Prevention of Kernicterus as a Complication of Hemolytic Disease and Other Forms of Jaundice of the Newborn

PARTICIPANTS

THOMAS A. BOGGS, M.D., Children's Hospital, Philadelphia, Pa. BRUCE CHOWN, M.D., Children's Hospital, Winnipeg, Manitoba, Canada. RICHARD A. DAY, M.D., Department of Pediatrics, State University of New York, Downstate Medical Center, Brooklyn, N.Y. LOUIS K. DIAMOND, M.D., Children's Hospital, Boston, Mass. PHILIP STURGEON, M.D., Children's Hospital Society, Los Angeles, Calif. WOLF W. ZUELZER, M.D., Children's Hospital of Michigan, Detroit, Mich.

EDITOR: Significant advances in the prevention of kernicterus and its long trail of neurological sequelae have followed a better understanding of the mechanisms of hemolytic disease and hemoglobin pigment disposal in the newborn. Some of the pertinent information and its implications is still to reach many pediatricians and hematologists facing these problems in their practice. A specific course of preventive action cannot, of course, be outlined to apply to all circumstances. It has been felt, however, that within certain limits, a good zone of agreement probably exists as to procedures to be employed, given a fairly well defined set of conditions. This discussion is designed chiefly to bring out: a) the choice and timing for the application of the knowledge and tools available; b) the degree of agreement on the issues involved among those most skilled and experienced in this field. The opinions here recorded were given independently by the participants. We are indebted to Dr. Thomas Boggs for help in the choice and framing of the questions. We shall begin by asking: What, in your judgment, are the main weapons available today to prevent kernicterus in the newborn?

STURGEON: Exchange transfusion, repeated when indicated, is to all intents and purposes the only effective means for reducing the incidence of kernicterus in the newborn. It would be erroneous, however, to leave the impression that kernicterus can be invariably prevented under all circumstances. This is particularly so in the premature; our experience is suggestive that, with methods of therapy now available, there is, from the practical standpoint, no critical bilirubin concentration below which the premature is safe.

BOGGS: There is only one therapeutic procedure available today which is effective in preventing kernicterus, exchange transfusion. It enables us to prevent serum bilirubin concentrations from reaching excessively high levels.
and to lower the concentration of this pigment after it has reached excessive levels. Exchange transfusion is, therefore, our number one and only weapon. Other considerations should, however, be mentioned. Kernicterus is almost never encountered except in association with high serum bilirubin concentrations in newborn infants. Certain conditions, sometimes avoidable, are prone to contribute to excessive jaundice in an infant. Therefore, it seems reasonable to attempt to prevent where possible, those situations predisposing to high serum bilirubin concentrations in the first few days of life. When the condition is unavoidable, anticipation of trouble will enable us to institute treatment in the form of exchange transfusion sufficiently early, should such treatment prove necessary. Those conditions most frequently predisposing to hyperbilirubinemia of the newborn are: hemolytic disease, sepsis, prematurity, anoxia, maternal diabetes and high intestinal obstruction. Unfortunately, there is no known agent which will prevent an Rh-negative woman from reacting against her Rh-positive infant or which will modify her reaction or protect the fetus.

Two drugs have been shown to contribute to the development of kernicterus in an infant. A vitamin K analog in large doses causes elevation of the serum bilirubin level in the newborn infant, and high doses of this drug should not be administered routinely. The use of Gantrisin in premature infants is associated with a high incidence of kernicterus in the absence of excessive concentrations of serum bilirubin. This drug seems to enable bilirubin to penetrate the blood-brain barrier at lower serum concentrations of the pigment. Its use in infants should be avoided. Lastly, the use of glucuronic acid as a means of lowering the serum bilirubin concentration should be considered experimental and in no way, at this time, a substitute for exchange transfusion.

DAY: I know of only one way to prevent kernicterus in the jaundiced newborn infant, and that is through the appropriate use of exchange transfusion. Every center with an adequate experience has found that this procedure can prevent kernicterus. I am not aware of any other form of treatment which has been shown actually to reduce the frequency of the condition. Glucuronic acid has been shown by Danoff et al. to lower the level of bilirubin in some jaundiced infants. However, this finding must be considered in association with another observation made by Silverman et al. on premature infants and Lois Johnson and co-workers on genetically jaundiced rats, that sulfa drugs also reduce bilirubin levels and at the same time increase the frequency of kernicterus. Sodium chloride will lower bilirubin levels. The important point is to know where the bilirubin is going. If it passes into extravascular tissues, benefit is not to be expected. Johnson’s observations on rats show no protection by glucuronic acid; in fact, kernicterus seems to occur especially in those animals responding with a fall in bilirubin. However, the search for a drug to prevent kernicterus should be an enticing one for the chemist.

CHOWN: Foreknowledge that an infant yet unborn may have erythroblastosis affords us a chance to prepare for what is to follow. Early replacement transfusion, repeated if necessary, is the other weapon at our disposal.
ZUELZER: We interpret kernicterus as a true bilirubin encephalopathy. Vigilance with respect to early and/or excessive jaundice and hyperbilirubinemia in the newborn period, regardless of cause, is therefore the *sine qua non* of successful prevention. In the presence of existing or threatening hyperbilirubinemia, the judicious use of exchange transfusion seems to be the only therapeutic weapon capable of preventing kernicterus at the present time. Attention should be paid to factors which tend to increase the accumulation of free bilirubin or might enhance its toxicity. Infants with hyperbilirubinemia in the absence of hemolytic disease or infections specifically affecting the liver, frequently have a history of difficult delivery or other paranatal difficulties conducive to anoxia. If this is true, improved obstetrical practices should lessen the incidence of severe jaundice and kernicterus. Since prematures appear to be especially susceptible, any success in the reduction of prematurity should be helpful. Moreover, certain iatrogenic factors such as the use of large doses of vitamin K and of certain sulfa preparations can increase the danger of kernicterus and must be avoided.

DIAMOND: There is only one weapon available today to prevent kernicterus in the newborn and this is exchange transfusion to lower the bilirubin level when it reaches a dangerous height. Up to about three years ago, the incidence of kernicterus in jaundiced newborns (chiefly caused by blood group incompatibility) had fallen to a low level of 1 to 2 per cent in most pediatric hospitals, and even to zero in some well organized maternity services. Within the last few years the number of cases of kernicterus has definitely increased. Physicians have undertaken the care of sensitized women in many hospitals not equipped to give good care to the newborn infant. They have then waited until jaundice was easily visible before transferring the patient to another hospital or calling a physician to perform exchange transfusion. In fact, in some instances, maternity services where sensitized women have been delivered have not even been prepared to evaluate the levels of bilirubin in newborn infants. For these reasons seriously jaundiced infants have been encountered more frequently than formerly and kernicterus has developed in some of them. Since kernicterus is a preventable condition, not occurring before the age of about 20 hours, there is ample time to carry out exchange transfusions if bilirubin levels are measured. In fact, even laymen now realize this and there are a large number of medicolegal suits all over the country against physicians who have permitted infants to develop kernicterus through failure to perform exchange transfusion adequately or in time. Further education to prevent unnecessary brain damage in jaundiced infants is greatly needed.

EDITOR: There seems to be unanimous agreement that exchange transfusion is the chief weapon in the prevention of kernicterus. Four of the participants stress the importance of foreknowledge of the possible occurrence of jaundice and early initiation of measures to offset its appearance or reduce its intensity; two mention contributing factors to be avoided, aside from hemolytic disease of the newborn. Bilirubin-mobilizing or -conjugating agents such as glucuronic
Since the principal object is to lower the serum bilirubin level, what is the maximum level which may be regarded safe, that is, unlikely to lead to kernicterus in the full-term infant during the neonatal period? When depending upon the diazo reaction as the bilirubin index of the need for an exchange transfusion, which should be used, the indirect or the total bilirubin reading?

BOGGS: We will perform as many exchange transfusions on a full-term infant as are necessary to maintain the total serum bilirubin level below 20 mg. per cent during the first week of life. Above this concentration, the risk of kernicterus is far greater than the mortality rate of exchange transfusion when the procedure is performed by experienced individuals. There is considerable feeling today that the indirect bilirubin is the responsible agent in causing kernicterus and that the direct bilirubin is probably harmless. However, this is not a proven fact. Available data correlating kernicterus and serum bilirubin concentrations are based on the total reading, and this is the value we use as a guide. Actually, the direct-reacting pigment represents only a small fraction of the total reading in all but a very few cases of hyperbilirubinemia occurring during the first week of life.

DAY: The maximum safe level of serum bilirubin for a full-term infant has not been set with certainty. The role of possible contributing factors, such as the presence of pigments resulting from hemolysis, as suggested by Abelson and others, remains incompletely assessed. Hematin, for example, is cytotoxic. Our understanding of the role of hypoxia, infection, ketosis, and perhaps other factors is incomplete. A level of 20 mg. per cent, however, seems to be not far from the upper limit of safety, as judged by clinical experience. There have been no experiments reported on the in vitro toxicity of direct (conjugated) bilirubin. Circumstantial evidence, however, is strong that it is not toxic. For that reason, it is logical that the indirect bilirubin level should serve as a guide.

STURGEON: A current analysis of our experience shows in 174 term infants, treated originally by exchange transfusion and repeated during the first 72 hours of life when the bilirubin concentration reached or exceeded 20 mg./100 ml., there were eight deaths in the neonatal period. None of these, however, showed staining of the basal ganglia at postmortem examination. Among the 166 survivors, now followed from 6 months to 2.5 years, there is no evidence of classical kernicterus. There is, however, one infant with mental retardation, two questionably retarded, one with questionable hearing loss and one with possible petit mal. In none of these latter did the bilirubin concentration reach 20 mg./100 ml. Furthermore, among the 166 there were, despite repeated exchange transfusions, 44 infants whose bilirubin concentration exceeded 20 mg. (20–30 mg.) for periods varying from one hour to several days. None developed kernicterus. In this group as in those whose bilirubin concentration remained well below 20 mg., there are some infants (3) with
possible mild central nervous system damage of a variety not attributed to classical kernicterus. Originally we had been using the total serum bilirubin as our guide to therapy. Approximately for the latter half of the study we have been relying on the indirect reacting bilirubin.

Zuelzer: Empirically, we aim toward keeping the serum bilirubin level below the widely accepted concentration of 20 mg. per cent. However, we do not know the level below which kernicterus cannot occur, or the level above which it will unfailingly develop. The serum level is a very imperfect indicator of the summation of many factors involved in the genesis of kernicterus. It reflects a changing balance between the rate of pigment accumulation and the ability of the infant's liver to conjugate and excrete the pigment. It also reflects a balance between bilirubin in the tissues and that which is held in the plasma. This latter balance in turn is affected by the quantity of plasma albumin and by available binding sites on the protein. On the other hand, the size of the potential tissue reservoir and the relative affinities of different tissues (such as fat, vasculature and brain) for bilirubin are factors bound to play a part but difficult to evaluate and not measured by the serum level. Duration of exposure to high bilirubin levels is also a factor to be considered. With so many undetermined variables, we feel there is no single answer to the question posed. The significance of any given bilirubin level is not necessarily the same after exchange transfusion as before. In considering indications for a first exchange we are guided by a level of 20 mg. per cent or the likelihood that this level will be exceeded. In infants who have already received an exchange transfusion, we do not regard this level as equally critical but tend to individualize on the basis of frequent observations in order to determine the rate of rise or fall, or the duration of a sustained level in the neighborhood of 20 mg. The “rebound” phenomenon which so frequently follows exchange transfusion in infants who are initially deeply jaundiced is interpreted by us as indicating movement of pigment in the right direction, i.e., from the tissues into the plasma which should now have improved binding capacity for the pigment.

Chown: The likelihood of kernicterus appearing in a mature erythroblastotic infant is about 1 in 10 for a serum indirect bilirubin of 20 to 25 mg. per cent; about 1 in 5 for 25 to 30 mg.; about 1 in 2 over 30. We are guided by the indirect bilirubin alone, but methods for defining and measuring the fractions are notoriously inaccurate.

Diamond: As far as now known, a level of 20 mg. per cent or less of indirect or unconjugated bilirubin can be safely tolerated by the average full-term infant not only during the neonatal period but even later. There is some question whether the prematurely born or immature infant is more susceptible and therefore may develop kernicterus with levels of less than 20 mg. per cent. Evidence for this has not yet been accumulated. There is no proof that only the neonatal period is a time of danger. As shown by Crigler and Najjar several years ago, even older infants subjected to high bilirubin levels may
develop kernicterus. It is only the indirect bilirubin reading which is important in this respect. Direct bilirubins of 20 mg. per cent or more are rarely encountered, but combinations of both direct and indirect bilirubin in equal amounts with total levels of 30 to 40 have been seen and have not been followed by an visible evidence of kernicterus.

EDITOR: A serum bilirubin level below 20 mg. in the neonatal period seems to be generally agreed to be seldom followed by kernicterus. Circumstances may develop, however, which may dictate performing a transfusion when the bilirubin is below that level. The opinion predominates that it is the indirect reading that counts. The age of the infant is, moreover, an important consideration.

At what age is it no longer necessary to perform an exchange transfusion in the face of an excessively high serum bilirubin level in the full-term infant? Or in the premature infant? Is the danger of kernicterus in a full-term infant who becomes deeply jaundiced in the neonatal period as great in the absence of maternal-infant blood group incompatibility as in its presence?

STURGEON: The experience mentioned in my answer to the last question suggests that in the full-term infant repeat exchange transfusions aimed at keeping the serum bilirubin concentration below 20 mg. during the first 72 hours is adequate to prevent classical kernicterus, and that after the age of 72 hours, exchange transfusions are not necessary. This experience, however, does not include a large number of term infants with exceedingly high bilirubin concentrations, (30-35 mg. per cent). Thus, the 72 hour limit may not be applicable under such circumstances. The analysis of our current results also encompasses 25 premature infants. Eleven of these died in the neonatal period; four had kernicterus (staining of the basal ganglia at postmortem examination) and the remaining seven apparently died from other causes. Two of the four who died with kernicterus had maximum bilirubin concentrations of approximately 12 mg.; in the other two the values were in the range of 22-25/mg. In the 14 survivors there is one case of kernicterus; the peak bilirubin reached in that case was 28 mg. in the first day of life, and despite three exchange transfusions it remained over 20 for the first four days. In the 13 normal surviving premature, seven had bilirubin concentrations exceeding 20 mg., often despite repeated transfusions. Our experience indicates it will be far more difficult to define levels of bilirubin below which the premature infant is safe, and ages after which hyperbilirubinemia is no longer dangerous. Available evidence and our experience indicate that the danger of kernicterus is present, irrespective of the etiology of the hyperbilirubinemia.

BOGG: The question as to at what age it is no longer of benefit or is unnecessary to perform an exchange transfusion in the face of hyperbilirubinemia is most difficult to answer. Undoubtedly the safest attitude is to recommend performing exchange transfusions to maintain the total serum bilirubin below 20 mg. per cent until such time as it declines and remains below this level without benefit of transfusion. Rarely will the bilirubin concentration stay above 20 mg.
per cent in the full-term infant after the seventh day of life. We have seen
the characteristic clinical picture of kernicterus develop in a full-term infant
on the sixth day of life. The same approach is applicable to the premature
infant, providing it is appreciated that in premature infants higher levels of
bilirubin will persist to a later age in days, counted from the day of birth.
We would perform an exchange transfusion on a premature infant on the
eighth day of life, if the total serum bilirubin concentration was 18 mg. per
cent or higher. The antigen-antibody reaction involved in hemolytic disease
of the newborn does not seem to play a direct etiological role in the develop-
ment of kernicterus. We are just as concerned about an excessively jaundiced
infant developing kernicterus in the absence of a maternal-infant blood group
incompatibility as in its presence. However, experience has shown that the
erthroblastotic infant is more prone to escape control than one who does not
suffer a blood group incompatibility, and we are, therefore, more likely to
perform exchange transfusion earlier in hemolytic disease.

DIAMOND: If the statement that excessive serum bilirubin level may result
in kernicterus even in older infants is correct, and we believe it is, there is
no age at which it is no longer necessary to perform an exchange transfusion
in the face of an excessive indirect serum bilirubin level. It is only because
the full-term infant tends to develop a functioning liver somewhat earlier,
that is by the third or fourth day, or occasionally no later than the fifth or sixth
day, that exchange transfusion is much less common after the third day in
the full-term infant. On the other hand, prematurely born infants may continue
to have a lack of the enzyme for conversion of bilirubin to the bilirubin
glucuronide for a week or even more. This makes it necessary to perform
exchange transfusion in premature infants over a longer period of time. The
cause of the hyperbilirubinemia, whether it be maternal-fetal blood group
incompatibility or any other mechanism is not as important as the level of
the bilirubin which develops. There is another way of interpreting this ques-
tion, however. In general, one is better prepared for the erythroblastosis
fetalis, and thus the risk faced by the jaundiced baby without erythroblastosis
may actually be greater, but only because that risk is less likely to be
recognized by the doctor.

DAY: The efficacy of exchange transfusion has become recognized, and it is
no longer permissible to withhold this procedure from the infant with hemo-
lytic disease. For this reason, it seems that we can never perform the study
necessary to compare the danger of jaundice from this source with the danger
from physiologic jaundice. The alleged protection which a few days of
“maturation” can afford is also hard to assess, because the bilirubin levels
usually begin to fall by themselves after four to six days in the case of term
infants, thus reducing the number of patients upon whom one might make
observations. The infants described by Crigler and Najjar, who developed
kernicterus as a result of an inherited form of jaundice, were free of neurologic
signs during the first week of life. A few days of maturation did not protect
them. The patient described by Rosenthal who developed kernicterus at three
years of age is also pertinent. Premature infants, whose peak bilirubin levels occur later than in the case of term infants, also develop kernicterus later. It seems like skating on thin ice to assume that term infants are protected at five or six days of age against levels of bilirubin known to be dangerous at two or three days.

CHOWN: In the full-term infant no exchange transfusion is necessary after the age of five days; in the premature, after the age of 10 days. Kernicterus in a full-term infant is almost unknown apart from erythroblastosis.

ZUELZER: I do not know of any valid data which would permit a categorical answer to this question. The experience with the Crigler-Najjar syndrome as well as experimental data on the Gunn strain rats show that sustained bilirubinemia can lead to kernicterus even past the first week of life. Also, we are ignorant of some of the factors which must influence the susceptibility, notably the blood-brain barrier. Moreover, when the question whether to perform an exchange transfusion in a six or eight day old full-term infant arises, one of two situations is likely to exist. One may be dealing with an infant who is known to have sustained an unusually severe hyperbilirubinemia and several attempts will already have been made, in all probability, to keep the bilirubin level down by exchange transfusion. The risk to such infants may still be considerable because of the sustained bilirubinemia. The other situation frequently encountered is when one is confronted for the first time by a patient already about a week old, more or less deeply jaundiced, whose previous bilirubin levels are unknown. Again it is likely that such patients have had prolonged hyperbilirubinemia. In either case a level well above 20, say from 25 on up would be regarded by us as an indication for exchange transfusion. With lower levels, a period of observation would be indicated so as to determine the direction of bilirubin level. In the premature infant the question is more readily answered because we regard the premature as definitely more susceptible to the risk inherent in hyperbilirubinemia than the full-term infant. Moreover, there are ample data to show that the peak mortality with and from kernicterus in prematures not affected by hemolytic disease lies between seven and 10 days, this peak incidence correlating well with the development of a peak bilirubin level. For these reasons we do not set a time limit on exchange transfusions for premature infants with hyperbilirubinemia. It is my impression that in the absence of not only hemolytic anemia or major illness, hyperbilirubinemia in a full-term infant, level for level, is less likely to lead to kernicterus. However, as it is phrased “in the deeply jaundiced” infant, the question would be academic, since we regard the existence of a high bilirubin level as the basic risk in the genesis of kernicterus, regardless of cause. We are more liberal in following infants without hemolytic disease (or other forms of hemolytic anemia) for longer periods of time, because the expectation that their bilirubin level will rise to the same height, or the chance that it will rise as rapidly, is less than in infants with hemolytic disease. The aim of early exchange transfusion is to remove bilirubin before a large amount of it can accumulate in the tissue reservoir, and of course the
removal of red cells susceptible to hemolysis. This being the case, the indications in the absence of hemolytic disease are less strict with respect to timing.

EDITOR: The majority seems to support the view that no time limit in days can be set beyond which hyperbilirubinemia is no longer dangerous in the full-term infant. In the premature infant it is even more difficult to define a time limit. The height of the level and type of the bilirubinemia is thought to be the important variable in both groups of infants, and not the mechanism itself of the jaundice.

One reason why exchange transfusions have not been used as widely as they should, even by those skilled in the procedure, is the fear of adding a serious burden to an already feeble infant. What are the principal contraindications to the performance of an exchange transfusion in the face of excessive levels of serum bilirubin?

ZUELZER: Infants in actual or impending cardiac failure due to severe anemia are not subjected to a regular exchange transfusion until a preliminary “circulatory exchange” with packed red cells has restored the child’s general condition. If the child’s condition is so poor that he cannot withstand the procedure, that is an obvious contraindication, regardless of the nature of the child’s illness. The size of a premature has not been a limiting factor, though it influences the volume exchanged.

CHOWN: Besides the contraindications that we already named, we keep in mind: 1) the operative risk: in expert hands, 1 per cent, in inexpert, not less than 5 per cent; 2) if after one replacement transfusion the projected bilirubin curve indicates a maximum likely to be little more than 20; 3) unquestionable evidence of kernicterus.

DAY: There are no contraindications to exchange transfusion if the levels of bilirubin are in the surely dangerous range. When there are pulmonary or cardiac complications, the procedure must be performed in such a way that hemodynamics are not disturbed. Wheeler and Ambuel discuss this problem in a recent issue of Pediatric Clinics of North America.

DIAMOND: There are no real contraindications to the performance of exchange transfusion in the face of excessive levels of indirect bilirubin. Occasionally it is best to do this cautiously if the baby is very sick or feeble, and possibly limit the amount of the exchange to half of the desired volume, repeating it more frequently in order to avoid shock or damage to the infant from too prolonged an operation.

STURGEON: We consider exchange transfusion to be at least temporarily contraindicated, despite excessive bilirubin concentrations, if during the procedure, pronounced and progressive signs of intolerance are noted. The great majority of our repeat exchange transfusions are done at 24 hour intervals. Occasionally, however, two may be done within a 24 hour period. We have not exceeded four exchange transfusions in any case. The usual amount of blood used varies from 60-80 ml. per pound.
BOGGS: We have been amazed as to how well an exchange transfusion is tolerated by even the most critically ill of infants. Hydropic babies will frequently show marked improvement through the judicious use of exchange transfusion. We have performed five exchange transfusions on a 900 gram infant who died five days following the last exchange transfusion. We believe that the contraindications to exchange transfusion when performed by experienced individuals are practically nil.

EDITOR: It seems almost unanimous that, when skillfully performed, there are virtually no contraindications to exchange transfusions in the face of excessive hyperbilirubinemia in the newborn. In feeble infants the transfusion should be performed more cautiously and stopped or postponed if signs of intolerance develop.

The jaundiced premature infant presents problems over and above those of the full-term infant. Why is the premature infant more likely to develop kernicterus with a given level of serum bilirubin during the neonatal period than the full-term infant? What is the maximum level of serum bilirubin which may be considered safe for the premature infant, as far as the development of kernicterus is concerned?

BOGGS: It seems that the premature infant is more vulnerable to hyperbilirubinemia and is more likely to develop kernicterus with a given level of serum bilirubin than the full-term infant. The reason for this is as yet unknown. It is our policy to perform exchange transfusions as necessary, to maintain the total serum bilirubin below 18 mg. per cent during the first eight days of life, in the premature infant.

DAY: The favorite explanation for the susceptibility of premature infants to kernicterus is that their blood-brain barrier is less effective. The passage of protein into spinal fluid is perhaps similar to the passage into the brain, though this is not known for sure. That the blood-brain barrier is a real thing, and that it matures, seems well established by the work of many. There are, however, other possible explanations. For example, the premature infant is more prone to acidosis and to hypoxia. He also may have a lower serum protein level. The fact is that the subject needs a lot of research. As to dangerous levels, here again we lack evidence. For one thing, there is a deficiency of standard calibrations of bilirubin methods. For another, follow-up studies have been insufficiently detailed to distinguish residual effects of bilirubinemia from other hazards of prematurity. We also lack good studies of the hazards of exchange transfusion in premature infants of different birth weights.

STURGEON: Our experience is in agreement with the impression that the premature infant is more prone to develop classical kernicterus than the term infant, and at lower concentrations of bilirubin. We have no information as to why this should be the case.

DIAMOND: There is no proof that the premature infant is more likely to develop kernicterus with a given level of serum bilirubin than the full-term in-
fant, but clinical impressions of this sort exist. It may be that other factors such as anoxia in the immature infant contribute to the danger of hyperbilirubinemia, or the nerve cells may be more susceptible. Further work in this area is very much needed.

CHOWN: Rigid proof is lacking that this is true for prematurity in itself. Among the factors which have been proven to contribute to kernicterus are, 1) erythroblastosis, 2) Gantrisin, 3) Synkavit (synthetic vitamin K) in high dosage. Infection and dehydration are thought to be almost certain contributory factors and among the likely ones is "inefficiency in the oxidative mechanism." We have not yet transfused for hyperbilirubinemia of prematurity alone. In premature infants with erythroblastosis, 18 to 20 mg. per cent is the maximum bilirubin level which we consider safe.

ZUELZER: The answer to the first part of this question must be speculative. The factors which seem likely to us to predispose the premature infant are: 1.) The amount of adipose tissue which can act as a reservoir or competitor for extravascular bilirubin. 2.) The state of development of the blood-brain barrier. 3.) The availability of serum albumin. 4.) The possibility of special susceptibility of the premature brain. 5.) Until now, the likelihood that the premature will be subjected to possibly harmful iatrogenic effects, particularly drugs capable of leading to hyperbilirubinemia or enhancing its toxic effects. These factors, of course, exist in addition to the now well documented predisposition of the premature infant toward the development of a high bilirubin level because of the incomplete development of its enzyme systems. It is particularly in prematures that time and again kernicterus has been found in the presence of maximum bilirubin levels well below 20 mg., and it appears that the premature infant is especially susceptible to the toxic effect of bilirubin.

EDITOR: It seems that most of the members of the discussion group agree: a) that a clinical impression exists that the premature infant is more likely to develop kernicterus with a given level of serum bilirubin than the full-term infant; b) that no convincing proof of this impression is available; c) that the causes given for this greater susceptibility are speculative, and d) that lower levels of serum bilirubin must be used as a guide for exchange transfusions in the premature than in the full-term infant.