ABNORMAL HEMOGLOBINS

FATAL HEMOLYTIC ANEMIA PRESUMABLY DUE TO THE COMBINATION OF SICKLE CELL AND THALASSAEMIA GENE. S. K. Nall, B. V. Kothuri, C. L. Jhaveri, P. K. Sukumaran and L. D. Sanghvi. From the Balabhai Nanavati Hospital and Human Variation Unit, Indian Cancer Research Center, Bombay, India. Indian J. NI. Sc. 71:244-249, 1957.

Severe hemolytic anemia in a Gujarati Hindu woman was associated with filamentous type of sickling. The electrophoretogram was indistinguishable from that of sickle cell anemia and the alkali resistant fraction measured 6%.—J. B. C.


Hemoglobins C and S are found with high frequency in Ghana. The S gene is being eliminated from the population by individuals suffering from sickle-cell anemia, sickle-cell hemoglobin C disease, microcytosis-like disease and perhaps in certain instances by bearers of the sickle-cell trait. Nevertheless a high incidence of this gene remains and there is evidence that this is because it protects the bearer against the lethal effects of P. falciparum malaria. The gene responsible for hemoglobin C is being eliminated to a much less extent by individuals suffering from pure hemoglobin C disease and sickle-cell hemoglobin C disease.

In a previous investigation it was found that in Southern Ghana the sickle-cell trait appeared to protect the bearer partially against P. falciparum malaria in all age groups, whereas no protection over the age of 1 year was noted by sicklers in the north. This lack of protection in the north was thought to be due to the intense malarial transmission there, the immunity rapidly acquired in the surviving nonsickler balancing the protection afforded by the trait plus the acquired immunity in the sickler. Another possibility was that hemoglobin C in the north protected against P. falciparum malaria. However in this investigation now carried out a 1040 Dagombas in Northern Ghana, there was evidence of partial protection by hemoglobin S but not by hemoglobin C.—R. H. G.


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A survey was made of 3,362 adults of the Baganda tribe, paper electrophoresis being done on the 545 of these sera that were demonstrated by the E. coli method to show sickling. There were three cases of sickle cell anemia and it is calculated that this represents a 14% survival to adult life, since it can be calculated from a sickling rate of 16.2% that this population at birth should have included 22 cases of sickle cell anemia.—R. H. G.

HEPATIC LESIONS IN SICKLE CELL ANEMIA. Y. S. Song. From the Division of Pathology and Microbiology, University of Tennessee, Memphis, Tenn. J. Path. 33:331–351, 1957.

The lesions of the liver in sickle cell disease appear to be related to various mechanisms: (1) long-standing severe anemia, (2) a prolonged hemolytic process with increased excretion of bilirubin and deposition of pigment, (3) repeated blood transfusions which might lead to exogenous hemochromatosis, (4) stagnation of sickled red blood cells in the sinusoids with sinusoidal obstruction, (5) vascular occlusion by agglutinative thrombi. Morphologic evidence of hepatic cell damage was noted in each of the 31 cases at necropsy. Cirrhosis was found in 9 of these cases. The cirrhosis which was of a macronodular or a postnecrotic type seemed to be a unique manifestation of fatal sickle cell disease.—O. P. J.


It has been shown previously that zinc acetate or sodium cyanide solution will, if added to blood, prevent the occurrence of sickling, and suggested that these substances remove carbonic anhydrase which may be necessary for sickling. This led the author to test the effect of the nontoxic carbonic-anhydrase inhibitor acetazolamide on the blood of an 8-month-old Negro baby with sickle cell disease. In sealed preparations acetazolamide caused a significant decrease in the number of sickle cells, and appeared to do so by preventing oxygen loss from the hemoglobin of the erythrocytes.

A single dose of 7 mg. of acetazolamide per Kg. body weight was then given orally and it has a pronounced inhibiting effect on sickling in vitro, particularly at 1 hour and 5 hours after administration of the drug, but less so at 3 hours and 6 hours. These results were also obtained with 2 mg. per kilo of body weight.

Venous blood was injected into formal saline solution under oil to fix the red cells in their circulating shape, and here the number of sickle cells was significantly smaller after a dose of 7 mg. per kilo than after 2 mg. per kilo, and there was an increase in sickle cells when the drug was withdrawn.

The patient was treated with acetazolamide for 29 days and there was a steady rise in the hemoglobin level. No toxic effects occurred.

When hemoglobin becomes reduced the globin molecule gains on H ion in the carboxyl group. This H ion is derived from the H₂CO₃ which carbonic anhydrase helps to form within the red cell. Therefore interference with carbonic anhydrase activity retards the reduction of hemoglobin. The inhibition of carbonic anhydrase lowers the plasma CO₂ tension and retards also the dissociation of O₂ from hemoglobin. Since the occurrence of sickling depends upon the presence in erythrocytes of reduced hemoglobin, a carbonic anhydrase inhibitor would tend to suppress sickle cell formation.—R. H. G.


In sixty normal subjects and 114 healthy thalassemic subjects the alkali-resistant hemoglobin was studied. In normals the values varied between 0.41% and 1.60% (mean value 0.33%). In healthy thalassemic subjects, alkali-resistant hemoglobin varied between 0.45% and 0.49% (mean value 0.53%). In 28.07% of the healthy thalassemic subjects, the values were above the normal range.—P. d. N.
ANEMIA OF THE NEWBORN


Blood of poor Indian mothers and their newborn was examined for plasma protein, serum calcium, blood cholesterol, and hematological indices. Apart from low albumin concentration, the other inadequacies in maternal blood resulting from malnutrition were not reflected in the blood of the newborn.—J. B. C.

THE ANEMIAS OF EARLY INFANCY AND HYPOTHYROIDISM. A PROPOSED RELATIONSHIP DUE TO AN ADJUSTMENT OF THE HEMOGLOBIN LEVEL TO THE LOW OXYGEN CONSUMPTION. M. Seip. From the Children’s Department, University Hospital, Oslo, Norway. Acta med. Scandinav. 157:77-83, 1957.

The “basic” oxygen consumption in early infancy is (in relation to the body surface) of the same order of magnitude as in adult patients with severe hypothyroidism. The hemoglobin level also stabilizes at roughly the same values in the two conditions, and at a lower level in premature infants with their lower oxygen consumption than in full term infants. The theory is advanced that the physiological anemia of early infancy and the “true” anemia of hypothyroidism have a similar etiologic mechanism, and are due to an adjustment to the low oxygen consumption.—M. S.


The thromboplastin generation test was used to evaluate the coagulation status in 51 full-term and 31 premature infants during the neonatal period. Rather striking abnormalities were encountered in most instances. These were corrected by vitamin K in the full term infants. The premature failed to respond. PTC deficiency was encountered frequently and was fairly proportional to prothrombin activity as measured by the Quick prothrombin time. PTC defects were corrected by administration of vitamin K in the full-term subjects but only rarely in the premature. The evidence obtained in this study demonstrates that premature are unable to utilize vitamin K and that a variety of hemostatic handicaps are normally present in these small infants as well as in full-term babies. The significance of these hemostatic alterations as being responsible for clinically manifest bleeding phenomenon remains obscure.—N. J. S.


The possibility that anemia in the newborn period may be due to fetal hemorrhage into the maternal circulation is emphasized by the clinical experience recorded here. The author has observed 7 infants in which anemia due to fetal blood loss has occurred. One patient and mother have been studied in detail with fetal erythrocytes demonstrated in the maternal circulation shortly after delivery. Serologic technics were used. The fetal erythrocytes disappeared from the maternal circulation in 80 days. At 80 days antibodies to D appeared in the circulation of the mother (cde/cde) in response to the fetal transfusion (Infants erythrocytes CDE/cde). Anti E antibodies appeared at approximately 100 days. The occurrence of anemia in the immediate newborn period in the absence of hemolysis or bone marrow failure should alert one to the possibility of fetal hemorrhage into the maternal circulation.—N. J. S.

An additional incident of transplacental fetal bleeding is recorded in which an infant, when delivered, showed evidences of posthemorrhagic shock. Recovery occurred following repeated transfusion. The mother had increased levels of fetal hemoglobin and bilirubin in her circulation shortly after birth. Histologic studies of the placenta demonstrated large numbers of fetal nucleated erythrocytes. No other abnormalities were noted in the study of the placenta.—N. J. S.


The occurrence of severe anemia in the first few weeks of life is reported as a manifestation of hereditary spherocytosis. The case study is of interest in emphasizing two aspects of this condition often not appreciated: 1. the relatively common occurrence of serious hemolytic aregenerative crises in the immediate neonatal period in this disease is discussed. 2. the patient described here developed pneumococcal meningitis 2 months following splenectomy. Pediatricians are becoming aware of increased susceptibility to severe and often fatal infections of infants and children following removal of the spleen.—N. J. S.


The problem of immediate neonatal manifestations of hereditary spherocytosis is discussed, and 5 personally observed patients are presented. Retrospective analyses of 43 additional patients with the disease seen in their clinic revealed unusual icterus during the first few days of life in 23.

In each of the patients seen in the first days of life exchange transfusion was used to prevent kernicterus by keeping the bilirubin at acceptable levels. Splenectomy was not performed because of the risk of overwhelming sepsis in splenectomized infants and children. The authors choose to observe the infants for evidence of anemia and inadequately compensated hemolytic activity.

It is appropriately emphasized that the offspring of a parent with hereditary spherocytosis should be observed carefully in the newborn period for evidence of abnormal icterus in a manner in which the infant of sensitized Rh-negative mother is regarded.—N. J. S.


After briefly mentioning several of the possible causes of acute hemolytic anemia in the first few days of life the author reports his experience with an 11-day-old patient admitted to the hospital with severe hemolytic anemia. The disease had developed suddenly after the baby had been dressed in clothing stored in mothballs and not washed. The naphthalene in the mothballs was felt responsible for the hemolysis. Supportive therapy was successful. The experience of others with this disease is reviewed.—N. J. S.

In 1935–41, serologic tests for hemolytic disease were not available, and the English records therefore show a low incidence. From 1942 the number of deaths from it shows the steady rise to 0.8 per 1000 live births in 1945–51. In 1952 a definite decrease in mortality is first recorded, and it was in 1952 that exchange transfusion was first widely used in England. However in 1953 the mortality was still 0.6 per 1000 live births, three times the rate to be expected if all severely affected infants were being satisfactorily treated by exchange transfusion.

The clinical records of all infants certified as dying from hemolytic disease of the newborn in England and Wales in 1953 and 1955 were examined. In each year about 400 infants were so certified, but the true number was about 310 each year. Factors contributing to the deaths were failure to predict the disease antenatally, failure to recognize any clinical evidence of the disease, and failure to give adequate exchange transfusion. Many hospitals treat such cases and the number of cases seen is often small so that the staff is not experienced. If all cases of hemolytic disease were predicted antenatally and treated when necessary by early adequate exchange transfusion, each year in England and Wales, more than 150 infants would be saved.—R. H. G.

Induction of Labour to Prevent Recurrent Stillbirth Due to Haemolytic Disease.

Induction of labor at 35 weeks was considered in 102 families with a previous stillbirth that had been attributed to hemolytic disease. Of these 60 were selected for induction because the preceding stillbirth was undoubtedly due to hemolytic disease and the father was homozygous D/D. Of the 60, 25 reached 35 weeks with a living fetus, not hydropic, and labor was induced in these 25: the result was that 23 babies were liveborn. All were severely affected by hemolytic disease, but with exchange transfusion, 18 survived. Exchange transfusion must be done promptly and some premature babies tolerate it badly, so that it may have to be done in two stages each taking half an hour with an interval of half to one hour between.—R. H. G.


There has been divergence of view as to whether premature induction of labor should be employed in addition to exchange transfusion in hemolytic disease of the newborn. Here the results of 143 pregnancies with rhesus incompatibility are considered. The patients were admitted either to one unit in which spontaneously delivery was preferred, or to another where selective induction of labor was carried out, exchange transfusion being given where indicated. In the induced group (76 cases) the mortality was 16%, while in the 63 cases with spontaneous labor it was 29%. The severity of the disease was probably greater in the induced group, 68 exchange transfusions being given as compared with 29 in the other group. Selective premature induction of labor is considered to reduce the total mortality from hemolytic disease of the newborn.—R. H. G.

The Importance of Quantitative Determination of Direct and Indirect Bilirubin in Haemolytic Disease of the Newborn. V. Jirsovi, M. Jirsa and M. Janovský. From the Institute for Mother and Child, and the First Medical Clinic, Charles University, Prague. Čsl. pediatrie 12:910, 1957.

On the basis of new knowledge concerning the properties of bilirubin a quantitative estimation of direct and indirect bilirubin in the serum of newborns suffering from hemo-
lytic disease should be regularly carried out. From the viewpoint of bilirubin metabolism, the hemolytic disease of the newborn can be divided into two forms: a milder one, where the primary deficiency lies in the disturbed conjugation of bilirubin with glucuronic acid, and a second form, where the excretion of the direct bilirubin into the bile ducts is simultaneously disturbed. Conclusions are presented concerning treatment of this form, necessitating a supportive therapy of the liver parenchyma; first experiences with the use of dithiocaprylic acid in the treatment of this form of hemolytic disease of the newborn proved to be successful.—M. N.


The authors questioned the value of blood collected in a conventional manner in acid-citrate-dextrose solution ("whole blood") compared with sedimented erythrocytes in exchange transfusion treatment of erythroblastosis fetalis. Sedimented erythrocytes as used in this study refers to whole blood from which about only 125 ml. of the plasma and diluent have been removed.

Two groups of infants with erythroblastosis were treated. Twenty-three received whole blood and 24 infants the more concentrated erythrocytes. The infants were carefully studied. Blood and plasma volume determinations, bilirubin levels as well as more conventional hematologic techniques were used.

The authors conclude that the more concentrated erythrocyte transfusion results in increases in the total hemoglobin mass without increasing the plasma volume. This does not result when more dilute whole blood is used. The necessity for repeat transfusions is lessened. The increase in concentration of bilirubin was lower and less rapid in the group receiving more concentrated erythrocytes.

It is important to note in this study that the volume used in the exchange was equal in both groups and that only 125 cc. of plasma and diluent were removed from the unit of blood in concentrating the cells. This study was not designed to evaluate the procedure advocated by some workers of using smaller volumes of much more highly concentrated erythrocytes in exchange transfusion. The use of the terms sedimented erythrocytes here could prove to be somewhat misleading.—N. J. S.

DRUG REACTIONS


Thirty patients were treated with nitrogen mustard at the dose of 3 mg. every two days up to the total dose of 27 mg. Recalcification time, prothrombin time, factor V, factor VII, fibrinogen, platelet count and thromboplastic activity in isolated platelets, were performed. A prolongation of the recalcification and prothrombin time represented the most significant pattern, while slight modifications of other factors were observed under the studied conditions.—P. d. N.


In twenty diabetic patients the variations of erythrocytes, leukocytes and blood coagulation (prothrombin and recalcification time) were studied during the administration of the new oral antidiabetic, D 860. No significant modifications of the blood cells were detected,
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while a slight tendency to the hypocoagulability could be observed. This latter finding can be considered as a favorable effect in connection with the treatment of senile patients.

—P. d. N.


LEUKEMIA


In a group of 63 patients with acute leukemia, the authors observed a total of 29 episodes of neurologic complications. These 29 episodes occurred in 24 of the patients: 22 of the 24 patients had died by the time the study was completed. The occurrence of neurologic complications was not related to the type of acute leukemia, to age, or to sex. The most common manifestation, and at the same time the most severe, was intracranial hemorrhage, which was noted 13 times in 12 patients, and was the cause of death in 10 cases. Infection (meningitis) occurred only once. Manifestations attributable to leukemic infiltration were seen 11 times, of which 8 were intracranial, and 3 involved peripheral nerves. The remaining 4 episodes appeared unrelated to the leukemia itself (hepatic coma; steroid psychosis; unexplained psychosis). Of interest was the finding that these neurologic manifestations might improve with antileukemic therapy, sometimes even in the absence of hematologic improvement.—S. E.

VITAMIN B₁₂


Though most of the vitamin B₁₂ in crude liver extracts is bound, it is not bound to protein as such, because the active vitamin can diffuse through cellophane. This seems to
indicate that, in the antipernicious anemia principle, the vitamin is bound to a molecule of fairly low weight—for example, a peptide. Almost all forms of vitamin B₁₂ available as food are bound to proteins of high molecular weight, and are thus nondiffusible through cellophane and nonassimilable by microorganisms. This suggested to the authors that a simple proteolysis may take place in the stomach, in which the “bound” protein attached to the vitamin is degraded into a peptide. In this “free” form it could then be simply absorbed by diffusion through the gut wall. The inconsistencies in the action of intrinsic factor preparations could be accounted for by variation in the molecular size of the bound protein component in such mixtures. Hence vitamin B₁₂, when bound to material of high molecular weight does not show activity when given orally to patients with pernicious anemia.

An active vitamin B₁₂ peptide complex was derived from fermentation of a Streptomyces mutant under standard conditions. The cobalamin peptide was released from the protein complexes within the cells and concentrated and purified by a series of steps involving ion exchange chromatography, countercurrent solvent extraction, activated-carbon treatment and ammonium-sulphate precipitation. The ratio of peptide to vitamin B₁₂ on a weight basis was 6.8:1 and, assuming a 1:1 molecular ratio of vitamin to peptide, the molecular weight of the complex would be about 10,000. The true figure was probably less as the complex was dialyzable and ultrafiltrable through cellophane and collodion membranes.

In cultures of megaloblastic marrow in 80 per cent homologous serum, maturation took place about as rapidly in the presence of vitamin B₁₂ peptide as with folic acid at 18 hours.

Six untreated cases of pernicious anemia were given vitamin B₁₂ peptide alone orally. The total dosage in the first three weeks did not exceed in any case, 1,500 µg. of vitamin B₁₂, the type of dosage being 100 µg. of vitamin B₁₂ (780 µg. of the vitamin B₁₂ peptide complex) daily for 8 days and half that amount for 14 more days. For maintenance various dosages were used, but 10 µg. of vitamin B₁₂ daily as the complex appeared to be satisfactory.

The authors believe that the defect in pernicious anemia is failure of simple proteolysis in the stomach. Normally vitamin B₁₂ occurs in nature as a complex containing a protein of high molecular weight, and in the stomach it is converted into a complex containing a peptide of low molecular weight that is dialyzable and assimilable by microorganisms. There is no need to postulate an intrinsic factor.—R. H. G.