 1,167 non-Caucasion infants (Negro, Oriental, Indian) and 363 whose gestational ages were less than 26 or more than 42 weeks. Further deletions, 1,495 infants, were due to uncertain gestational ages, failure to record the race, or the desired measurement.

Twenty-six infants with recognized gross pathological conditions, anencephaly or hydrocephaly, erythroblastosis with hydrops, babies of diabetic mothers, and those with multiple congential anomalies, known to affect birth weight, were removed from the sample because better limits for physiological growth were being sought.

Omitted also were 51 large infants of short gestation (26–35 weeks) whose weights were far above the 90th percentile. Plotted on a scattergram they gave the ap-

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pearance of being a distinct and different population.[2] They were born to mothers considered to have had menstrual-like ceding after conception.

Head circumferences were thus available for 4,720 and length for 4,716 babies. The recording of both weight and length measurements made possible the calculation of weight-length ratio for 4,706 infants.

Length and head circumferences were obtained by the pediatrician in the first 24 hours after birth. One of two methods were used to determine length: the baby was either suspended by the ankles or he was measured supine, with his head against the top of the bassinet and one leg extended.

Head circumference was measured with a disposable tape at the largest occipitofrontal circumference.

When weight and length were both available, the weight-length ratio was calculated according to Rohrer's ponderal index,[3] thus:

$$\frac{100 \times \text{weight in grams}}{\text{Length}^3 \text{ in centimeters}}$$

It is one of the various weight-length ratios in which the geometric law of dimensionality is maintained, namely, that three dimensional volume, or if specific gravity is approximately constant, weight of similar bodies are proportional to the cube of their linear dimensions. Then if the ratio is not constant, there is a change in form or density of the bodies with age.

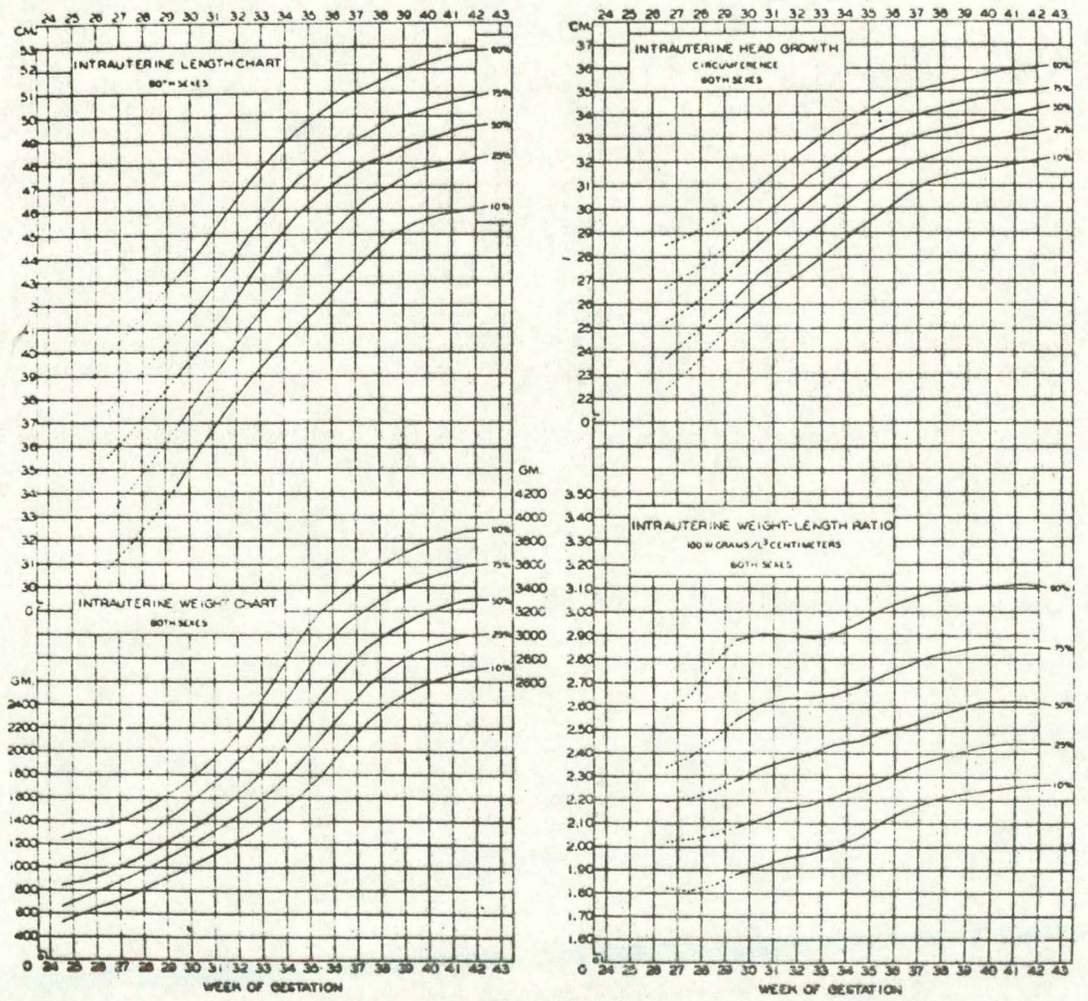

FIG. 1. Percentiles of intrauterine growth in weight, length, head circumference and weight-length ratio.

TABLE I

INTRAUTERINE GROWTH IN LENGTH

Gest Age (wk)	No. Pts.	Mean	Smoothed Percentiles (cm) Both Sexes				
			10th	25th	50th	75th	90th
26	30	36.5	30.8	32.9	35.5	37.5	39.9
27	21	37.0	31.8	34.1	36.6	38.6	41.0
28	46	38.5	33.0	35.5	37.8	39.8	42.2
29	53	39.0	34.4	36.8	39.0	40.9	43.1
30	47	40.5	36.1	38.3	40.3	42.2	44.5
31	54	41.4	37.5	39.7	41.6	43.5	45.9
32	62	43.5	38.8	41.1	43.2	45.0	47.2
33	69	44.8	39.9	42.3	44.7	46.2	48.4
34	111	45.2	41.0	43.4	45.8	47.3	49.4
35	149	46.8	42.0	44.6	46.7	48.1	50.2
36	189	47.5	43.1	45.6	47.4	48.8	50.9
37	345	47.8	44.1	46.5	48.0	49.3	51.3
38	595	48.5	44.9	47.1	48.4	49.8	51.7
39	957	48.9	45.5	47.6	48.8	50.1	52.0
40	1,084	49.4	45.8	47.9	49.2	50.5	52.3
41	589	49.6	46.0	48.1	49.5	50.8	52.6
42	315	49.8	46.2	48.2	49.7	51.0	52.8
T	4,716						

In general, this index describes how heavy the baby is for his length and age; the larger numbers portray a heavy baby for his length and the smaller number describes an infant who is thin for his length.

Percentile charts of trend and variation in length, head circumference, and weight-length ratio with age were constructed according to the method previously described for weight.[1]

The 10th, 25th, 50th, 75th, and 90th percentiles for each week of gestation were read from ogives of the original data. The resulting percentile curves from 26 to 42 weeks of gestation were then twice smoothed by arithmetic three-point means. The paucity of infants at 24 and 25 weeks of gestation influences the values at 26, 27, 28, and 29 weeks by this method and, therefore, the end of this curve is indicated by a broken line.

There were no statistically significant differences in means for each week of age in weight, length, or head circumference between Spanish American and Caucasian infants and, therefore, the two groups were combined. There were small, but significant sex differences in weight after 38 weeks of gestation, but none demonstrable between sexes for either length or head circumference at any age.

Twins and triplets were studied separately from singletons and found to be different after 35 weeks of gestation. However, their inclusion in the data did not alter the median values because they constitute a small proportion of the total number.

Figure 1 is a composite of percentile curves for intrauterine growth in weight,[1] length, head circumference, and weight-length ratio. For practical reasons, both sexes are combined for each of the percentile charts. Tables I, II, and III give the percentile figures and means.

In the previous study,[1] curves of intrauterine growth in weight were compared with data selected from the literature. During the past year, percentile charts from other parts of the country have become available,[2-4] and can now be assessed.

The main difference between the Colorado percentile curves and those from Balti-

TABLE II

INTRAUTERINE GROWTH IN HEAD CIRCUMFERENCE

Gest Age (wk)	No. Pts	Mean	Smoothed Percentiles (cm) Both Sexes				
			10th	25th	50th	75th	90th
26	24	26.1	22.4	23.6	25.2	26.6	28.5
27	20	26.1	23.2	24.4	25.8	27.2	28.9
28	40	26.9	24.3	25.4	26.7	28.0	29.4
29	49	27.9	25.3	26.4	27.6	28.8	30.2
30	49	28.9	26.2	27.4	28.6	29.7	31.1
31	53	29.8	26.9	28.2	29.6	30.5	31.9
32	58	30.1	27.6	29.0	30.4	31.4	32.7
33	65	31.5	28.4	29.8	31.2	32.1	33.4
34	103	31.9	29.2	30.6	31.9	32.9	34.0
35	149	32.4	30.0	31.3	32.5	33.4	34.5
36	186	32.9	30.6	31.8	32.9	33.8	34.9
37	353	33.2	31.1	32.3	33.2	34.1	35.2
38	611	33.4	31.4	32.5	33.4	34.3	35.4
39	961	33.6	31.6	32.8	33.7	34.6	35.7
40	1,097	33.8	31.8	33.0	34.0	34.8	35.9
41	587	34.1	32.0	33.2	34.2	35.0	36.0
42	315	34.2	32.1	33.4	34.3	35.1	36.2
T	4,720						

more and New York is in the weight of infants of short gestational ages. The 50th percentile weights of the infants in the two Eastern cities are greater than Colorado infants from 30 to 35 weeks of gestation. The 75th and 90th percentiles are much greater than Colorado's from 26 to 35 weeks.

The smaller Colorado weights may well be related to the inclusion of data on outborn infants transferred to the Premature Infant Center whose admissions depended on a birth weight of 2,500 gm or less, and also to the exclusion of large infants with short gestational ages because there was doubt about the reliability of the information. Furthermore, a number of infants with unrecognized disease remaining in the sample could possibly influence the curve downward.

The Colorado percentiles, excluding a segment of unusual births, indicate approximate limits of physiological growth, while the New York and Baltimore curves have detected a specific group of high risk infants and emphasized the magnitude of the problem. Only time and use will demonstrate the best approach.

Percentile curves of intrauterine growth in length and head circumference were not found in the literature. Therefore, means were calculated from the Colorado data for comparison with the means on length and head circumference from Mall, Scammon, Ylppo,[5] and Crosse.[6] Mall's mean lengths and Scammon's calculated curve are approximately the same as Colorado data from 26 to 36 weeks. Ylppo's figures, Scammon's and Crosse's data are slightly below the means of Colorado infants. By 40 weeks, all the measurements are greater than those of Colorado babies.

The occipito-frontal circumference of newborns in published reports is most often given according to birth weight or length, rather than gestational age. However, the few data available according to gestation,[6,7] are near the Colorado means except at 40 weeks when they are greater.

The percentiles of length and head circumference herein are, therefore, repre-

TABLE III

INTRAUTERINE WEIGHT-LENGTH RATIO

Gest Age (wk)	No. Pts	Mean	Smoothed Percentiles Both Sexes				
			10th	25th	50th	75th	90th
26	29	2.22	1.82	2.02	2.19	2.34	2.58
27	20	2.22	1.81	2.03	2.21	2.38	2.66
28	46	2.22	1.83	2.05	2.24	2.46	2.79
29	54	2.37	1.88	2.09	2.29	2.55	2.88
30	51	2.41	1.93	2.13	2.33	2.61	2.91
31	62	2.45	1.95	2.16	2.37	2.63	2.90
32	72	2.31	1.96	2.17	2.39	2.63	2.89
33	70	2.45	1.99	2.21	2.42	2.65	2.91
34	111	2.47	2.04	2.25	2.45	2.68	2.95
35	152	2.54	2.11	2.30	2.49	2.73	3.01
36	188	2.56	2.16	2.33	2.51	2.77	3.05
37	344	2.61	2.20	2.37	2.55	2.81	3.08
38	589	2.61	2.22	2.40	2.59	2.83	3.09
39	950	2.66	2.24	2.43	2.62	2.85	3.10
40	1,076	2.66	2.25	2.44	2.62	2.85	3.11
41	579	2.67	2.26	2.44	2.62	2.85	3.11
42	313	2.65	2.26	2.44	2.61	2.84	3.10
T	4,706						

sentative of earlier data except at the fortieth week of gestation where Colorado babies are slightly, but consistently, smaller in all dimensions than those reported from other areas.

The weight-length ratio reveals some interesting patterns not apparent in the separate percentile curves of weight and length. There is an increasing weight-length ratio as gestation progresses; the babies become heavier for length as they near full term.

Also, there appear to be spurts of gain in weight in excess of length at 30 to 31 weeks of gestation, and a steady rise from 34 to 38 weeks of gestation, after which time, there is a fairly constant relationship between length and weight.

Length has an inflection point at 33 weeks, weight not until 34 weeks; hence, the weight-length ratio continues to increase until weight is slowing off.

COMMENT

As greater emphasis is placed on detecting neonatal hazards immediately after birth, additional aids to diagnosis are needed. A useful adjunct to other observations during the early hours after birth is the recording of the baby's weight, length, and head circumference on the intrauterine growth charts.

The position of the infant's measurements on the charts may indicate that he is within the usual boundaries of growth for his gestational age, he may be near to or outside of the extremes of normal growth, or there may be discrepancies between the percentile positions of weight, length, and head circumference.

Infants who are large for their gestational ages may be so because of genetic factors. A small positive correlation (r ranged from 0.12 to 0.30) was found between weight of the newborn infant and maternal height.[8] Maternal diabetes, either overt or latent, enhances the growth of the fetus in all dimensions.[9,10] The infants of diabetic mothers not only are heavy for their period of gestation, but also are long and have large head circumferences. Also, infants who have transposition of the aorta are larger than normal.[11]

Intrauterine growth failure associated with several etiologically distinct entities is more frequent than growth acceleration. These conditions include, beside genetically small babies, congenital malformations, intrauterine infection such as rubella and undernutrition *in utero*.

Some of the congenital malformations associated with intrauterine growth retardation are Down's syndrome,[12] Turner's syndrome,[13] Silver's syndrome,[14] Trisomy 18,[15] DeLange's syndrome,[16] and microcephaly.[17]

The recognition of infants with undernutrition *in utero* is difficult especially at the earlier gestational ages. It is possible that the intrauterine growth curves will aid in their detection by revealing discrepancies in the size of the head, length, and weight.

On the basis of suckling animal experiments,[18] and by observation of human infants subjected to undernutrition, the persistent growth of the brain and skeletal system at the expense of the rest of the body has been demonstrated. The subjects have a false appearance of an elongated body and an enlarged head. Permanent stunting or dwarfing may occur.

Data are being collected on a variety of conditions which are generally believed to affect fetal growth in order to determine whether they modify weight, length, weight-length ratio, or head circumference.

The intrauterine growth charts should be of value in the identification of children for further investigation, and in recognizing the higher risk infants.

SUMMARY AND CONCLUSIONS

Charts of intrauterine growth in length, weight-length ratio and head circumference as estimated from liveborn measurements are presented. These, in conjunction with intrauterine weight charts, permit the identification of infants with unusual intrauterine growth patterns.

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NEONATAL MORTALITY RATE: RELATIONSHIP TO BIRTH WEIGHT AND GESTATIONAL AGE

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Neonatal mortality rate: Relationship to birth weight and gestational age

Data on neonatal mortality rates, by birth weight and gestational age, are presented in a variety of ways to indicate their usefulness in everyday practice. The conventional rates by birth weight groupings have been useful in the past, but data by both birth weight and gestational age are necessary for evaluation of current perinatal practices. Mortality rates in small blocks and in curvilinear zones by birth weight and gestational age are useful in evaluating the outcome of individual pregnancies and newborn infants. Each of these methods serves a specific need, and the advantages of each are described. The importance of using both birth weight and gestational age, when reporting mortality rates in neonatal populations, is emphasized.

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BECAUSE of improved diagnostic and treatment programs available for both mother and baby, there is a need to identify pregnancies at increased risk so that optimal care is made available. As family planning becomes increasingly accepted, the importance of a satisfactory outcome of each pregnancy is emphasized. A variety of maternal or fetal diseases influence the outcome of pregnancies, but in only a few specific conditions, e.g., maternal diabetes and Rh isoimmunization, can the effect be quantitated with some confidence. However, considerable data are available relating the effects of birth weight and gestational age to neonatal mortality rates. Mortality risk based primarily on birth weight has been used widely; but in evaluating an individual pregnancy, a more exact definition of mortality risk, based on both birth weight and gestational age, is required. When maternal or fetal disease exists, the relative risk to the fetus of preterm delivery can then be balanced against the risk of the basic disease if the pregnancy continues. Moreover, after a baby is delivered, his risk—based on his birth weight and gestational age—can be determined in anticipation of the need for special care.

The practical problems involved in determining gestational age routinely have been considered a deterrent to its general

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acceptance. However, as more accurate menstrual histories are obtained and physicians gain experience in estimating the gestational age of the infant from physical characteristics and neurologic development,[1-3] it is likely that the use of gestational age will become routine.

It is the purpose of this paper to demonstrate the practical value of neonatal mortality statistics when they are defined by both birth weight and gestational age.

CLINICAL MATERIAL AND METHODS

Information was obtained from coded data transcribed from the hospital charts of all live-born infants delivered at the University of Colorado Medical Center from July 1, 1958, to July 1, 1968. During this 10 year period, there were 16,287 live births and 380 neonatal deaths. Of this number, 1,851 records (including 39 neonatal deaths) had inadequate information on gestational age; hence, the data used to compile the various charts requiring gestational age were based on 14,436 births and 341 neonatal deaths. The population being studied is medically indigent, a small number being private patients. The racial distribution is approximately 55 per cent Anglo-American, 30 per cent Mexican-American, and 15 per cent Negro.

Neonatal mortality was defined as death occurring during the first 28 days following birth. Mortality rates were determined from these data, using a variety of birth weight and birth weight-gestational age groupings.

The smallest cell blocks, that is, 1 week gestational age and 250 Gm. birth weight increments, are presented as interpolated rates, based on a mathematical fit from the original data.

RESULTS

Mortality rates by birth weight. Mortality rates expressed according to conventional birth weight groupings are shown in Table I. The 500 Gm. weight groups are large enough to show a definite trend in the mortality rate; the larger the infant, the better the survival rate until 4,000 Gm. is reached; above 4,000 Gm. there is a slight increase in the mortality rate. From these figures, conventional comparative statistics can be determined: the total neonatal mortality rate in this population is 2.3 per cent or 23 per 1,000; the incidence of low birth weight (2,500 Gm. or less) is 13.6 per cent; the neonatal mortality rate in low-birth-weight infants is 14.4 per cent, compared to a rate of 0.4 per cent in babies with birth weights greater than 2,500 Gm.

Table I. Neonatal mortality rate by birth weight at Univerity of Colorado Medical Center, 1958 to 1968

Birth weight (Gm.)	*No. admitted*	*No. died*	*Mortality rate (%)*
4,001 +	531	4	0.8
3,501 – 4,000	2,528	7	0.3
3,001 – 3,500	6,040	22	0.4
2,501 – 3,000	4,977	29	0.6
2,001 – 2,500	1,429	40	3.0
1,501 – 2,000	449	63	14.0
1,001 – 1,500	190	83	44.0
501 – 1,000	108	97	90.0
500 or less	35	35	100.0

1. Incidence of low birth weight (2,500 Gm. or less) = 13.6 per cent.
2. Neonatal mortality rate, total = 2.3 per cent.
3. Neonatal mortality rate in infants with birth weights > 2,500 Gm. = 0.4 per cent.
4. Neonatal mortality rate in low-birth-weight infants = 14.4 per cent.
5. Neonatal mortality rate in low-birth-weight infants with birth weights 500 to 2,500 Gm. = 12.8 per cent.
6. Neonatal mortality rate in low-birth-weight infants with birth weights 1,000 to 2,500 Gm. = 8 per cent.

Mortality rates by birth weight and gestational age.

Large groupings. The same data are expressed in large groupings by birth weight and gestational age in Fig. 1.[4] The per cent mortality in these blocks clearly portrays the beneficial influence of longer gestation on the outcome of newborn infants. A 2 per cent mortality rate in infants with birth weights of 1,500 to 2,500 Gm., who are born at 38 weeks and over, is surprisingly low and is an acceptable figure for the total newborn population. In the next lower birth weight group (1,000 to 1,500 Gm.), the mortality rate improves from 50 per cent in the shorter gestation range to 13 per cent in the longer gestation.

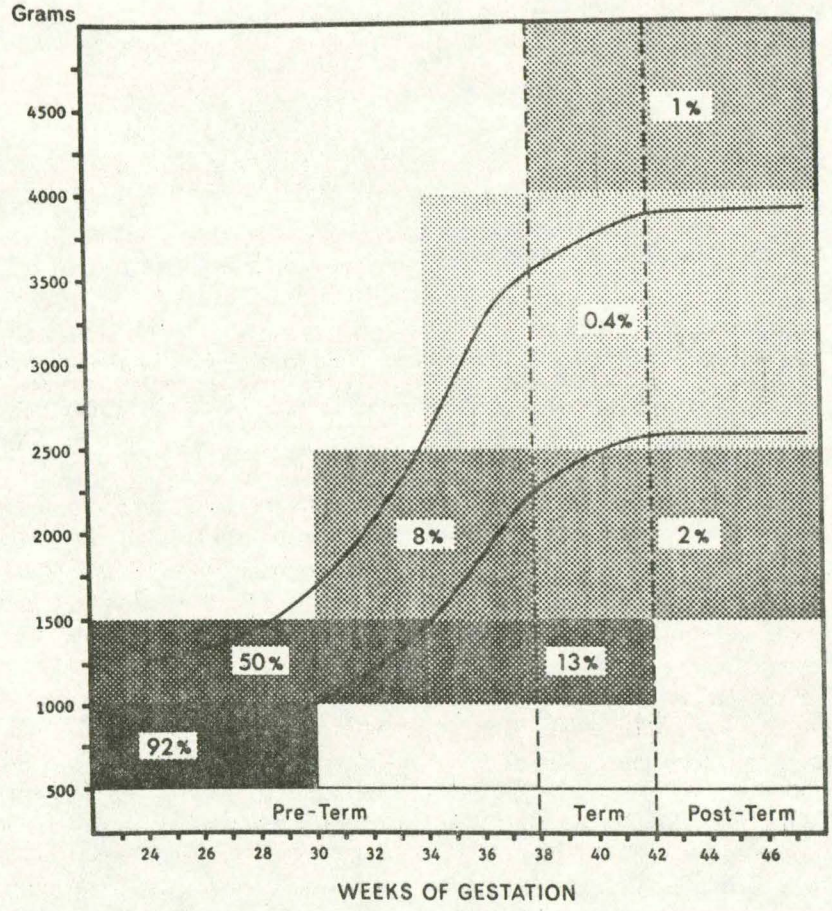

Fig. 1. Neonatal mortality rate (per 100 University of Colorado Medical Center newborn infant admissions, July 1, 1958 to July 1, 1968) by large birth weight-gestational age groupings is shown. The improvement in the mortality rate with advancing gestational age is apparent (From Battaglia, F. C.: Am. J. Obstet. Gynecol., April, 1970, published by the C. V. Mosby Company.)

Small groupings. The total amount of data available for this study permitted grouping infants into 500 Gm. birth weight and 4 week gestational age blocks (Fig. 2) and still detects distinct trends in the mortality rate by birth weight and by gestational age. When the data were examined in smaller blocks, i.e., 1 week gestational age and 250 Gm. birth weight increments, the rates were often erratic, due primarily to small numbers in some of the blocks. It was possible to avoid these uneven rates by utilizing a smoothing procedure. Fig. 3 provides smoothed estimates for the small blocks. These figures were derived by interpolation from empirically fitted curves in both the birth weight and gestational age directions.

Curvilinear zones. When the data in Fig. 3 are examined more closely, it is apparent that the mortality rate by birth weight and gestational age does not change sharply according to blocks, as implied in Fig. 1, but changes gradually with increasing birth weight and gestational age. A central point of the lowest mortality rate is identified in full-term babies of appropriate weight for gestation and, from this central point, the mortality rate increases as one deviates in any direction. The curvilinear effect can be emphasized by connecting blocks having similar mortality rates, as shown in Fig. 4.

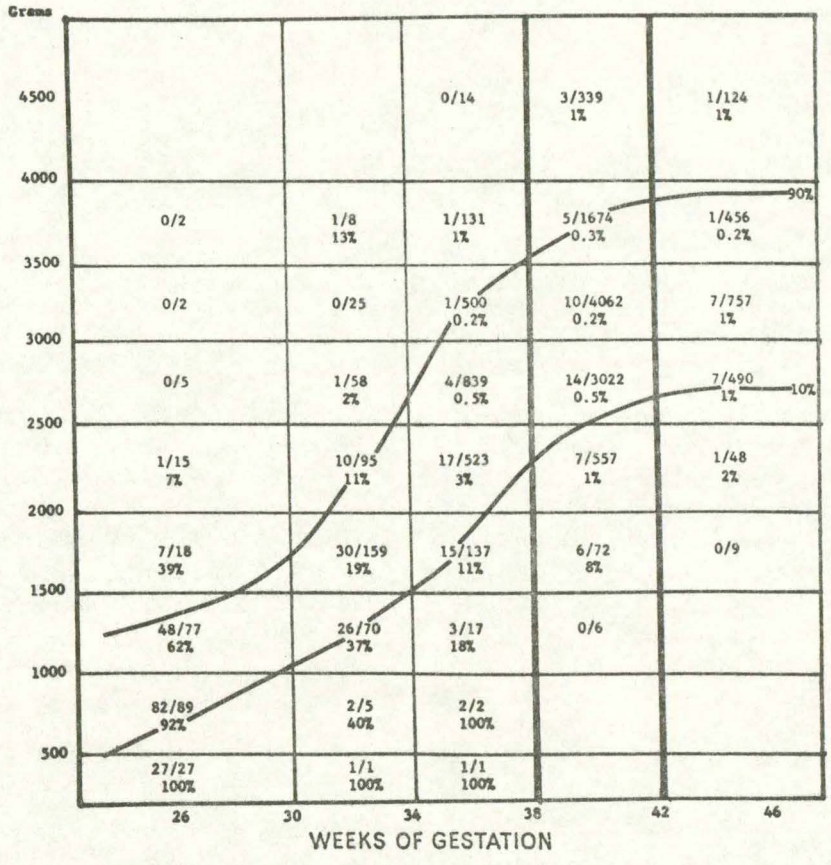

Fig. 2. Neonatal mortality rate by birth weight and gestational age. There is a decrease in the neonatal mortality rate with increasing birth weight when gestational age is kept constant, and a decline in the mortality rate with increasing gestational age when birth weight is constant except for the peripheral data.

The zone of the lowest mortality rate (0.2 per cent) occurs in infants of 3,250 to 3,500 Gm. birth weight, born at 39 to 41 weeks of gestation. It is surrounded by a zone in which the mortality range is up to 2 per cent. This zone includes the full-term, small-for–gestational age (SGA) infants, shown in Fig. 1, as well as preterm babies with appropriate-weight-for–gestational age (AGA) and babies who are large-for–gestational age (LGA).

CLINICAL APPLICATION

Mortality rates based on the total number of live births, or by birth weight subgroups, are generally used to compare results found in very large populations. Infant mortality rates (deaths in the first year of life) are used more commonly for international comparisons—those of the United States, compared to those of other nations, having received considerable publicity in recent years. The relative standings of states and regions within the United States in regard to neonatal and infant mortality rates have revealed trouble spots and prompted investigation into causes of high rates.

Data by birth weight and gestational age have a more immediate use in perinatal practice. The data presented in large blocks (Fig. 1) may be used to compare different newborn services with one another and in evaluating the influence of care in a particular service in succeeding time intervals. The mortality rate over the 10 year period 1958 to 1968 at the University of Colorado Medical Center was remarkably stable. However, during the last two years (1966 to

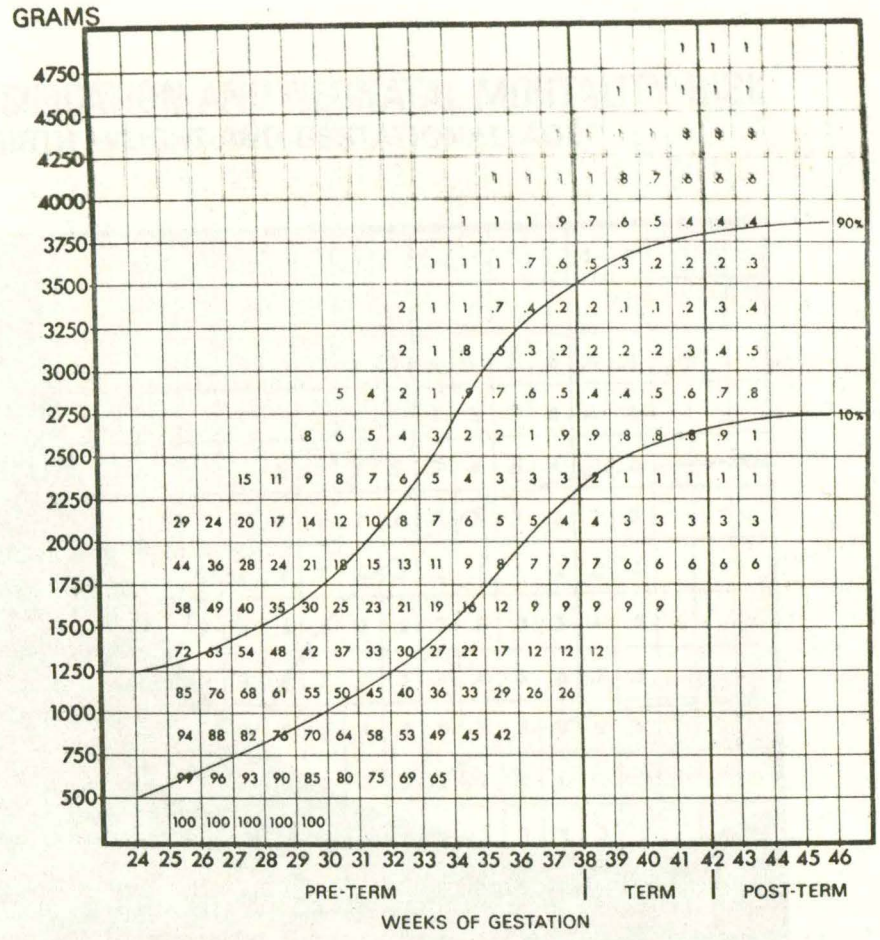

Fig. 3. Newborn classification and neonatal mortality risk by birth weight and gestational age. Neonatal mortality rate by small birth weight-gestational age blocks, based on data from Fig. 2. These figures were derived by interpolation from empirically fitted curves in both the birth weight and gestational age directions. (Interpolated data based on mathematical fit from original data, University of Colorado Medical Center newborn infants, July 1, 1958 to July 1, 1969.)

1968) there was a slight reduction in all blocks except the preterm AGA group (8 per cent), but the differences did not reach statistical significance.

Mortality rates by small birth weight and gestational age groupings are of special interest to the obstetrician and to the neonatologist (Fig. 3) who are evaluating an individual infant. The obstetrician can weigh the risk due to the underlying maternal or fetal disease against the risk of preterm delivery, while the pediatrician uses the information to assign the appropriate postnatal care to the infant.

The concept of curvilinear zones of mortality rates, based on birth weight and gestational age, is not new. Karn and Penrose presented such curves in 1951 and Silverman[5] discussed them as an interesting concept in 1961, but they have not been put to practical use. The Colorado data (Fig. 4) have proved to be useful in the Newborn Service at the University of Colorado Medical Center in assigning the level of care to be given a particular infant. Based on birth weight and gestational age, each newborn infant is assigned a risk from the graph. If his mortality risk is greater than 10 per cent, he is expected to need continuing special care, regardless of other factors.

DISCUSSION

Mortality data by both birth weight and gestational age are essential if one is to judge the chance of survival of a given infant, even when additional maternal and fetal factors affecting morbidity may be present. Because of this basic relationship between birth weight, gestational age, and mortality rates, it is incumbent upon investigators, statisticians, and perinatologists who report mortality statistics, to take into consideration the joint effect of birth weight and gestational age, especially if the outcome of mortality rate is being related to quality of care.

The data from the University of Colorado Medical Center are not necessarily representative of other populations. Many factors, such as racial composition, socioeconomic strata, and incidence of high-risk pregnancies, are unique to each perinatal service.

The use of birth weight and gestational age to predict neonatal mortality rates, without including many maternal and infant factors which are known to contribute to neonatal death, has been offered as the first step in screening large newborn populations in order to identify infants who are at risk. For example, the male infant has a higher mortality rate than does the female; in this study, the rate was 1.4 per cent for males and 0.9 per cent for females. However, no significant effect on the mortality rate could be demonstrated between the sexes when birth weight and gestational age were taken into account. The data in this paper give baseline information on mortality rates, from which estimates for a given infant can be made depending on sex, plus a number of other prenatal and natal complications.[6]

The mortality rate for infants whose gestational age was unknown was 2.1 versus 2.4 for those with a stated date, based on the mother's last menstrual period. During the years 1958 to 1965, the clinical estimate of gestational age was not made. During 1965 to 1968, it was performed irregularly, but is now being recorded systematically. However, the calculated date of delivery from the mother's menstrual history, whether or not the clinical estimate agreed, was used as the basis for these rates. Otherwise, an important high-risk group of infants would have been lost, i.e., the term-sized infants of 26 to 30 weeks of gestation, who have a 5 fold increase in mortality rate over term infants of similar weight.[7] When no date for the last menstrual period is stated, the clinical estimate can serve for the prediction of mortality risk.

The influence on mortality rate of the ethnic groups in the population must await further evaluation. Few such data are available. Erhardt and associates[8] have reported a large body of data from New York City in relatively small birth weight-gestational age blocks; mortality figures for white and nonwhite populations were given separately because of the difference in distribution and mortality in the two populations.

Yerushalmy,[9] long a proponent for the use of both birth weight and gestational age in evaluating outcome of newborn infants, has submitted data based on large birth weight-gestational age groupings as a method of dealing with these factors. The mortality rates presented by him appear to be high in relation to those given in this report. For example, the over-all mortality rate for infants with birth weights of 1,500 Gm. or less was 71 per cent, compared to 64.5 per cent in the present series. It would be interesting to know the distribution of his patients in smaller birth weight-gestational age blocks.

Although intensive care newborn nurseries have been developed in many areas, no striking improvement in neonatal mortality rates has been apparent. These centers may have increased mortality rates because of a change in the population in the nurseries coincident with the development of the intensive care nursery, i.e., a larger percentage of higher risk infants referred to it for care.[10] Several nursery services with relatively stable infant populations have been able to demonstrate significant improvement in mortality rates coincident with the establishment of intensive care.[11-13]

Usher,[14] Miller and Futrakul,[15] and

Sundell and associates[16] have emphasized the need to relate outcome of infants who have the respiratory distress syndrome to birth weight and gestational age since this disease is primarily one associated with preterm birth.

Recently, Behrman and associates[17] have reported fetal and neonatal mortality rates by small birth weight-gestational age groupings from a middle-class, white population, and including only single births. These data represent an optimal outlook for infants in this country; the over-all mortality rate was only 1.38 per cent. Uneven rates in small blocks are apparent, but in blocks in which large numbers occur, the rates are remarkably similar to those obtained at the University of Colorado Medical Center, even though the total mortality rate for University of Colorado Medical Center infants was 2.3 per cent.

SUMMARY

Various ways of expressing neonatal mortality rates have been discussed and the advantages of each has been explained. The use of both birth weight and gestational age in assessing neonatal mortality rates is reasonable and practical.

The authors wish to thank Mrs. A. June Tucker for her long-time interest and help in maintaining and organizing the data needed for this publication.

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TRANSPORT OF THE NEWBORN

15. TRANSPORT:

1. Have a device available - transport isolette (possibly shared with another/or other hospitals) is best but a Gordon- Armstrong or similar type of unit can be made to work reasonably well.

2. At least 2 nurses trained to transport babies (must know how to bag breath a baby correctly)

3. Have the ability to insert an umbilical venous catheter and know the standard dose of Sodium Bicarbonate for resuscitation. *

4. Adequate device for delivering oxygen en route

5. Adequate device for suctioning en route

6. Awareness of the referral centers and their transport capabilities

7. Be sure to send referral information requested by the newborn center

* See section on resuscitation

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[8] Transport - High Risk Newborn Infants, Chairman, c/o Dr. J.H.V. Marchessault, Executive Secretary, Canadian Paediatric Society, Department of Paediatrics, Faculty of Medicine, University of Sherbrooke, Sherbrook, Quebec, Canada.

LABORATORY SUPPORT, X-RAY SUPPORT, INVOLVEMENT OF THE FATHER

16. LABORATORY SUPPORT: We feel that any hospital delivering babies should have in addition to the usual designated laboratory facilities, the capability of doing micro blood sugars and micro blood serum bilirubins.

17. X-RAY SUPPORT: They should be able to do adequate chest films on newborns, including portables.

18. INVOLVEMENT OF THE FATHER: The father should be encouraged to become involved in the events of labor, delivery, and the after care of the infant. He should be allowed to be with his wife during labor, and if the couple both desires it, he should be with the mother in the delivery room. With proper preparation, the father can be a strong supporting factor for the gravida.

Most fathers enjoy and appreciate the opportunity to have contact with their infant during the hospital stay. This practice is becoming widely accepted, in all types of physical arrangements - whether it be a central nursery or rooming-in. If the father is instructed to wash his hands well and wears a gown over his street clothing there seems to be no increased risk of infection to the newborn. The early contacts of the family unit, father, mother, and infant, greatly enhance the cementing of family ties. The father should be encouraged to become involved with the care of the infant if he so desires, and may feed, diaper, and even bathe the baby in many obstetrical units.

Doris Haire, RN, author of many books and articles on family-centered maternity care, is a strong advocate of the involvement of father, mother, and infant. Her research has clearly shown the safety of these practices, providing proper handwashing and gowning is carried out.

19. NURSING PROCEDURES:

A. Infection Control -

1. Handwashing: Many of the common infectious agents responsible for colonization and for disease in the nursery are transmitted from infants by the hands of nursery personnel. Therefore, scrupulous attention must be paid to handwashing. Proper handwashing before entering the nursery is mandatory, and hands should be considered contaminated unless they are washed just before and just after handling an infant and after touching contaminated materials.

   To encourage handwashing, both materials and facilities should be easily accessible. Handwashing includes the use of an antiseptic agent and proper technique.

2. Gowning: All nursing personnel should wear short-sleeved gowns to facilitate washing to the elbows. If an infected or potentially infected infant is handled, the nurse should wear a long-sleeved gown over her uniform or scrub gown, and discard it after use.

3. Infected Personnel: All personnel must be taught that if they have even a mild infection it is of the utmost importance that they do not come in contact with newborn infants. No one with a respiratory, skin, hepatic, gastrointestinal, or other communicable infection should be permitted to work in the nursery, delivery room, or formula room.

B. Staffing -

1. In staffing a nursery area, a minimum of different nursing personnel should be programmed to work in the newborn area.

2. In the larger hospital, the nursery area is staffed as a separate unit. We recognized that in the smaller hospital, the nursing staff is caring for both infants, as well as general floor patients. It should be emphasized that the nurse caring for the infants should have contact with only clean surgical or clean medical cases so that there is less chance for an infection being introduced into the nursery area.

C. Ability to suspect and detect hypoglycemia and institute therapy. (This is accomplished through direct inservice education - give nurses information concerning signs and symptoms and then give them the guidelines of what to do) - (See section - Hypoglycemia)

ANTIBACTERIAL EFFECTIVENESS OF ROUTINE HAND WASHING

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ABSTRACT. A broth rinse method was used to determine the indigenous bacteria of the hands of nursery personnel and to demonstrate its stability under the test conditions. The efficacy of five wash agents in removing infant-acquired organisms from the hands was then explored. All agents were equally effective including water when followed by drying on a paper towel.

The data show that the routine-type quick hand wash usually employed by busy aides and nurses is effective in removing patient-acquired organisms and provide additional emphasis on the importance of the hand wash procedure in prevention of spread of bacteria from patient to patient. *Pediatrics*, 52:264, 1973, HAND WASHING, pHISOHEX, BETADINE, TRANSMISSION OF BACTERIA.

There is evidence that a significant method of spread of bacteria from patient to patient is via the hands of personnel attending the patients.[1, 2] Evidence for the effectiveness of brief "routine" hand washing in removing patient-acquired organisms from their hands is limited.

The current practice of concentrating patients requiring special attention in particular areas for the best possible nursing care (the critically ill into intensive care units and the newborn infants into nurseries) may increase the hazards of nosocomial infections. The purpose of this report is to determine the efficacy of the routine brief hand washing occurring in one such area in removing patient-acquired bacteria and to compare various wash agents for their effectiveness in the quick wash procedure.

MATERIALS AND METHODS

Wash Agents Tested

The following preparations were used: 3% hexachlorophene (pHisoHex), liquid saponified coconut oil (prepared in the hospital pharmacy), 7.5% povidone-iodine, 0.75% free iodine (Betadine Surgical Scrub Solution), an ethyl alcohol emulsion, 70% in a creamy water-in-oil emulsion prepared in the hospital pharmacy, Ivory soap bars, and tap water.

Study Population

The work described was carried out intermittently from May 1971 through March 1972 in nurseries of the Sloane Hospital for Women, Columbia Presbyterian Medical Center, New York City. Nurses and infant care technicians (referred to hereafter as "infant nurses") were regularly assigned to the nurseries where they washed their hands repeatedly while on duty with pHisoHex from a dispenser. Until November 1971 infants were washed with diluted pHisoHex and rinsed with water on admission to the nursery; thereafter in their nursery stay they were wiped clean, when necessary, with a water-moistened cloth Subsequently, during the study interval water alone was used for washing and wiping.

Routine Hand Wash Procedure

Preliminary observation of personnel in the nurseries indicated the following rather standard hand wash procedure: wetting the hands with tap water, dispensing a small unstandardized amount of pHisoHex

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TABLE I

VIABLE BACTERIA IN HAND RINSES OF NURSES AFTER USING pHISOHEX ROUTINELY AND THEN AFTER USING COCONUT OIL SOAP FOR TWO TO THREE WEEKS

Infant Nurse		*cfu* per ml broth rinse*							
		pHisoHex as Routine Hand Wash				*Coconut Oil Soap as Routine Hand Wash*			
		Total	*Staph**	*Strep*	*Coliform*	*Total*	*Staph*	*Strep*	*Coliforms*
S		5×10^4	5×10^4			7×10^4	7×10^4	1×10^3	
M		1×10^4	1×10^4			1×10^4	1×10^4		50
		1×10^4	1×10^4	2×10^3		1×10^4	9×10^3	4×10^3	5
C		2×10^4	7×10^3	1×10^4	55				
G		4×10^4	4×10^4	1×10^3		1×10^5	1×10^5	60	
Sequential wash	1×	4×10^4	3×10^4			1×10^5	1×10^5	40	
	2×	3×10^4	3×10^4			1×10^5	1×10^5	90	
	3×	2×10^4	2×10^4	2×10^2		1×10^5	1×10^5	94	

* Staph = staphylococci; Strep = streptococci; cfu = colony-forming units in terms of whole numbers. Blank spaces = organism not detected.

on one palm and spreading it over the hands in two to three brisk washing movements, rinsing with tap water and drying with a paper towel which was subsequently used to turn off the faucet. The wash agent was in contact with the hands for a few seconds only. For the present study personnel were requested not to deviate from this, their usual procedure, except for substituting the various wash agents as indicated. One of us (K.S.) acted as monitor of procedures in all experiments.

Broth Rinse Method of Recovering Bacteria

Bacteria which could be readily removed from the hands were determined by rinsing both hands in 10 ml trypticase soy broth in a sterile polyethylene bag (6 x 9 x .004). First one hand and then the other was clenched and opened five times in the broth at the bottom of the bag. The rinse was decanted into a sterile test tube for immediate bacteriological study. Tween 80 (1%, v/v) and sodium thiosulfate (1% w/v) were routinely added to the broth for all tests to inactivate any residual hexachlorophene in pHisoHex and iodine in Betadine respectively. Both the latter were used as test agents.

Counts of Bacteria

Measured loops (.01 and .001 ml) were used to deliver and to spread samples of the undiluted and mixed broth rinse onto one half of each of 100 x 13-mm plates containing the following agar media: trypticase soy with 5% defibrinated horse blood, mannitol salt, mitis salivarius with tellurite and MacConkey. In addition, 0.2 ml of the broth rinse was routinely spread on MacConkey and occasionally 0.1 ml on mitis salivarius agars. The plates were incubated for 24 to 48 hours at 35C with 5% carbon dioxide in air with the exception of mannitol salt agar plates which were incubated in air. Total numbers of colony-forming units on the blood agar plates and the numbers comprising major morphological types were recorded; gram stains were used to categorize the types. The selective media were included to support presumptive identification of types or groups of bacteria and to act as a duplicate for assay of colonies comprising a group. Organisms grouped as "staphylococci" might include other members of the micrococcaciae. Coagulase tests were not routinely carried out with mannitol-fermenting staphylococci.

theroids were noted in three (7%) but not as a majority organism. Yeast and *Neisseria* were infrequently found. Coliforms, present in 13 (29%) of the rinses, were obtained from the hands of nine (38%) of the personnel, one of whom carried them as predominant organism on one occasion. In general the coliforms were lactose fermenters representing a minority of 3% or less of the population.

Multiple sampling (3x to 5x) of three individuals showed relative constancy of total numbers of colony-forming units (cfu), the greatest difference being approximately tenfold.

It should be noted that no attempt was made to identify less usual varieties of bacteria with frequencies of 1% or less except for coliforms.

Stability of Indigenous Bacteria. The data of Table I show no significant qualitative nor quantitative difference in the predominant bacteria removed from the hands of four randomly selected nurses who had washed with pHisoHex routinely for months before testing and then by request shifted to routine use of coconut oil soap for a minimum of two weeks before retesting. Two weeks were considered more than adequate for the removal of any residual hexachlorophene.[3] One of the persons listed (G) washed her hands sequentially (three times) with pHisoHex after the initial broth rinse, with a broth rinse being obtained after each of the washes. Each wash was followed by water rinsing and drying with a paper towel. The same procedure was adopted for the soap experiment. The data show no significant difference in total population nor proportion of staphylococci (> 99%) with sequential washing with either agent: even the low proportion of streptococci was relatively constant. The other three nurses (Table I) used the same procedure after the soap experiment. No significant decline in indigenous flora occurred. None of the nurses had handled a baby just prior to testing.

TABLE III

COMPARISON OF FIVE HAND WASH AGENTS FOR EFFECT ON PATIENT-ACQUIRED BACTERIA, INFANT NURSE M AS SUBJECT

Wash Agent	*Experiment No.*	*Infant* Contact*	*cfu per ml in Broth Rinse*								
			Staphylococci			*Streptococci*			*Coliforms*		
			Broth Rinse No.†								
			1	2	3	1	2	3	1	2	3
pHisoHex	1	Soiled	8×10^3	3×10^5	2×10^5		1×10^4			2×10^3	
	2	Soiled	1×10^4	4×10^4	5×10^4		9×10^4	3×10^3		2×10^2	
Betadine	1	Buttock	3×10^4	8×10^4	6×10^4		8×10^4			3×10^3	
	2	Soiled	1×10^4	3×10^4	5×10^3		2×10^5	1×10^2	20	1×10^2	
Alcohol emulsion, 70%	1	Soiled	8×10^2	1×10^4	1×10^4					7×10^2	
	2	Buttock	5×10^4	2×10^5	6×10^4		1×10^5	5×10^2		4×10^3	5
Soap (Ivory)	1	Buttock	8×10^3	2×10^4	6×10^4					7×10^4	2×10^2
	2	Buttock	1×10^4	8×10^4	2×10^5	1×10^4	3×10^3		2×10^3	2×10^2	60
Tap water	1	Buttock	1×10^3	2×10^3	2×10^3					2×10^2	20
	2	Buttock	7×10^3	2×10^4	2×10^4					1×10^4	2×10^2

* Soiled = changed diaper containing stool; buttock = patted buttocks of baby with clean diaper.

† Rinse 1 = before handling infant; rinse 2 = after handling; rinse 3 = after wash with indicated agent.

Blank space = organism not detected.

TABLE IV

COMPARISON OF FIVE HAND WASH AGENTS FOR EFFECT ON PATIENT-ACQUIRED COLIFORMS

Infant Nurse	Wash Agent	Experiment	Coliforms per ml in Broth Rinse No.* 1	2	3
	pHisoHex	1		4×10^3	3×10^2
		2		5×10^2	
	Betadine	1	1×10^3†	2×10^2†	15†
		2	20	3×10^2	
S	Alcohol emulsion, 70%	1	NT‡	2×10^3	75
		2		2×10^3	1×10^2
	Soap (Ivory)	1		2×10^2	
		2		2×10^2	
	Tap water	1		2×10^4	2×10^2
		2		2×10^2	
	pHisoHex	1	10	1×10^6	3×10^4
		2		2×10^4	
	Betadine	1	30	3×10^3	
		2	20	2×10^5	5×10^2
C	Alcohol emulsion, 70%	1	15	3×10^3	
		2		9×10^4	2×10^2
	Soap (Ivory)	1	20	many§	2×10^2
		2		3×10^2	45
	Tap water	1	10	3×10^3	2×10^2
		2		3×10^2	

Infant Nurse	Wash Agent	Experiment	Coliforms per ml in Broth Rinse No. 1	2	3
	pHisoHex	1		6×10^2	4×10^2
		2		2×10^2	10
	Betadine	1		85	20
		2			1×10^2
F	Alcohol emulsion, 70%	1	1×10^2	7×10^3	30
		2		2×10^4	2×10^3
	Soap (Ivory)	1	2×10^2	2×10^3	80
		2		4×10^5	2×10^2
	Tap water	1		2×10^2	
		2		2×10^5	6×10^3
	pHisoHex	1		1×10^5	10
		2	6×10^2	1×10^4	6×10^2
	Betadine	1	4×10^2	1×10^3	2×10^4
		2	50	1×10^3	5×10^3
A	Alcohol emulsion, 70%	1	55	2×10^3	2×10^4
		2	NT‡	NT‡	NT‡
	Soap (Ivory)	1	9×10^2	6×10^2	2×10^2
		2	25	2×10^2	15
	Tap water	1		15	2×10^2
		2	9×10^2	4×10^4	3×10^3

* Rinse 1 = before handling infant; rinse 2 = after handling; rinse 3 = after wash with indicated agent;
† Cocco-bacillary (Mima-Herellea Group?).
‡ NT = not tested.
§ Proteus present.
Blank space = coliforms not detected.

Similarly, multiple (five times) consecutive broth rinses of the hands of three nurses (two using pHisoHex routinely; the other the soap for two weeks) showed a constancy in population density and predominant organism.

Effect of Hand Washing and the Broth Rinse Procedure on Patient-Acquired Bacteria

The apparent constancy of resident flora despite repeated washing facilitated observations of bacteria acquired during the infant handling and of their removal by washing procedures. We chose changing a baby's stool-containing diaper or patting the buttocks of a baby with a clean diaper as the procedures for infant handling primarily because they offered optimum opportunity for acquisition of coliforms as an index of patient-acquired bacteria under natural circumstances. Secondarily, they might provide measurable increases in organisms considered indigenous to the hands. The hands of three infant care

nurses were tested as follows (Table II): before handling a baby (broth rinse 1), after handling a baby (rinse 2), after broth rinse 2 (rinse 3), and after a routine quick wash with pHisoHex (rinse 4). The data indicate that infant-acquired streptococci or coliforms (broth rinse 2) were easily detected. Their proportion was not markedly decreased by the rinse procedure itself (rinse 3), but they were removed or greatly reduced by washing with pHisoHex (rinse 4). Evaluation of acquired staphylococci was limited by their high frequency before infant contact.

Comparison of Five Wash Agents for Their Effectiveness in Removing Patient-Acquired Bacteria

The procedure used was the same as that for the data of Table II but omitting broth rinse 3. Five infant nurses cooperated in a series of experiments intermittently covering a period of many weeks. With one exception, each wash agent was tested at least twice. pHisoHex was the daily routine hand wash substance used in the nurseries during this period.

The results of two experiments with each agent for one of the nurses is shown in Table III. An acquisition of coliforms is manifest in all but the experiment (soap 2) in which significant numbers were present before handling the baby. Streptococci were acquired in five experiments and were recovered initially in only one. Both the streptococci and coliforms were either eliminated or greatly reduced in number with all the wash agents. There was a tenfold or greater increase of staphylococci in two of the tests which was not reduced by washing with the test agents.

The data from the other four nurses are given in Table IV where, for simplification, only the bacilli are considered. Infant-acquired coliforms in broth rinse 2 are indicated for most of the experiments, with nurses S and C consistently showing elimination or a tenfold or greater decrease after washing with any of the agents. Nurse A was unusual in the frequency with which coliforms were present before handling a baby and in the frequency (five of nine tests) of no change in titer or even an increase in coliforms after washing with the various agents. She was not an enthusiastic participant, but her wash procedures were monitored.

For the purpose of these experiments, those tests in which there was no evidence of acquisition of coliforms were excluded when data from more than two experiments with a wash agent were available. Noteworthy is the observation that changing a stool-soiled diaper did not insure a measurable pickup of coliforms.

Plate Impression Technique

Random sampling of the hands of eight nursery personnel by the plate impression method showed total cfu in the range of 10 to 117 with one exception (> 700). Streptococci were recovered in four samples and coliforms in two. As expected, staphylococci were the overwhelmingly predominant organism. The hands of four nurses were also tested as in Tables III and IV using pHisoHex and Betadine as wash agents. Infant handling resulted in a marked increase in staphylococci in six and of streptococci in four of the eight experiments. Coliforms were acquired in three (two in palm only). However, after infant handling the plates were too crowded in six of the eight experiments to assess total numbers of cfu and proportions of groups of bacteria. Washing with either agent reduced total cfu and types of organism to the level present before infant contact.

Three nurses were tested before and after sequentially (four times) washing their hands with pHisoHex. Staphylococci, the predominant organisms, remained relatively constant throughout all washes. One of the nurses carried gram-negative coccobacilli (presumptive *Herellea*) which also were not washed away; colony counts, however, were irregular.

Data from a limited number of imprint tests embracing many aspects of the broth rinse study were in support of our observations and conclusions obtained with the broth rinse method. The simplicity and the clarity of colony counts obtained by the broth method led us to continue its use as the technique of choice. However, judgment of an increase in staphylococci with infant handling followed by a decrease with washing may be easier to assess with the imprint method.

DISCUSSION

The data of Tables III and IV show that infant-acquired bacteria are removed from the hands or their numbers greatly reduced by the quick perfunctory wash actually used in an active nursery, and that, under this condition the wash agent used appears to be of no real significance. Coliforms, for instance, were clearly acquired from infants in 44 (90%) of the 49 experiments and wash procedures using any agent reduced their number by 90% or greater in 41 (93%) of this total. We hold no brief for minimal hand washing: our object was to examine the efficacy of the existing wash procedure. It is reassuring to have data showing that our constant emphasis on the sanctity of the hand washing gesture is justified.

It is not surprising that the agent used is not significant with a hasty hand wash. The agent is in contact with the hands for only a few seconds and even rapidly bactericidal substances require time (in seconds) to act. It seems likely that recently acquired organisms are removed from the hands by the mechanical abrasive action of rubbing, rinsing, and drying on a paper-towel rather than killed by a special hand wash preparation.

These findings augment observations of others operating usually under more specific circumstances. Mortimer *et al.*[4] reported that hands of personnel play a major and possibly the most important role in the nursery transmission of *Staphylococcus aureus*. They suggest that the effectiveness of scrubbing may not be dependent on the preparation used but may simply reflect the physical action of scrubbing or washing plus the removal of organisms by rinsing. The data of Lowbury *et al.*,[5] while collected under complex and highly artificial circumstances (pretreatment with alcohol, inoculation of hands with large numbers of test organisms), is basically compatible with ours in showing efficiency of washing and lack of significance of washing agent used in removing "transient" organisms. In addition, several groups[6,7] have shown that washing with hexachlorophene-containing agents or soap during a period of weeks makes no significant difference quantitatively or qualitatively in the bacterial flora which can be removed from the hands.

The point we wish to make is that even a hasty hand wash with any wash agent is effective in removing significant quantities of acquired bacteria from the hands and, therefore, should be a rigidly enforced part of the patient care routine after and before every patient contact. It should be noted that we do not claim removal of all acquired organisms with each hand wash, but only that significant reduction occurs in most instances. The phrase "significant reduction" may explain the difference between our findings and those of Eisenach *et al.*[2] who found hand washing ineffective in removing resistant coliforms from the hands of personnel in their intensive care unit.

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20. PREPARATION OF THE MOTHER FOR HOME CARE: The hospital and its medical staff have the responsibility and opportunity to help parents become familiar with their infant and his care. The physician responsible for the infant's care should keep the mother informed of her infant's condition during their hospitalization.

Mothers should be encouraged to participate in the care of their own infant, even is the infant is in an incubator. The mother's care of the infant should be supervised by a trained and understanding nurse.

Instructions on infant care is the combined responsibility of the medical and nursing staff, who must agree on the content and method of teaching. Space and equipment should be provided in the hospital for the educational program. Instruction may be given individually and/or in small groups; but, it must be of a nature which will preclude any authoritarian, moralistic, or judgmental attitudes and be flelible enough to allow the mother to handle her infant with ease and understanding. The nature of a warm approach may be best carried out at the mother's bedside. However, formula preparation and infant bathing instructions are best carried out in a small group in areas designated for these purposes.

A well-prepared nurse should be specifically assigned to give individual and group instruction. She should be carefully selected, and consideration should be given to her interests, capabilities, training, and experience.

Care should be taken so no conflict arises between the instructions given in the hospital and those given by her private physicians and community agencies.

Casual, discussion-type instruction should start early, preferably during the prenatal period between the mother and her physician. Much professional