BLOOD TRANSFUSION and BLOOD GROUPS


Among the findings following a near-lethal exposure to radiation are spontaneous bleeding and anemia. Because of the promience of thrombocytopenia and anemia in the abnormal syndrome of irradiation sickness, it was thought that frequent administration of fresh whole blood might be of considerable therapeutic value in the control or prevention of this type of hemorrhage. One hundred and seventy-three dogs were exposed to single doses of x-irradiation at the following dosage levels: 175, 225, 275, 325, 375, and 450 r. The animals were divided into two groups—one served as controls and the other received the transfusions of citrated fresh whole blood three times a week beginning on the fourth postirradiation day.

The following studies were conducted on both groups of animals: (1) the whole blood clotting time; (2) the Quick one-step prothrombin time; (3) the erythrocyte, leukocyte, and thrombocyte counts; and (4) hemoglobin determinations. Transfusions did not increase the survival percentage over that of controls. Gross hemorrhages were found in the tissues at autopsy as frequently in the transfused dogs as in the nontransfused dogs. No significant or consistent drop in prothrombin activity was found in either group of animals. Transfusions also failed to prevent or correct postirradiation thrombocytopenia or leukopenia. In fact, the only benefit derived from the transfusion was a correction of the anemia.

The authors also noted that many of the animals displayed symptoms of transfusion reactions. These reactions had not been found in the nonirradiated dogs.

In summary, frequent administration of fresh blood transfusions in dogs failed to improve the survival or ameliorate spontaneous bleeding after exposure to total body x-irradiation.—R.C.C.

THE BLOOD VOLUME EXPANSION PRODUCED BY GELATIN, SERUM ALBUMIN, AND PLASMA.

G. M. Hyde, N. I. Berlin, R. J. Parsons, and B. Whittington. From the Section on Experimental Medicine, Donner Laboratory, University of California, Berkeley, and Pathology Laboratory, Highland-Alameda County Hospital, Oakland, Calif. Surg., Gynec. & Obst. 96: 657-660, 1952.

Measurements of changes in blood volume were made after infusion of gelatin, serum albumin, and plasma in twenty patients and a comparison drawn with the previously reported data on dextran. Of the various substances, dextran showed the greatest initial rise and maintained the longest effect. The initial rise with gelatin was not quite as great as with dextran. Serum albumin showed an early sharp rise, followed by a fall and
then a progressive rise to the maximal height of dextran. Plasma was the least effective of these plasma volume expanders.—H.W.B.


The suitability for transfusion of blood collected, stored, and infused in a recently developed plastic system was investigated. Thirty-seven blood samples preserved in acid-citrate dextrose solution were stored in the plastic equipment at 4 C. for periods up to twenty-nine days. In vivo survival studies indicated that 70 to 80 per cent of the infused cells of bloods stored as long as twenty-five days retain normal functional capacity after infusion. Corroborating data was obtained in a series of in vitro measurements.—H.W.B.


In view of the conflicting reports regarding the significance of the maternal Rh antibody studies during pregnancy, the authors have re-examined this problem in thirty Rh-negative mothers employing a standardized indirect antiglobulin technic. This technic was felt to give consistently reliable results.

In this series a clear association was found between a high titer immediately prior to delivery and severe hemolytic disease of the newborn. No stillbirths occurred when the maternal antibody was low. Infants affected with icterus gravis were found in pregnancies in which the final maternal titers before delivery were 64 or greater. A terminal rise in maternal titer appeared to be of grave prognostic importance.—C.E.R.


A-specific hemagglutinins have been demonstrated in saline extracts of the seeds of Dolichos biflorus, and these appear to be A, specific. Two hundred samples of A and seventy-five of AB cells from Indians were tested both with a human anti-A, serum and a saline extract of Dolichos biflorus, and it was found that a 1 in 64 dilution of the latter extract would accurately differentiate between the subgroups of A.—R.H.G.


As part of a program of investigation of the hemopoietic system and blood of the cotton rat, the agglutination reactions of the erythrocytes were considered. In order to obtain some information regarding isoagglutination and heteroagglutination the cells of cotton rats were reacted with the plasmas of other cotton rats, with human plasmas, the sera or plasmas of some other vertebrates, and the sera of some invertebrates. The plasmas of the cotton rats were also tested for heteroagglutinin for human erythrocytes. No isohemagglutination was observed in 5 minutes at either 22 to 25 C. or 37 C. Heteroagglutinin for cells of the cotton rat were found in all of the several types of human blood tested. Plasmas of the cotton rats contain heteroagglutinin, for the most part nonspecific, for human blood cells. Absorption of human plasmas with cells of the cotton rat removed the heteroagglutinins for these cells, as well as beta isoagglutinins from human type A blood plasma.—O.P.J.
PARAHEMOPHILIA IN THREE SIBLINGS (Owen's Disease). WITH STUDIES ON CERTAIN PLASMA COMPONENTS AFFECTING PROTHROMBIN CONVERSION. B. Alexander and R. Goldstein. From the Yamin Research Laboratory, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass. Am. J. Med. 13: 255-272, 1952.

This is a beautifully presented analysis of the clotting defect present in three siblings with parahemophilia. The situation afforded an excellent opportunity for the rather numerous and carefully planned laboratory studies which were carried out and which have resulted in a much clearer concept of the relationship between the several plasma components concerned in prothrombin conversion.

In essence this disorder, a form of pseudohypoprothrombinemia, is due to a deficiency of Ac-globulin, essential for the rapid conversion of prothrombin to thrombin by thromboplastin and calcium. From the presented data it appears that Ac-globulin, present in fresh normal whole blood or plasma, is identical with labile factor (Quick), factor V or proaccelerin (Owen) and the factor of Fantl and Nance, and entirely distinct from SPCA (serum prothrombin conversion accelerator) and its plasma precursor. A deficiency in SPCA, also required to accelerate prothrombin conversion, constitutes another form of pseudohypoprothrombinemia. A reclassification of the true and pseudohypoprothrombinemias is presented.—H.W.B.


The name “Christmas disease” is given to a hemophilia-like syndrome because the surname of the first of the seven patients described in this paper was Christmas. It differs from hemophilia in that a small amount of the blood or plasma of patients suffering from Christmas disease will reduce the clotting time of hemophilic blood or plasma. So far the condition has been found only in males but the mother of one of the cases had a lengthened coagulation time and deficient prothrombin consumption, and a family history was elicited in others. The inheritance seems to be similar to that in hemophilia, but the defect may not be completely recessive.

The fundamental defect in both hemophilia and Christmas disease is a failure to form intrinsic thromboplastin, but in the latter disease the missing factor is a serum factor related to, but differing from, factor VII of Koller, and the authors call this new factor the Christmas factor.

In the treatment of hemorrhage in cases of Christmas disease, concentrated preparations of antihemophilic globulin are ineffective.—H.H.G.


It has previously been postulated by Kay et al. that a deficiency of antithrombin may be a factor in the development of thrombosis, although other workers were unable to confirm this. Others have reported an increase of antithrombin in nearly all cases of acute pancreatitis as well as in cases of obstructive jaundice due to carcinoma of the pancreas.

The author studied twenty-eight normal controls; and sixty-two patients with thrombotic or hemorrhagic diseases.

The technic of Astrup for the measurement of antithrombin in plasma or serum was employed. The effort was made to measure antithrombin specifically, as distinguished from the effects of heparin plus co-factor, and the adsorption of thrombin by fibrin. The addition of heparin to plasma, either in vivo or in vitro, will produce an apparent increase in antithrombin as shown by this technic. It will also prolong the clotting time in the
control test. These effects of heparin can be neutralized with a small amount of protamine, which does not appear to inhibit antithrombin.

The most marked changes in plasma antithrombin were found in patients with obstructive jaundice, although there was no correlation with liver function or the type of jaundice. There were marked increases as well as decreases.

No decrease below normal was found in patients with thrombosis and many patients had an increase.

Most cases receiving bishydroxycoumarin showed some increase in antithrombin.

A few patients with bleeding tendency showed elevated antithrombin levels, but with no evidence that this was a causative factor. Four patients with hemophilia had normal values.—T.R.T.

STUDIES ON THE INHIBITION OF PROTEOLYTIC ENZYMES BY SERUM. I. THE MECHANISM OF THE INHIBITION OF TRYPsin, PLASMIN, AND CHYMOTRYPSIN BY SERUM USING FIBRIN TAGGED WITH I$^{131}$ AS A SUBSTRATE. II. DEMONSTRATION THAT SEPARATE PROTEOLYTIC INHIBITORS EXIST IN SERUM; THEIR DISTINCTIVE PROPERTIES AND THE SPECIFICITY OF THEIR ACTION. III. PHYSIOLOGICAL ASPECTS OF VARIATIONS IN PROTEOLYTIC INHIBITION. THE CONCURRENCE OF CHANGES IN FIBRINOGEN CONCENTRATION WITH CHANGES IN TRYPsin INHIBITION. N. R. Shulman. From the Sloan-Kettering Institute for Cancer Research and the Department of Medicine, Memorial Hospital, New York, N. Y.; and the Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md. J. Exper. Med. 96: 571-618, 1952.

The numerous observations reported in this series of three papers add substantially to our scanty knowledge of the antiproteolytic activity of serum. The first paper compares the mechanisms of the inhibition of trypsin, plasmin, and chymotrypsin by serum using fibrin tagged with radioactive iodine as a substrate, a method permitting more accurate quantitative measurements than previously employed technics. In studying the enzyme-inhibitor relationships it was found that the amount of enzyme inhibited was directly proportional to the amount of inhibitor (serum) used, that inhibition was independent of the amount of enzyme used, and that the enzyme-inhibitor reaction could not be reversed by dilution. The inhibition of trypsin, plasmin, and chymotrypsin is in all probability, therefore, a stoichiometric and irreversible reaction. Observation of the effect of the substrate concentration upon inhibition demonstrated that the inhibition of trypsin and chymotrypsin by serum was non-competitive. The substrate exerted a retarding effect on the activity of plasmin, however, which was believed due to a specific plasmin inhibitor present in fibrinogen as an impurity.

Although it has been generally assumed that inhibition of proteolytic enzymes is caused by a single substance in serum, the second paper shows quite clearly the existence of more than one proteolytic inhibitor in serum and also that these several factors act selectively on plasmin, trypsin and chymotrypsin. No apparent difference could be detected between the trypsin and chymotrypsin inhibitors but inhibition of these enzymes was effected quite independently of the inhibition of plasmin. Furthermore, the physical and chemical properties of plasmin inhibitor differed from those of the trypsin and chymotrypsin inhibitor. From the evidence presented, it appears that increases of proteolytic inhibition in disease are due to increases in normal inhibitors rather than to the presence of abnormal substances in the serum.

The third paper contains an analysis of the variations in proteolytic inhibition in certain disease states with an attempt to ascertain the relationship between these changes and other biologic measurements. Elevation of trypsin and chymotrypsin inhibition was associated with conditions in which there was tissue destruction, and correlated closely with changes in sedimentation rate and fibrinogen concentration. Increased plasmin inhibition occurred too infrequently to permit correlation with clinical data.

At the present time the significance of the association between variations in trypsin inhibition and changes in fibrinogen concentration in both normal and pathologic states is undetermined. Elevated trypsin inhibition, like increased fibrinogen concentration, can be considered only as a nonspecific indication of disease and tissue destruction.—H.W.B.
ABSTRACTS


An active fibrinolytic system was produced in the circulating blood of rabbits by intravenous injections of streptokinase (SK). With adequate doses, evidence of the presence of this lytic system appeared within thirty minutes and, depending upon SK concentration and duration of infusion, remained present for periods up to twenty hours. Quantitative determinations of related factors revealed that concomitant with the development of the streptococcal fibrinolytic phenomenon there was a marked fall in plasminogen, a moderate decrease in serum inhibitor and fibrinogen, and a rise in acid soluble nitrogen.

The effect of this lytic system on intravascular clots, artificially induced by local application of sodium morrhuate within the rabbit’s ear vein, was then determined. In twenty-three of twenty-five rabbits the clot liquefied and disappeared during infusion of SK into the opposite ear. The time required for complete lysis ranged from three to seven hours after starting the infusion. Maintenance of an active lytic system for an additional three to four hours was necessary to prevent clot re-formation.

The toxicity of the injected preparations was considerable and is under study at the present time. ACTH, while apparently effective in minimizing toxic effects, had the drawback of promoting clot re-formation.—H.W.B.


The observed changes in urine and serum fibrinolytic activity in dogs, exhibiting a hemorrhagic syndrome subsequent to large dose whole body irradiation, reflected quite well the general condition of these animals. There was a precipitate rise in urine fibrinolytic activity four to five days prior to death in all dogs in which the main cause of death was pulmonary hemorrhage. A somewhat similar rise in fibrinolytic activity of the serum was noted in the animals which did not survive. In the surviving dogs, the urine and serum fibrinolytic activity approached control levels at about the twenty-fourth post-irradiation day.

While the authors are quite cautious in their interpretation of these observations, certain factors which may operate in the activation of the fibrinolytic enzyme in vivo, such as the role of the lungs, were suggested by the findings and are discussed. It is further pointed out that, in the future, measurements of urine and serum fibrinolytic activity may have clinical application in the prognosis and eventual development of rational methods for treatment of radiation injury.—H.W.B.


Two groups of rabbits were subjected to two types of trauma and the fibrinogen concentration of blood samples drawn at several periods up to twenty-four hours determined. Relatively bloodless surgery followed by shock induced by minimal tissue damage produced a negligible decrease in plasma fibrinogen concentration. More extensive tissue damage, however, caused a definite decrease in plasma fibrinogen within six hours. Both procedures produced a significant increase in plasma fibrinogen concentration after twenty-four hours. These findings appear to explain the apparent discrepancy which has been noted between the reports of increased fibrinogen levels twenty-four hours after several types of tissue injury and operative procedures and the observations of a marked lowering of fibrinogen levels immediately following thoracic surgery and abruptio placentae. The authors favor the concept that release of thromboplastin from damaged tissue (lung, placenta, and other tissue as shown in these experiments) is the mechanism responsible for
the decrease in plasma fibrinogen levels. It does not seem, however, that the possibility of the fibrinolysin phenomenon can be definitely excluded until a more complete study of the subject has been made.—H.W.B.


It has been shown previously that hibernating ground squirrels exhibit a prolonged blood clotting time. The present work was done to determine what factor was decreased to account for this phenomenon.

A reduction in amounts of prothrombin was found and the authors point out that this is probably a mechanism in these hibernating animals to prevent the formation of thromboses during this time of slow circulation.—R.C.C.


These authors have reported previously that ground squirrels exhibit a prolonged blood clotting time when hibernating.

The present work has shown that this is not limited to the ground squirrel. The golden hamster will simulate hibernation if its surrounding temperature is decreased. Under these conditions the clotting time was increased from a normal average of 4 minutes and 52 seconds to 50 minutes and 45 seconds.

The authors feel that this mechanism is a means on the part of the animal to prevent the formation of thromboses in blood that is flowing very slowly.—R.C.C.


These authors have described an improvement on the Lee and White technic for measuring blood clotting time. The improvement consists mainly of a vial holder and a scale by which the degree of slant of the tube can be regulated and measured. This eliminates the personal equations involved in picking up the vial and tilting it at no precise angle.—R.C.C.


Human blood was obtained by venipuncture and oxalated; 0.2 cc. of tyrosinase was added to 2 cc. of blood and the system was incubated in a water bath at 37 C. A simultaneously run control contained tyrosinase inactivated by boiling. At successive intervals aliquots were removed for measurement of clotting time. The clotting time increased directly with time after the tyrosinase addition. The inactivation of the clotting system of whole human blood is independent of the presence of blood cells since results similar to those just mentioned were obtained with plasma.

To study the effects of tyrosinase on the clotting mechanism in vivo, the enzyme was injected into the heart of laboratory white mice. Blood samples from the tip of the tail were drawn into fine capillary glass tubes at intervals for measurement of clotting time. Although the clotting time increased within 1.5 hours after injection, the clotting mechanism returned to normal in 3 hours.

The problem of immunization of mice to tyrosinase was investigated by using a single animal for a series of injections over a period of one to two months. Results showed that injections of tyrosinase cause a production of antibodies which inhibit the enzyme in vivo.
In one mouse the clotting time was increased to 11 minutes when tyrosinase was injected the first time; fifteen days later the clotting time was 5 minutes; eight days later the tyrosinase induced no change in the clotting time.—R.C.C.

THROMBOCYTOPENIA

THE EFFECT OF THE "THROMBOCYTOPENIC FACTOR" OF IDIOPATHIC THROMBOCYTOPENIC PURPURA ON PLATELET LEVELS AS MEASURED BY DIRECT AND INDIRECT METHODS.


The blood from six patients with idiopathic thrombocytopenic purpura was collected in ACD solution, the plasma removed, and subsequently injected into six nonthrombocytopenic subjects. Four subjects were normal, one had infectious hepatitis and one was recovering from bronchopneumonia. The platelets were counted at intervals by two methods: the indirect method of Dameshek, and Tocantins' modification of the Rees and Ecker methods.

When using the indirect method of counting, there was a prompt fall in platelets in all six recipients. This did not occur in the data using the direct method.

No signs and symptoms of purpura were produced in any of these six cases.

The basic difference in the two methods of counting is that in the direct method there is a 1 to 200 dilution of the blood, whereas in the indirect method there is about a 1 to 5 dilution.

The authors postulate that the theoretic factor causing platelet fragmentation is probably diluted by the direct method to the extent that most of its action is inhibited.—T.R.T.

BOOK REVIEWS


This book is divided into three sections: (a) the partition of body water and its physicochemical structure; (b) methods used in the study of the physiology of body water; and (c) pathologic disturbances affecting the body fluids. The book is a combination of a scholarly and extensive review of the physiology of fluid and electrolytes and the authors' own noteworthy contributions in this field. A very exhaustive bibliography of over 2500 references attests to the thoroughness of the authors' review.

The contents of the book are well organized and written in a clear, easily understood manner. There is, however, somewhat more detail and repetition than the English reader is accustomed to. Many controversial topics, such as the factors involved in the distribution of water between the intra- and extracellular compartments, are presented in a fair and intelligent manner.

The authors present evidence to support the view of Dill and Gilman that intracellular dehydration is the stimulus for thirst. The not uncommon finding of thirst in the presence of definite dilution of the extracellular fluid—i.e., congestive heart failure with low serum sodium concentrations—without any evidence of intracellular dehydration is difficult to fit into the authors' view.

The section on the nature of the antidiuretic hormone might well have included mention of the purification and composition of antidiuretic hormone by du Vigneaud and his colleagues.
ABSTRACTS