THE Rh FACTOR


The major pathologic lesions in 20 newborn infants with hemolytic disease are described in considerable detail. The majority of the lesions appear to be directly related to and secondary to hemolysis of red cells. The lesions in icteric infants, hydropic infants and those without external evidence of disease are similar and differ essentially only in degree, depending on the duration and intensity of action of the maternal antibody on the infant's tissue. Icterus of many tissues, including the brain, was prominent. Compensatory hemopoiesis occurred in almost all organs and included the production of granulocytes and megakaryocytes. Severe injury to the hepatic parenchyma may occur due to large masses of proliferating blood cells displacing and compressing the cord of hepatic cells. This may produce obstructive icterus. In addition to these lesions, abnormalities of the thyroid gland, adrenal gland and pancreas are consistently seen. Their relation to the disease is not established.—R.B.C.


This study was undertaken in an effort to determine whether the birth of an Rh-negative baby could be predicted antepartum in a sensitized Rh-negative woman, and whether the women in the sample under consideration exhibited any special characteristics in common. Thirty instances of normal Rh-negative infants born to sensitized Rh-negative mothers were studied. Small amounts of Rh antibodies occurring inconsistently in antepartum tests were regarded as nonspecific and of no consequence. Appreciable amounts of Rh antibodies were consistently present in 17 Rh-negative women who later bore Rh-negative infants. The titer increased in intensity in 7 and remained constant in 10. When Rh antibodies were constantly present, there was evidence of a high degree of Rh immunization. The only basis for the prediction of an Rh-negative infant to be born to a sensitized Rh-negative woman is first, the determination of the Rh status of the husband, and second, the trend of the antepartum Rh antibody titer. If the husband is heterozygous (RhRr) and the titer remains constant, the baby will likely be Rh negative.—R.B.C.


It is of considerable importance that antenatal methods of predicting the occurrence of
hemolytic disease of the newborn be devised. It is obvious that a history of sensitization of the mother by transfusion of Rh positive blood or by the birth of a child afflicted with hemolytic disease is of value in predicting the outcome of subsequent pregnancies. Such a history is not always available. In such a situation the authors have found that the routine testing for Rh sensitization, throughout every Rh-incompatible pregnancy, is of definite value in the antenatal prediction of hemolytic disease of the newborn. Five factors should be taken into consideration: (1) the presence of "blocking" antibodies, (2) a significant quantity of antibody, (3) their existence for more than ten weeks before delivery, (4) their presence on every successive test and (5) the presence of ABO compatibility between mother and baby. When all five factors were "positive," only 2 out of 28 Rh-positive babies escaped hemolytic disease. If one factor was "negative," 28 out of 30 babies escaped the disease, and if two factors were missing, all babies were healthy.—R.B.C.

ATTEMPTS AT DESENSITIZATION OF WOMEN IMMUNIZED BY THE RH FACTOR. I. THE USE OF ETHYLENE DISULFONATE. W. C. Moloney. From the Rh Laboratory, Boston City Hospital and the Department of Medicine, Tufts Medical School, Boston, Mass. Am. J. Obst. & Gynec. 60: 616-625, 1950.

Hemolytic disease due to iso-immunization by the Rh factor occurs in about 0.66 per cent of newborn infants. With the use of transfusion therapy, especially of the exchange type with female donors, more than 90 per cent of infants born alive with hemolytic disease are saved. This therapy is not always successful, however, and there also remains the question whether exchange transfusion modifies or prevents kernicterus which may occur in from 10 to 15 per cent of infants with hemolytic disease of the newborn. Various attempts have been made to prevent the development of hemolytic disease of the newborn. Methods suggested have been the use of pertussis and typhoid vaccine, in the hope that these antigens will "compete" with the Rh antigens for the maternal immune mechanism, the use of ethylene disulfonate and the use of Rh hapten. In the present paper, observations were made on a series of Rh negative pregnant women, iso-immunized to the Rh factor, who were given ethylene disulfonate in 10 cases and distilled water in 2 cases. Of the 10 women treated with ethylene disulfonate, 1 infant survived following exchange transfusion, 3 infants were Rh negative and escaped hemolytic disease and 6 infants failed to survive. The author concludes that ethylene disulfonate exerts no influence on antibody production due to Rh iso-immunization, and that the drug does not prevent hemolytic disease of the newborn.—R.B.C.

THE RESULTS OF TREATMENT WITH RH HAPTEN. E. G. Hamilton and M. B. Brockland. From the Departments of Obstetrics and Gynecology, St. Louis University School of Medicine, St. Louis, Mo. Am. J. Obst. & Gynec. 60: 813-819, 1950.

In view of reports in the literature relating to the use of a substance assumed to be Rh hapten in treating an edematous erythroblastic baby, the present authors decided to use the same substance in the treatment of Rh-sensitized pregnant women. In the dosage used in the study, Rh hapten did not produce a negative Rh antibody titer in pregnant or non-pregnant sensitized Rh-negative women. Treatment carried out during pregnancy did not appear to influence favorably the baby's survival rate.—R. B. C.


The authors attempted to duplicate the work of Carter (Am. J. Clin. Path. 17: 646, 1947; J. Immunol. 61: 79, 1949), who claimed to prepare "Rh hapten" which was clinically useful to reduce the titer of sensitized Rh-negative women. They prepared batches of Rh hapten from lots of Rh-positive cells, and gave injections of the resulting material to several groups of patients.

In 4 nonpregnant women who had been sensitized against the Rh factor by previous pregnancies, there was no increase in the anti-Rh titer, and there even might have been
some tendency for the titer to fall. In 22 pregnant women who had previously been sensitized against the Rh factor, there was usually a slight fall in titer after 1 or 2 injections; the titer then rose to pretreatment levels. Only rarely, however, did the titer subsequently exceed the pretreatment levels. Identical effects on the titer were noted whether the babies of these pregnant women turned out to be Rh positive or Rh negative. Identical results occurred both with the authors' material, and with Rh hapten obtained from 2 other sources.

It was felt that there might indeed be some neutralizing effects of the material, but, if so, the effects were extremely weak. Certainly, there was no demonstrable clinical value under the conditions of these experiments. Thus, of 22 pregnant women treated, 2 gave birth to normal, Rh-negative offspring; 5 gave birth to Rh-positive children who survived (but 3 had favorable histories); and in the other 15, the offspring died in utero, at birth or after birth. The good outcomes, it was felt, could be explained as well because of the natural variability of the disease, as because of any effects of hapten.

The conclusions were reached that this material was of no clinical value in altering fetal prognosis in Rh sensitized women, and that hapten therapy should not be held out as a hope for such women.—S. E.

**BLOOD COAGULATION and HEMORRHAGIC DISEASE**


Evidence is presented which indicates that calcium is not essential for the coagulation of blood, and that the anticoagulant activity of oxalate and citrate can be explained as due to their ionic charge. Calcium-free plasma is said to have clotted on fivefold dilution, but not in the presence of fluoride or citrate ions. It is stated that these results indicate that it is "rather the presence of these ions than the absence of calcium which prevents blood containing them from clotting."—T.R.T.,Jr.


A solution of purified bovine fibrinogen was clotted in silicone tubes by the addition of bovine thrombin. Retraction of undisturbed clots did not occur in the absence of intact blood platelets. The addition of a suspension of washed human platelets to the fibrinogen solution did not cause the clots to retract. However, when a small amount of human serum, bovine albumin, gum acacia or egg white was added, prompt clot retraction occurred. In the presence of serum or an effective substitute, the degree of retraction of clots was related to the concentration of platelets in the preparation. Intact platelets were required, and suspensions of macerated platelets were without effect in promoting clot retraction.

When other factors were constant the degree of retraction was directly related to the platelet concentration. When the platelet concentration was constant, the degree of retraction was inversely proportional to the fibrinogen concentration. Dense fibrin clots required higher concentrations of platelets for retraction than clots formed from more dilute fibrinogen solutions. Clot retraction was somewhat impaired at lowered concentrations of thrombin. The rate and degree of retraction were also influenced by temperature and ionic concentration but pH changes in the physiologic range were without effect.—C.E.R.


Purified prothrombin can be dried from the frozen state without immediate loss of activity. Thereafter, progressive loss of prothrombin activity occurs, characterized by refractivity to the action of calcium plus thromboplastin plus Ac-globulin. In about one year most of the prothrombin is altered and in addition some is insoluble in aqueous solu-
tion. Prothrombin inactivated by the freeze drying technic can be activated autocatalytically in 25 per cent sodium citrate solution. The altered prothrombin has essentially the same electrophoretic pattern as purified prothrombin.—R.B.C.


The production of toxic substances by the placenta has been postulated by various investigators as the cause of the toxemia of pregnancy. Two of the suggested substances have been thromboplastin, which, if present in excess, might produce intravascular clotting, and fibrinolysin, which might produce incoagulable blood. Inhibitors to these substances are present in the blood. A hypothesis is developed whereby with placental anoxia or the withdrawal of hormonal support the above substances are liberated from the placental cells in such an amount that the naturally occurring inhibitors are unable to neutralize them, thereby permitting the blood clotting and fibrinolytic systems to become active. Increased blood coagulation and thrombosis first occurs. Then the fibrinolytic system, which initially may promote clotting, later decreases clotting by destroying fibrinogen. It may produce hemorrhage and cytotoxic effects.

Such a hypothesis suggests that for therapy it is necessary to remove the placenta or neutralize the toxic substances by administration of specific inhibitors for both the coagulant and fibrinolytic systems. The removal of the placenta is a well-documented satisfactory treatment but may necessitate sacrifice of the fetus. Literature on the use of inhibitors is scanty and unsatisfactory. In the present study, the use of heparin to neutralize the coagulant system was ineffective in the therapy of toxemia of pregnancy and the authors conclude that its failure is strong evidence against the thromboplastin theory. They emphasize that the failure of heparin does not test the hypothesis that there is a disturbance of the fibrinolytic system in toxemia of pregnancy. There have been reports in the literature of a coagulation defect in pregnancy in which a marked decrease in fibrinogen was observed and a circulating fibrinolysin demonstrated. This has been observed in premature separation of the placenta. Further work investigating the fibrinolytic phase of toxemias of pregnancy is indicated.—R.B.C.


A defect in the coagulation mechanism may develop following severe premature separation of the placenta. Coagulation studies in 3 patients revealed a decrease in the fibrinogen concentration and prothrombin activity and the presence of a circulating fibrinolysin. In 15 other patients with mild placental separation, these abnormalities were not present. It was observed that when plasma fibrinogen was less than 50 per cent of normal, the initial clot, if incubated at 37 C. will disintegrate within a few minutes. As the blood changes are not always present when the patient is first seen, repeated observations, including incubation of the clot at 37 C. is indicated at frequent intervals. If this defect is observed, replacement therapy with blood and fibrinogen is of primary importance. This is of more significance than the method of delivery to be done.—R.B.C.


One hundred and ten cases of thrombocytopenic purpura are reviewed. The spleen was palpable in only 13 patients and in 12 of these the thrombocytopenia was found to belong to the secondary or symptomatic group. No discussion in detail is presented of the cases without splenomegaly. The authors conclude that the presence of a palpably enlarged spleen
practically rules out the primary type of thrombocytopenic purpura. They also observe that leukopenia (viz. a leukocyte count of less than 6,000) is an almost constant finding in secondary thrombocytopenic purpura.—T.R.T., Jr.

PURPURA FOLLOWING EXPOSURE TO DDT. F. B. Karpinski, Jr. From the Department of Pediatrics, Western Reserve University, and Babies and Childrens Hospital of Cleveland, Ohio. J. Pediat. 37: 373–379, 1950.

Five cases of purpura occurring in children following exposure to DDT mixtures are reported. Many of the symptoms reported to occur in animals suffering from DDT poisoning occurred in these children. These included anorexia, generalized tremors, nervousness, hyperexcitability, impaired coordination and clonic-tonic type convulsions. Purpuric manifestations were extensive and associated with marked thrombocytopenia in 4 of 5 cases. Recovery was prompt with a change in environment and without specific medication. Although evidence was not absolutely conclusive that DDT was the offending agent, the author concluded that DDT appeared to be responsible for the development. With reasonable precautions the toxicity of DDT is of a low order. However, toxic reactions have occurred after DDT exposure including evidences of an effect on the bone marrow. Hence, DDT should be added to the list of substances that may produce purpura.—R.B.C.


The author has demonstrated by means of simple but definitive experiments that clot retraction is dependent upon four factors: the number of platelets, the concentration of thrombin, the surface surrounding the clot and the red cell volume of the blood.

The relationship between clot retraction and thromboembolism is discussed. The serum expressed by retraction of the clot is rich in nascent thrombin, which provides a logical explanation for the propagation of a clot. Platelets adhere to an injured intima, and as these platelets disintegrate, thrombin is formed which produces a fibrin clot attached to the vessel wall. The retraction of the clot then releases more thrombin, which, in a sluggish circulation, creates coagulation of the blood about the primary thrombus. This process is thus self perpetuating.

A further discussion differentiates between these effects as they influence phlebothrombosis and thrombophlebitis, and points out that because clot retraction is rapid in severe anemia, transfusions should be considered to counteract this factor as a preventive measure against thromboembolism.—T.R.T., Jr.


The authors present evidence in support of the hypothesis that "increased histamine blood levels appear to increase directly the qualitative disintegrative ability of the platelets." They also offer data from experiments in dogs, showing a decrease in platelet counts after intravenous infusion of very high concentrations of histamine.

Clinical studies in 80 patients being treated for migraine with histamine showed no change in platelet counts, but there was an average decrease in whole blood coagulation time of 12.6 per cent.—T.R.T., Jr.


The first stage of intravascular thrombosis is, according to the classical theory, the agglutination of thrombocytes. This is enhanced by fibrin or profibrin flocculation around
the platelets. The authors have measured the agglutination by a photoelectric method under various conditions. Histamine, bacterial toxins, cobra and bee toxin accelerate the agglutination also in the presence of anticoagulants preventing the fibrin formation. Photographs of these agglutinated platelets taken with the electron microscope did not show any traces of fibrin or fibrinogen. The authors conclude that the platelet agglutination is a phenomena independent of fibrin formation. The latter is the second stage of thrombus formation and can be prevented by heparin. The first stage of thrombosis is the platelet agglutination based upon local vascular damage and the presence of toxic substances in the plasma.—C.M.


Two new cases are described with the typical findings. The hereditary character of the disease was proved in one patient whose uncle suffered from a clinical picture very similar to hemophilia with hemorrhages in the joints. The other case showed important microscopic capillary abnormalities which indicates the correctness of MacFarlane's opinion; he considers the disease to be primarily a vascular disturbance.—C.M.


The clinical, pathologic and postmortem findings are reported in a patient with congenital afibrinogenæmia dying at the age of 19 with tuberculosis.—S.T.C.


The clinical and hematologic data of 5 patients with purpura hemorrhagica who were followed through seven pregnancies are presented. In addition 39 sufficiently well documented cases of pregnancies complicated by this disease are reviewed. An analysis of the entire group revealed that the maternal mortality was 8.7 per cent, and that of the child, 26.1 per cent. Approximately one-third of the children born dead and one-half of those born living had purpuric manifestations, although it is believed that had sufficient laboratory data been available in all cases, the incidence of congenital thrombocytopenic purpura would have been considerably higher. As far as is known, the disease in the child is self-limited for the hemorrhagic manifestations disappeared, and in most instances platelet counts returned to normal within several months.

Of particular interest is the lack of correlation between the disease in the child and the presence or absence of the spleen in the mother. It is suggested that congenital thrombocytopenic purpura is the result of some substance depressing platelet formation in the infant which is transmitted from the mother across the placental barrier.

Further complete studies of this disease in children, particularly those born of splenectomized mothers in whom the presence of accessory spleens could be fairly well excluded, might well contribute greatly to our understanding of the pathogenesis of idiopathic thrombocytopenic purpura.—H.W.B.


A brief case report is presented of a 49 year old male believed to have Henoch's purpura who had experienced frequent attacks of abdominal pain, vomiting and melena for thirty years and more recently, had episodes of purpuric lesions. The purpura and abdominal symptoms disappeared following the institution of pyribenzamine and had not recurred during the fifteen months he was on maintenance therapy.
Although details of the case are insufficient for full evaluation, the symptomatic relief afforded by the drug in this case probably justifies its trial in similar cases for which there is no specific therapy.—H.W.B.

ACTH: EFFECTS ON HEMATOPOIETIC SYSTEM

ALTERATIONS IN PLASMA PROTEINS, PLASMA VOLUME, AND VOLUME OF PACKED RED CELLS IN PATIENTS RECEIVING ACTH OR CORTISONE. B. V. Jager, H. Brown and M. Nickerson.

From the Department of Medicine, College of Medicine, University of Utah, the Salt Lake County General Hospital, and the Veterans Administration Hospital, Salt Lake City, Utah. J. Lab. & Clin. Med. 37: 431–443, 1951.

The changes in hematocrit, erythrocyte, sedimentation rate, plasma fibrinogen, serum albumin, globulin, gamma globulin and mucoprotein were studied in 19 patients during and after therapy with ACTH or cortisone. Fifteen of these patients had one of the “collagen” diseases. The cases included rheumatoid arthritis (7), lupus erythematosus (5), periarteritis nodosa (1), acute rheumatic fever (1), hepatic cirrhosis (2), acute leukemia (1), multiple myeloma (1) and chronic pyelonephritis (1).

The findings, in general, were: a reduction in plasma fibrinogen, a disappearance of anemia in only 3 patients, an unpredictable and variable change in albumin and mucoprotein, and frequent increases in plasma volume.

The mechanisms by which these changes may be effected are discussed.—T.R.T., Jr.


Three cases are reported, the first a woman with arthritis who was found to have a hemolytic anemia associated with inflammatory changes at the left lung base, a strong autoagglutinin and autohemolysis and positive Kahn test. Coombs’s test was difficult to interpret because of the autoagglutinin and hemolysis. Administration of ACTH was accompanied by a dramatic remission. After treatment was stopped there was some indication of recurrence of hemolysis but this disappeared soon without further treatment. Six months later the blood was normal, no abnormal antibodies could be detected and the Coombs test and Kahn reaction were negative.

The other 2 cases were characteristic of congenital hemolytic anemia apart from absence of family history. In neither did administration of ACTH have any dramatic or lasting effect.—S.T.C.


From the Medical Clinics, Peter Bent Brigham Hospital; Children’s Medical Center and the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine and Pediatrics, Harvard Medical School, Boston, Mass. J. Lab. & Clin. Med. 37: 444–457, 1951.

Three patients with idiopathic acquired hemolytic anemia were studied while receiving therapy with ACTH. In all patients the Coombs titer and the mechanical fragility of the red cells declined toward or to normal. In 1 patient the ability of the serum to agglutinate normal cells at an acid pH disappeared during therapy with ACTH but returned after therapy was discontinued. The authors state that ACTH was useful in preparing 2 patients for splenectomy but that it alone is of only transient value.—T.R.T., Jr.


Studies were made of the eosinophil count, using capillary blood and Hinklemans solution as a diluent. The normal range was found to be between 25 and 300 eosinophils per
cu. mm. Fasting resulted in a drop of 40 per cent in the eosinophils in 23 per cent of the individuals tested. Adrenal cortical extract produced no significant effects.

Adrenalin produced a 50 per cent decrease in eosinophils in only 14 of 25 individuals. This is at variance with results published by others.—T.R.T., Jr.


The results obtained with either ACTH or cortisone therapy in 5 patients with acute lymphatic leukemia (4 children), 3 with chronic lymphatic leukemia and 1 with Hodgkin’s disease are reported with case illustrations. Although only 1 of the group, a child with acute leukemia, failed to show any beneficial response whatsoever, the clinical improvement in the others was extremely variable in degree and duration and at best could be considered of only temporary nature. None of the patients exhibited a complete hematologic remission. The observations in these cases in general parallel those reported by other investigators.—H.W.B.

NEWS AND VIEWS

Foreign Newsletter – Turkey

E. Frank

To the Editor:

Turkey, particularly Anatolia, is a treasure-house for blood diseases. When in 1934 I began my work as professor of medicine here at the reformed University of Istanbul I thought myself a pretty well experienced hematologist but I soon discovered that a hematologist must practice geographical pathology, must study diseases on the spot, not only from descriptions in books.

One of the first facts that struck me was that at the clinic we often saw very severe anemias of the pernicious type which responded very well to liver extracts but had hydrochloric acid in normal or even abundant quantities in the gastric juice. Gradually we realized that the disease, now called nutritional macrocytic anemia in Anglo-Saxon countries, was widespread in Anatolia. At that time this disease was little known, and as the parts of the country were neither tropical nor subtropical, we thought at first it could not be identical with the tropical variety described by Lucy Wills in India. By now we know that without question these anemias here are the same disease; that tropical anemias, for the greater part, have nothing whatsoever to do with the tropics, but that they are caused by specific conditions and habits of nutrition of the natives and that these conditions in Turkey do not differ much from those in India or, according to Snapper’s descriptions, in China.

During the last two years we have naturally been interested in how these anemias react to folic acid and vitamin B12. Although opinions still differ widely, it can not even be considered a certainty that the so-called Wills factor really exists as distinct from the two anti-anemic principles. We have recently established that the statement that nutritional anemias have a megaloblastic bone marrow indistinguishable from that of real pernicious anemia needs to be corrected in two respects: (1) Though the bone marrow is megaloblastic, the proportional share of the nucleated red cells in the elements of the bone marrow does not surpass—as in pernicious anemia—greatly that of the white elements; on the contrary, it