New Concepts in the Management of Neonatal Jaundice: Use of Enzyme Induction and Phototherapy*

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In the last two years two new methods for treatment of neonatal hyperbilirubinemia have been successfully introduced. The first consists of administration of phenobarbital to newborn infants and to pregnant women for at least two weeks prior to delivery. The second consists of exposing the neonate to light. Before these treatments were available, only with exchange transfusions (which are time consuming, expensive, and carry a risk of about one to 55 percent even in experienced hands) or, very rarely, with dialysis could one predictably lower the concentration of serum bilirubin.

Why do newborn infants have hyperbilirubinemia, and why are we so concerned about controlling the bilirubin level? The life span of a newborn infant's red blood cell is shorter than that of an adult. As senescent cells and their fragments become sequestered in the reticulo-endothelial system the hemoglobin molecule is split into two fragments: globin which is brought into the protein metabolic pool, and heme which is further catabolized. Microsomal heme oxidase, a rate limiting enzyme, then acts on heme to form biliverdin as the principal product. Biliverdin is further reduced and degraded to indirect-reacting unconjugated, lipid soluble bilirubin. Most of the bilirubin is reversibly bound to albumin. In this form it can be distributed in blood to a variety of tissues. A small fraction of circulating bilirubin is unbound in a dissociation equilibrium with albumin bound bilirubin. Normally, it is the unbound bilirubin fraction that continuously diffuses across the surface of the liver cells. The bilirubin is taken by the cell membrane lipids and transferred to proteins within the liver cell. Similar processes occur in fat cells, epidermal cells and neurons. Bilirubin can be pulled out of cells by increasing the albumin concentration of plasma. Within the liver cell bilirubin is separated from protein and conjugated. Normally, the conjugation process helps to maintain the diffusion of biliru-

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bin into cells by lowering the intracellular concentration of protein bound bilirubin. The conjugation process involves the transfer of an active glucuronide moiety from uridine diphosphoglucuronic acid (UDPGA) to bilirubin by the microsomal enzyme, uridine diphosphoglucuronyl transferase (UDPGT). The conjugated bilirubin is water soluble and is subsequently excreted into the bile or urine.

It has long been felt that physiologic jaundice in the neonatal period is due, at least partly, to low content of UDPGT in the livers of newborn infants. However, recent animal studies suggest that there may be adequate amounts of enzyme present. Approximately 50 percent of full-term and a greater percentage of low-birth-weight infants have physiologic jaundice.

Jaundice may occur for a number of other reasons. The most common causes, and the most dangerous with respect to risk of bilirubin encephalopathy, are those related to hemolysis or accelerated breakdown of mature red blood cells. Isoimmunization due to fetal-maternal ABO or Rh incompatibility is the leading cause of hemolytic jaundice. Other causes include sepsis, erythrocyte enzyme deficiencies and congenital spherocytosis. Jaundice may also arise from defects in hepatic uptake of bilirubin, as occurs in Gilbert's disease. Further, defective conjugation of bilirubin in hepatic microsomes may lead to jaundice. Approximately 1 percent of breast fed newborn infants develop severe hyperbilirubinemia, which persists for three to 12 weeks. Milk from mothers of these infants can inhibit to a very significant degree glucuronyl transferase activity *in vitro*. These inhibitory milks contain pregnane-3-(alpha), 20 (Beta)-idol which is produced in the actively secreting mammary tissue. Also leading to jaundice are disturbances in hepatic excretion of bilirubin, as occur in the Dubin-Johnson and Rotor's syndromes.

Kernicterus or bilirubin encephalopathy occurs almost exclusively in newborn infants with severe indirect-reacting hyperbilirubinemia. In the nursery they show opisthotonis; lethargy; flaccidity or spasticity; high-pitched cry; and poor suck, moro and grasp reflexes. If they survive the newborn period they may be mentally retarded or have choreoathetosis, cerebral palsy, deafness or evidence of minimal brain damage. When they succumb to this condition in the neonatal period, the brain usually shows localized yellow staining. Strong evidence suggests that this is due to free indirect-reacting lipid soluble bilirubin which readily crosses biologic membranes including the blood-train barrier. Although in normal plasma the free indirect-reacting bilirubin is minute, it may be increased in hemolytic disease of the newborn in the presence of organic anions which compete with the pigment for binding sites on albumin, or in acidotic states where the binding of albumin for bilirubin is reduced. It has long been realized that such factors as asphyxia, hypoglycemia and hypoproteinemia may increase susceptibility to kernicterus.

There is considerable evidence that bilirubin causes decreased cellular oxygen uptake; it also inhibits oxidative phosphorylation while producing characteristic morphologic changes in large neurons in tissue culture, such as enlargement of the mitochondria.

The search continues for a reliable guide to define what constitutes a dangerous concentration of serum bilirubin. As a working guide to the need for exchange transfusion, these figures continue to stand up well: 20 mg/100 ml for the full-term infant with erythroblastosis, 18 mg percent for the premature infant with erythroblastosis, and 20–25 mg/100 ml for the non-erythroblastotic infant. It continues to puzzle and frustrate clinicians that kernicterus can occur sporadically in premature infants with low serum bilirubin concentrations, and that some full-term infants with serum concentrations above 30 mg percent are amazingly resistent to its development.

Control of Hyperbilirubinemia by Enzyme Induction

Yaffe and associates (1966), and Crigler and Gold (1966) independently reported the first clinical trials of phenobarbital for treatment of congenital non-hemolytic jaundice. In Yaffe's patient, treatment with 15 mg of phenobarbital three times daily lowered the serum bilirubin concentration and jaundice disappeared. When treatment was stopped, the serum bilirubin concentration rose to its original high levels; reinstitution of therapy again decreased serum bilirubin levels and jaundice disappeared. Parallel studies by Yaffe on salicylamide, metabolized like bilirubin, showed that the defective capacity to conjugate glucuronide before phenobarbital became normal after treatment. In Crigler's case, the size and rate of turn-over of the bilirubin pool was measured before and during phenobarbital treatment. Results indicated that phenobarbital enhanced the excretion of the bilirubin rather than causing its redistribution into extra-vascular pools.

A large body of data showing the stimulatory effects of drugs such as phenobarbital on the metabolism of normal body constituents led to its trial in the above two patients. Studies during the past decade have shown that the activity of enzymes in liver microsomes is markedly increased when animals are treated with various hormones, drugs, insecticides, and carcinogens (Conney, 1967). This increased activity appears to represent an increased concentration of enzyme protein and is referred to as *enzyme induction*. The induction of liver microsomal enzymes is important pharmacologically, for it leads to an accelerated transformation of drugs *in vivo* and so alters the duration and intensity of drug action in animals and man.

Bilirubin formed *in utero* by the fetus can cross the placenta and be excreted by the maternal liver. After birth, however, the infant's hepatic bilirubin clearance is not sufficient to prevent its accumulation during the first week of life. We wanted to know whether careful treatment of pregnant women with phenobarbital for at least two weeks before delivery could enhance the metabolism of bilirubin in the newborn infant and reduce neonatal serum bilirubin levels. We chose to treat the pregnant women rather than the newborn infants with phenobarbital, to determine whether enzyme induction could be accomplished in the fetus *in utero* and to avoid a delay in induction of enzyme activity which might be anticipated if treatment was started at birth.

Thus, 12 pregnant women were treated with sodium phenobarbital, 30–120 mg per day for two weeks or longer prior to delivery (Table 4). Subsequently, concentrations of total serum bilirubin in their offspring and in 16 control babies were compared during the first four days of life. Premature babies and those sensitized by maternal-fetal Rh or ABO in compatibility were excluded from this study. All but one of the women received injection of 1.5 percent mepivocaine hydrochloride for continuous epidural analgesia during labor and delivery. Medications normally administered to some of the pregnant subjects were not controlled, but evaluation of the medications given to the control and the phenobarbital groups showed no significant difference.

Table 4 lists the dose and duration of phenobarbital treatment received by each of the pregnant women, and shows the maximum level of serum bilirubin observed in their infants in the first four days of life. The highest level of neonatal serum bilirubin in the phenobarbital group was 4.7 mg percent, whereas 12 of 16 control babies had peak serum bilirubin levels above this value. Since all but two of the women were treated with the same daily dose of phenobarbital, it was not possible to determine what dosage regimen most effectively lowers the concentration of serum bilirubin.

TABLE 4

Schedule of phenobarbital treatment during pregnancy and its effect on the maximum level of total serum bilirubin in the neonatal period*

Group and dose of phenobarbital (mg/day)	Duration of treatment (days)	Maximum neonatal serum bilirubin level (mg/100 ml)
Controls:		
0	0	1.3–10.4
Phenobarbital:		
60	14	4.2
60	14	2.8
60	14	2.7
60	14	2.7
60	22	3.6
60	24	1.1
30	30	1.8
60	31	1.6
60	40	4.7
60	60	1.0
120	105	1.2
60	11 yr.	4.4
		$(2.7 \pm 0.4^{\dagger})$
		$(5.9 \pm 0.5^{\dagger})$

* The value of serum bilirubin for each subject represents the maximum obtained for that subject during the first 4 days of life.

† Mean ± S.E.

TABLE 3

Effect of Phenobarbital on Bilirubin Metabolism in Animals

1. Stimulates bilirubin glucuronyl transferase activity in liver microsomes
2. Stimulates clearance of exogenously administered bilirubin from plasma in animals
3. Stimulates hepatic uptake of bilirubin
4. Stimulates bile flow and biliary excretion of bilirubin
5. Stimulates proliferation of smooth membranes of the endoplasmic reticulum

TABLE 5

Effect of phenobarbital received during pregnancy on concentration of total serum bilirubin in the neonatal period*

	Serum bilirubin (mean ± S.E.) (mg/100 ml)	
Day	Control	Phenobarbital
1	3.8 ± 0.4	2.1 ± 0.4
2	5.0 ± 0.6	2.5 ± 0.4
3	5.7 ± 0.7	2.2 ± 0.4
4	5.2 ± 0.8	1.8 ± 0.4

* Each value represents the mean and S.E. obtained on each day for the control and phenobarbital groups.

In Table 5, the mean daily concentrations of serum bilirubin are compared in control infants and babies of phenobarbital treated women. Daily levels of serum bilirubin were significantly low in the phenobarbital group. The maximum mean value for serum bilirubin in these infants was 2.5 mg/100 ml; this concentration occurred on the second day of life. In control babies, however, the maximum mean level of serum bilirubin was 5.7 mg/100 ml; this value was found at three days of age. The level of serum bilirubin in each group was not related to the type of feeding received.

All babies in the study were vigorous at birth and thereafter.

These data suggest that the administration of phenobarbital for two weeks or longer before delivery altered the usual course of physiologic hyperbilirubinemia. Serum bilirubin levels were reduced and maximum serum bilirubin values occurred earlier in babies born to women treated with phenobarbital. The low concentration of serum bilirubin in these babies suggests that phenobarbital, acquired by the fetus transplacentally, enhanced the hepatic metabolism and biliary excretion of bilirubin in the fetus and the newborn infant. Our findings were confirmed by Trolle (1968).

One question that immediately comes to mind is whether phenobarbital may be harmful to the pregnant woman or to her newborn infant. A large number of women with epilepsy or pre-eclampsia have been treated with phenobarbital for at least two weeks during pregnancy without recognizable difficulty. Regarding the danger phenobarbital may cause a newborn infant, in our series no difference was detected in the behavior of infants of treated and untreated mothers. Similarly, no differences have been detected in other series. Trolle (1968) measured the serum phenobarbital level in some of his babies, and in no case did the concentration exceed 21 mg/ml, which is well below the sedative level.

Another consideration is the possibility that phenobarbital could displace bilirubin from albumin. This could lead to a diffusion of dissociated bilirubin from the blood and interstitial fluid to the intracellular fluid, thus increasing the risk of development of kernicterus. In this regard we did not see increased skin jaundice in those babies born to phenobarbital treated women, nor did Trolle in his series. In addition, we made serial measurements of the reserve binding capacity of serum for bilirubin, using the HABA dye method, and found no difference in the serum binding capacity between the control and phenobarbital treated groups. Our findings, in conjunction with those reported by Yaffe and Crigler, indicate that the decrease in serum bilirubin concentration after phenobarbital treatment cannot be considered dangerous. All the observations suggest, therefore, that phenobarbital may be of therapeutic value in controlling neonatal hyperbilirubinemia.

Control of Hyperbilirubinemia by Phototherapy

Lucey, Ferreiro and Hewitt (1968) reported a controlled study which showed that early prolonged exposure of premature infants to artificial light might prevent or at least modify the degree of hyperbilirubinemia. Cremer, Perryman and Richards (1958) of Australia first demonstrated that serum bilirubin concentrations of some newborn infants could be reduced by exposure to sunlight or artificial blue light. Several groups of English, South American, French and Italian workers subsequently reported very favorable experiences with this method of treatment. This therapy had not found acceptance in the United States—probably due to doubts as to its effectiveness, concern that the photodecomposition products might be toxic, and unawareness of many reports in the foreign literature.

Lucey (1968) tested the effectiveness of artificial blue light in preventing hyperbilirubinemia among 111 premature infants. Treated infants from 12 to 144 hours of age were placed in light; serum bilirubin concentrations were then carried out. The control and treated infant groups were comparable with respect to birth weight, gestational age, fluid intake and weight loss. The results showed a statistically significant difference between the two groups on the fourth and sixth days of life. No differences were noted in the sleeping and feeding habits of the infants in the light treatment group.

How does light affect bilirubin metabolism? The level of indirect reacting bilirubin present in a solution of human albumin and bilirubin decreases when it is exposed to light of certain wavelengths. As the level of bilirubin decreases, first biliverdin and then a series of not yet fully characterized related substances appear in the solution. The best available evidence suggests that the derivatives of photo-oxidation are in part pyrrolic pieces of bilirubin resembling dipyrrole. There is to date no published animal data supplying any convincing evidence of the toxicity of the products of photo-decomposition. The studies of Ostrow (1968) using radio-labelled C_{14} bilirubin in Gunn rats clearly demonstrate that these products are rapidly excreted in the bile and urine, and that they are indistinguishable from the normal products found in Gunn rat bile and urine. It appears, therefore, that photodecomposition is a normal alternate route of excretion of bilirubin and is increased or activated in newborn infants by the use of light.

In jaundiced infants exposed to light, the presence of icterus in shielded areas of skin suggests that the photo-oxidation occurs in the skin. Too, biliverdin which is produced in the test tube, when a bilirubin-albumin solution is exposed to light is not observed in the skin or plasma of light-treated infants.

Potentially, light may have an effect on bilirubin metabolism at several different points in its *in vivo* metabolism (Behrman and Hsia, 1969). Light might affect the microsomal heme oxidase system, which might increase the amount of bilirubin carried in the serum and presented to the liver. It might alter the albumin binding sites for bilirubin, making it easier for bilirubin to escape in the tissue. It might affect the protein receptors for bilirubin within the liver cells or other cells. Light might stimulate a variety of mitochondrial enzymes, including UDPGT. It might affect the yet poorly characterized bilirubin and other excretory mechanisms in the liver.

Other biological effects of light have also been noted. Ultraviolet light causes capillary dilation as in sunburn, activates tyrosinase which results in skin darkening, and causes a photo-chemical transformation of ergosterol to active forms of vitamin D. Further, there are indirect effects that, though less well known, are of potential concern. The duration of light exposure in young animals can turn on or markedly delay the onset of puberty. Light has a profound effect on biologic rhythms such as body temperature, food consumption, physical activity and adrenal cortical secretion. In animals, light has a profound influence on gonadal weight and ovulation. Newborn piglets exposed to light without the use of eye shields have developed retinal detachment.

Although no obvious acute clinical toxicity has been recognized in light-treated newborn infants, no organized retrospective or prospective follow-up study of change in neurologic and behavioral sequelae is available. There is still considerable doubt and concern about all the potential biological effects of light on bilirubin metabolism in humans and in animals. Additional knowledge of these matters is critical in evaluating the potential dangers of phototherapy.

Most investigators have started phototherapy soon after birth; others have started at 12 to 72 hours after birth or when jaundice was first noted. Therapy has been continued for varying periods of time, continuously or intermittently through the sixth day of life. At the Medical College of Virginia, the light is placed over the isolette containing the infant and treatment is continued for 96 hours. The light chamber consists of ten GE#20 daylight bulbs attached to an aluminum and steel frame. The lamps emit most strongly in the blue-yellow wavelengths form 400 to 500 mU, and are most effective in rapidly photo-oxidizing bilirubin from 420 to 440 mU. Blue lamps and cool white lamps, with slightly different wavelength emissions, are also used. Red lamps emitting wavelengths above 600 mU are not effective; lamps that emit the lower ultraviolet wavelengths are less effective and more dangerous to the eyes than visible light. The infant's eyes are covered with a simple bandage; no clothing is placed on the infant so as much skin as possible is exposed to light. The intensity, duration, and pattern of light exposure has varied considerably among the groups of infants who have been subjected to phototherapy by different investigators. The intensity of light has ranged from 100 to 500 footcandles. At the Medical College of Virginia 200 footcandles are used.

During a symposium on bilirubin metabolism in the newborn infant held in Chicago in June, 1969, an attempt was made to delineate tentative guidelines in light therapy (Behrman and Hsia, 1969). The following guidelines were formulated:

1. The etiologic diagnosis for jaundice should be established, as far as is practical, before starting any therapy including phototherapy.
2. Phototherapy should not be used prophylactically in term infants.
3. Phototherapy should be used for infants in whom the risks of hyperbilirubinemia are thought to out-weigh the risks of phototherapy.
4. Infants who, when first seen, have sufficient indications for an exchange transfusion should not have their transfusion delayed for trial of phototherapy.
5. Phototherapy should not be started until an abnormal rise in serum bilirubin has been demonstrated. In general, the serum indirect bilirubin concentration should be at least 10 mg percent at the time phototherapy is initiated.
6. Wavelengths between 300 and 600 mU from 200 to 400 footcandles should be effective in reducing serum bilirubin concentrations in many premature infants.
7. Eyes of the infant should be shielded with patches to protect the developing macula. In order to avoid corneal ulceration, it is also critical to make sure that the eye is closed and remains closed when patched.
8. Body temperature should be monitored to minimize the risk of over heating.

A number of questions with respect to phototherapy still remain unanswered. There is no evidence that jaundiced premature infants treated with light have fewer developmental abnormalities than untreated infants, that there is a decreased need for exchange transfusion in premature babies with hyperbilirubinemia due to isoimmunization or sepsis, or that light therapy is effective at high bilirubin levels. No organized follow-up data are as yet available regarding sequelae of light therapy. No information is available to evaluate optimal duration of light exposure or determine whether exposure should be continuous or intermittent. No good comparison is available to judge the relative effectiveness and safety of blue versus white or daylight lamps in photo-oxidizing bilirubin in humans. Data available comparing the effectiveness of light in the Negro and in the Caucasian is limited and inconclusive. No data is available comparing the effec-

tiveness of light versus phenobarbital versus a combination of light and phenobarbital for treatment of hyperbilirubinemia.

With these questions in mind, we (Dr. David Draper, Dr. Orestes Valdes and myself of the department of pediatrics; Dr. Ali Hossaini of the Blood Bank; with the cooperation of the pediatric house staff at the Medical College of Virginia) have embarked on a comprehensive study of phenobarbital and light therapy. The study is designed to compare light versus phenobarbital versus a combination of light and phenobarbital for the prevention and treatment of hyperbilirubinemia in low-birth-weight infants. The comparisons will include the effectiveness of each on Negroes compared to Caucasians; effectiveness of each in hyperbilirubinemia due to hemolysis and other causes; effectiveness of each when hyperbilirubinemia is complicated by respiratory distress syndrome, intestinal obstruction and hypoglycemia; and effect of each on the need for subsequent exchange transfusions in infants who have previously received such transfusions. In addition, a long-term follow-up to determine possible sequelae of these treatments is planned.

In the study, low-birth-weight newborn infants are treated with either phenobarbital alone at a dosage of five mg/kilo/gram per day for five days, exposure to light for 96 hours at 200 footcandle intensity, or a combination of phenobarbital and light. Only preliminary data are available at the present time and are shown in Table 6. Of seven untreated control patients, six had serum bilirubin levels over 10 mg percent during the first five days of life. However, three of eight phenobarbital-treated infants, none of the seven light-treated infants, and none of the seven phenobarbital and light-treated infants had serum bilirubin levels above this value. The Figure shows the mean daily serum bilirubin levels in each group. Beginning with the second day of life there is a marked difference in serum bilirubin levels between the controls and the two light-treated groups. Infants who received phenobarbital alone showed a lowered serum bilirubin level beginning on day four. Infants who received only light therapy showed slight rebound bilirubinemia after the light was discontinued. Though we must be cautious in drawing firm conclusions from these preliminary data, two points seem clear. Phenobarbital and light treatment each modify the course of hyperbilirubinemia in the premature infant. Light reduces the bilirubin level more quickly and more dramatically than phenobarbital treatment since the latter probably depends upon enhancement of hepatic microsomal enzyme activity, which takes several days to occur. At the present time, the data are insufficient to determine if the addition of phenobarbital to light offers an advantage over light alone. One might suspect, however, that the combination might produce a sustained reduction of serum bilirubin level and avoid the rebound

phenomenon seen on the fifth day with light alone.

In our study, only one of the infants who received phenobarbital became lethargic, but the lethargy persisted even after the drug was discontinued. No side effects from light therapy were recognized, and a funduscopic examination in the nursery in the majority of children failed to reveal any abnormalities.

Summary

All the observations suggest that phenobarbital and light may be of therapeutic value in controlling neonatal hyperbilirubinemia. In pregnancies in which one might anticipate increased bilirubin formation by the

TABLE 6

Peak total serum bilirubin levels of low birth weight newborn babies during the first 5 days of life

Group	Total No. of Babies	No. Above 10 mg/100 ml	Percentage
Controls	7	6	85.5
PB*	8	3	37.5
Light	7	0	0
PB + Light	7	0	0

* PB—Phenobarbital
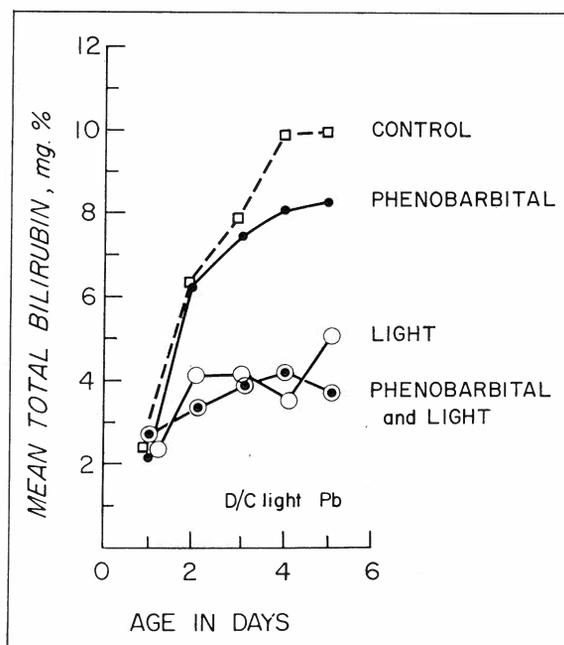
Figure—Effect of phenobarbital (5 mg/kilo/day, orally) and light (200 footcandles, daylight bulbs) on daily total serum bilirubin levels of low birth weight newborn babies.

newborn baby, the use of phenobarbital during pregnancy and in the neonatal period, and exposure of the infant to light may provide methods other than exchange tranfusion to reduce the concentration of serum bilirubin in the infant. Clinical trials should proceed cautiously, however, since phenobarbital is known to stimulate the activity of liver microsomal enzymes that metabolize, steroids, hormones, and other normal body substrates. It is not known whether this effect would be harmful if it occurred in the human fetus or neonate. Pediatricians should consider phototherapy in the same cautious manner as they would the use of a new drug available for the treatment of newborn infants. Considering the state of ignorance on this subject, research into the long-term effects of phototherapy is clearly needed.

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