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BLOOD COAGULATION AND HEMORRHAGIC DISEASE

CIRCULATING ANTICOAGULANTS: A Technique for their Detection and Clinical Studies. C. L. Conkly
R. C. Hartmann and W. I. Morse II. From the Clinical Microscopy Division, Department of Medicine,
The Johns Hopkins University and Hospital, Baltimore, Md. Bull Johns Hopkins Hosp. 84:

A test for circulating anticoagulants is described utilizing the effect of platelet-free plasma on normal
blood. The preparation of the platelet-free plasma depends on scrupulous technic, siliconed syringes,
test tubes and pipets, handling the blood at low temperatures and two separations by centrifugation at
7000 and 12,000-14,000 rpm. By this method amounts of added heparin as low as 0.001 mg. per ml.
platelet-free plasma were detectable. In clinical studies, eight instances of a circulating anticoagulant
were detected. In only one did the addition of toluidine blue suggest the presence of a heparin-like
substance. In 9 cases of thrombocytopenia, the anticoagulant assays were negative. These interesting
studies point up the probability that circulating anticoagulants are probably present much more com-
monly than suspected in the past and the suggested technic offers another approach to the study of
hemorrhagic diatheses. From the standpoint of widespread use the meticulous technic necessary for
the successful preparation of platelet-free plasma unfortunately is a limitation on its general availability.

W. N. V.

HUMAN PROTHROMBIN: QUANTITATIVE STUDIES ON THE PLASMA LABILE FACTOR AND THE RESTORATIVE
EFFECTS OF NORMAL, HYPOFIBRINOGENEMIC, AND HEMOPHILIC PLASMA ON THE PROTHROMBIN OF STORED
PLASMA. B. Alexander and A. de Vries. From the Medical Research Laboratory, Beth Israel Hospital,
and the Department of Medicine, Harvard Medical School, Boston, Mass. J. Clin. Investigation 28:

The conclusions of Loomis and Seegers (Am. J. Physiol. 148: 563, 1947), namely, that deterioration of
fibrinogen accounts for lengthening of the prothrombin time in stored plasma, and that ‘reactive fibrino-
gen’ is necessary for prothrombin activity measured by the one-stage technic, have been tested by the
authors of this report, employing as a reagent afibrinogenemic plasma from a subject with spontaneous
fibrinopenia. Inasmuch as the retarded prothrombin time of stored plasma was fully restored upon the
addition of this plasma, it is concluded that fibrinogen is not the factor whose deterioration is responsible
for the alteration in the clotting properties of stored blood, a conclusion that is further substantiated
by the restorative properties of normal plasma rendered fibrinogen-free by means of thrombin. This
factor (labile factor), which is also present in BaSO4 plasma (prothrombin-free) as well as in hemo-
philic plasma, is required in adequate amount for normal prothrombin activity. It is pointed out that the
use of prothrombin-free (BaSO4-treated) plasma, containing not only the labile factor, but also fibrinogen
and antihemophilic activity in normal amounts, is preferable to saline as a diluent in the performance of
the one-stage prothrombin test, since a reduction of the concentration of these important non-prothrom-
bin constituents is thereby avoided.

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A study was made by Mentzer to determine the relation between the chemical structure of various compounds similar to dicoumarol, and their anticoagulant activity. His conclusions are similar to those of Link and his collaborators, but whereas the American authors believe that the B cycle is necessarily an hydroxy-4-pyrone, Mentzer estimates that other cycles, such as thyopyrone, quinon, pyridin, cyclo-pentanedione, are able to confer to the molecule the same activity as the B pyronic cycle. In conclusion, all the active compounds have the same structure which can be schematized as follows:

\[ X = \text{B} - (\text{CO} - \text{O}) \text{ or } (\text{CO} - \text{NH}) \text{, or } (\text{CO}) \text{ or } (\text{S}) \]

If R is an atom of chloride, or of hydrogen, or a complex of at least 6 carbon atoms, the molecule behaves as an antivitamin-K. All the compounds also have in common the O atom in B; this O atom can belong to an enolic or ketonic group, but the blockage of this oxyhydrile function suppresses the activity.


This interesting case report describes a hemorrhagic diathesis in a pregnant woman at term, characterized by a critical decrease in fibrinogen. By use of blood transfusions and fraction I of Cohn it was possible to remove a dead fetus surgically, after which rapid recovery of the mother occurred. The authors discuss the possible role of fibrinolysins in this type of acquired afibrinogenemia.


The finding of fluid and incoagulable blood at autopsy is not an uncommon occurrence. However, the explanation of this phenomenon has not been subject to critical investigation and it is for this reason that the present study was undertaken. Blood was obtained from the heart and great vessels of 61 cadavers at routine but not consecutive autopsies. Observations on the fibrinolysin in supernatant "serum" were made by using a modification of Macfarlane's method (1937). A regional difference in the rate of spontaneous intravascular coagulation as well as in fibrinolytic activity was found. Cadaver fibrinolysin is nondialyzable, precipitated at neutral pH in 10% saturation of ammonium sulphate and its activity is destroyed by pepsin. It appears to be a globulin. The appearance of fibrinolysin seems to be part of the body's general reaction to injury and it is probably produced by endothelium.


In a study of 10,000 newborn children over a period of five years, the authors found a seasonal variation in the incidence of melena, cerebral hemorrhage, and cephalhematoma. The peak period was identical for each, and occurred during winter and spring, with diminution during summer and autumn. Since the trauma of delivery presumably did not have a seasonal variation, an explanation for the incidence variations was sought in possible changes in the clotting mechanisms and in the capillary fragility.

The most marked prothrombin reductions, the authors state, have been noted (in the literature) to occur in the winter and spring. No other defects of clotting mechanism were known to be of seasonal incidence.
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The authors tested capillary fragility in 233 healthy children at various times of the year, using both positive- and negative-pressure methods; and found that the incidence of increased capillary fragility increased in winter and spring, diminished in summer, and was minimal in late summer. In addition, they noted that conjunctival petechiae in the newborn, which are supposedly due to rupture of capillaries during labor, were most numerous in spring and winter. There was thus a distinct parallelism in incidence of cerebral hemorrhage, cephalhematoma, conjunctival petechiae, and excessive capillary fragility.

The authors suggest that the use of vitamins K and P during the latter months of pregnancy may prevent these hemorrhagic tendencies.


A case of hemophilia with the complication of acute appendicitis is presented. The patient received intensive antihemorrhagic therapy, but despite a normal clotting time he continued to bleed profusely and expired four days postoperatively. A discussion of the significance of continued hemorrhage in the presence of a normal in vitro clotting time and its relation to the fundamental defect in hemophilia is presented. The authors conclude that the mere deficiency of the substance "antihemophilic globulin" cannot be the sole abnormality of coagulation in hemophilia. Emphasis is placed on the failure of the coagulation time to indicate the severity of the hemorrhagic tendency or the degree of response to treatment, the difficulty in choosing a suitable case for operation, and the great difference in controlling interval hemorrhage as opposed to bleeding from an external site.

The authors reviewed the literature for instances of internal operative procedures in patients with hemophilia. Of four previously reported cases in whom the diagnosis of hemophilia was unequivocal, two died from hemorrhage following operation while two recovered.

G. E. C.


Following the observation of a slight decrease in blood coagulation time in adults with migraine treated with intravenous histamine, 6 hemophilic children were given histamine injections in increasing amounts (usually 0.3, 0.6, 0.8, and 1.0 mg.) on successive days during active cycles of bleeding. Determinations of the coagulation time were made on whole blood, plasma, and platelet-free (?) plasma obtained by centrifugation in waxed chilled tubes. A greater and more prolonged, although not permanent, decrease in coagulation time occurred in the hemophilic group with cessation of bleeding. The total number of platelets was not affected.

The authors conclude that this decrease in coagulation time is due to increased platelet disintegration (possibly of new and more normal platelets); their sole premise being that the defect in hemophilia is the result of abnormal qualitative platelet function. Although it has been shown that platelets are also essential for normal thromboplastic activity, the role of a plasma factor in hemophilia is not considered. This report is of interest, however, and further clinical trial and investigation with histamine in hemophiliacs appears warranted and may possibly reveal the mechanism of action, which at present is not clear.

G. B. M.


A technic was devised for varying the number of platelets without otherwise altering the plasma. The effect of the number of platelets was studied and the following observations made: (1) The greater the number of platelets, the sooner clot retraction begins and the smaller the final clot; (2) clot retrac-
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sion is characterized by a relatively long latent period followed by an accelerated phase and protracted completion; (3) within a wide range in the number of platelets no significant change in coagulation time can be observed; (4) as the number of platelets is diminished the speed of prothrombin consumption is decreased, but within normal limits the final amount of prothrombin converted approximates a fixed value; (5) below a critical number of platelets the consumption of prothrombin stops after a relatively short time. This suggests that plasma contains an agent that inactivated the platelet enzyme; (6) in thrombocytopenic purpura of sufficient severity, the consumption of prothrombin may be markedly diminished. This suggests that in thrombocytopenic purpura a serious defect in coagulation is present which has heretofore been unrecognized because it is masked by a normal coagulation time.

G. E. C.

ETUDE DES MEGACARYOCYTES ET DES PLAQUETTES DANS DIVERS SYNDROMES HEMORRAGIQUES. (STUDY OF MEGACARYOCYTES AND PLATELETS IN VARIOUS HEMORRHAGIC SYNDROMES.) L. Revol and P. Morel.


The authors discuss the normal features of megakaryocytes in marrow smears. They found in normal marrow more megakaryocytes than are usually stated to be present (up to 2,000 per million nucleated cells), but they agree about the percentage of the different cells, from the megakaryoblast to the old cells. They study platelet formation after splenectomy and find that platelets are essentially produced by the cytoplasm, but sometimes a fragmentation of the nucleus is observed. In 6 cases of idiopathic thrombopenias they found what Revol himself described in 1939, and what was confirmed by several authors, that is, an increase of megakaryocytes (above 1,600 for 1 million of nucleated cells) but without increase of the young forms, as it is commonly said.

After splenectomy they found in 4 cases a striking platelet formation in megakaryocytes which was to be found as soon as one and a half hours after the operation, with a maximum at the third day. At the same time, the number of megakaryocytes was reduced (from 5,900 to 3,900 in the average). In 2 cases, however, in spite of the same initial bone marrow, splenectomy was not followed by the same platelet formation and the thrombocytopenia was not cured.

In 2 cases of acquired thrombocytopenia, the megakaryocytes were numerous in the marrow smears; after splenectomy in the first case, and transfusions in the second case, a very slow platelet formation was observed. In 3 cases of infectious thrombocytopenia, the megakaryocytes were plentiful, but there were numerous cytologic alterations.

In 6 cases of hemorrhagic syndromes without thrombocytopenia they usually found an active bone marrow rich in megakaryocytes. They discuss the effect of splenectomy and the advisability of this procedure.

Twenty-seven good microphotographs illustrate this interesting study which ends with conclusions about the indications of splenectomy. A very great number of megakaryocytes, the lack of platelet formations seem to indicate the splenectomy.

J. P. S.

GAUCHER'S DISEASE WITH THROMBOCYTOPENIA, AN INSTANCE OF SELECTIVE HYPERSPLENISM. A CASE REPORT. F. W. Davis, Abraham Genecin and Ernest W. Smith.


The authors report an instance of thrombocytopenia unassociated with anemia or leukopenia in which hypersplenism secondary to Gaucher's disease was apparently the etiology. Splenectomy resulted in correction of the thrombopenia and the hemorrhagic diathesis.

W. N. V.

THE INFLUENCE OF BRIEF PERIODS OF STRENIOUS EXERCISE ON THE BLOOD PLATELET COUNT. E. B. Gerbeim and A. T. Miller, Jr.

From the Laboratory of Applied Physiology and Department of Physiology, University of North Carolina School of Medicine, Chapel Hill, N. C. Science 110: 64, 1949.

Reports in the literature on the effects of exercise on the platelet count are in conflict. This work was performed in an attempt to solve whether exercise actually does change the platelet count. Exercise consisted of running on a treadmill for five minutes at a speed of 7 miles an hour and a grade of 17.5 per cent, or for two minutes at 12 miles an hour at zero grade. Blood was obtained before exercise, immediately after exercise, and 10, 30, 60, and 90 minutes after exercise. In spite of the fact that there was a
60-100 per cent increase in the leukocyte count, there was no increase in the platelet count. The authors suggest that the increased velocity of circulation may have destroyed the very labile platelets which may have covered up any increase in platelets.

R. C. C.


The authors present data on 10 cases of thrombopenic purpura, 10 of which were treated medically and 10 treated by splenectomy. Five recurrences were noted in the splenectomized group and 2 in the medically treated group. Three of the patients with recurrence had the acute form of the disease and two the chronic. The pathogenesis of the syndrome is discussed with emphasis on the importance of the capillary factor and the possible role of the entire reticuloendothelial system.

The results are rendered somewhat difficult to evaluate by the fact that 14 of the patients were under the age of 12 years and 11 under 10 years of age and because 6 of the medically treated group and none of the surgically treated group had had symptoms for less than four weeks.

W. N. V.

The Effect of Rutin in the Control of Bleeding into the Retina. R. W. Hollenhorst and H. P. Wagemer.


The clinical literature of the use of rutin in conditions of increased capillary fragility is discussed. The article serves as a useful review of the subject, but the authors justifiably stress the variability of reports and their inability to draw any definite conclusions with the evidence at hand.

C. A. F.


From the Department of Surgery, University of Minnesota, Minneapolis, Minn. Surg., Gynec. & Obst. 88: 337-350, 1949.

The results of treatment of 92 cases representing 105 extremities with deep thrombophlebitis are reported, together with a detailed discussion of the diagnostic signs, methods of treatment, type of venous thrombosis, and the primary disease process. For practical purposes both the bland and inflammatory thromboses were called thrombophlebitis. With the exception of eight patients who were treated with vein ligation, anticoagulants (dicumarol and heparin) were used with an average of ten days of bed rest in, unless contraindicated, mild Trendelenburg position.

Although most of the patients had had one pulmonary embolism at the time of diagnosis of thrombophlebitis, the results of anticoagulant therapy were considered satisfactory in that the incidence of secondary embolism was reduced from an expected 30 per cent to 2.17 per cent and that of secondary fatal embolism from an expected 25 per cent to zero. An analysis of the primary condition indicated the importance of prophylactic postoperative anticoagulant therapy in patients with cancer and in those undergoing major gastrointestinal surgery, hysterectomies and hip fixations.

The controversy as to the relative merits of anticoagulant therapy vs. vein ligation in the prevention and treatment of thromboembolism will probably remain unsettled for some time. It would seem, however, that both have a place in the management of this disorder and that the indications for each should be determined more on the basis of the type of thrombophlebitis, the underlying disease and condition of the patient, availability of laboratory control, and the estimated risk of fatal embolus. It is quite possible that the incidence of death from pulmonary embolism is much lower than generally believed (see Surg. Gynec. & Obst. 88: 373, 1949).

H. B. M.

Transfusion


In the hope that a means might be supplied for reducing the high incidence (4.5–7.2 per cent) of homologous serum jaundice or of eliminating this risk altogether in transfusion recipients, and in view of the essential unavailability of effective irradiation techniques for the sterilization of blood and blood derivatives, the authors have investigated the merits of nitrogen mustard (HN2) as a sterilizing agent. Selection of this compound for study was based on the following considerations: its presumed effect on nucleoproteins; its ready susceptibility to spontaneous hydrolysis in buffered aqueous solution, forming relatively nontoxic end-products; the parallelism of its activity with that of ionizing radiations; and its availability in purified form suitable for parenteral administration.

It was demonstrated that HN is capable of effective bactericidal and virucidal action in whole blood, blood plasma and blood serum without causing major alterations in the properties of either the plasma components or the red blood cells. Virucidal potency appeared to be greatly enhanced by decreasing the pH to 7.2 or below, possibly attributable to a reduction in the rate of HN2 decomposition, or to a lessened reactivity with other competing substances and at these pH levels sterilization was considered to be accomplished with concentrations of the drug not exceeding 500 mg. per liter. No evidence of antigenic or other toxic reactions was produced in two dogs and two humans receiving repeated injections of plasma so treated. Plasma complement, immune bodies, phosphatase, and fibrinogen were apparently unaffected by exposure to sterilizing doses, but a marked reduction of prothrombin activity was observed. In vitro studies failed to demonstrate a significant increase in the rate of erythrocyte deterioration in stored blood following the application of virucidal dosages of HN2, in vivo erythrocyte survival studies, however, have not as yet been completed.

C. P. E.

IRON THERAPY AND METABOLISM

Preparation and Standardisation of Saccharated Iron Oxide for Intravenous Administration.

Details of methods of preparation and toxicity tests on various samples of saccharated oxide of iron are described. The toxicity varied considerably and seemed to be the result of gradual precipitation of free iron. This in turn, it was thought, might depend on the rate of metabolism of the sugar part of the molecule. Mice given lethal doses showed hemorrhagic lesions, probably due to multiple capillary emboli from iron precipitation. As a consequence of the difficulties encountered in producing uniform preparations the authors suggest that biologic standardization is essential.

S. C.


In studies of 6 subjects exposed to humid heat, these authors found iron in amounts of 1 to 3 mg./liter of sweat. They estimated a daily loss of about 6.5 mg. iron under minimal sweating conditions. This magnitude of iron excretion is not in harmony with present concepts of iron metabolism. In fact, such a daily loss would appear to be more than the normal individual is able to absorb. Obviously, further studies are necessary before these findings can be interpreted.

C. A. F.

PIGMENT METABOLISM

Influence of Follic Acid on Porphyria. V. Kravářová. From the 3rd Medical Clinic, Charles University, Prague. Čes. Lék. čes. 87: 633, 1948.

A woman suffering from a cutaneous form of porphyria was eliminating 200 gamma uroporphyrin (and the same amount of coproporphyrin III) per liter of urine. Porphyria was accompanied by severe hypochromic anemia and raised level of plasma iron. Folic acid, administered in the daily dose of 15 mg., proved to be highly effective: skin manifestations disappeared, pigmentation cleared up, general feeling improved and uroporphyrin disappeared entirely from the urine.

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Differentiation of stercobilin and urobiline is made possible by the pentdyopent reaction. Clinical examinations showed that the hitherto assumed urobilinuria is actually a stercobilinuria. Presence of urobiline IX a in urine is always sign of a pathologic process. Stercobilinuria and elimination of stercobilin in the feces is found in pernicious anemia, hemolytic jaundice, malaria and in parenchymatous icterus. Pure urobilinuria can be encountered in icterus of total biliary occlusion. Preponderant uribilinuria can be seen in beginning parenchymatous liver affection. Increase of stercobiline comes later. The clinical differentiation of both substances opens new diagnostic possibilities.

C. M.


Twenty-one normal infants of approximately similar weight were studied during the neonatal period by means of daily red blood cell counts and hemoglobin determinations, red cell volumes and plasma bilirubin levels. In most of the infants, determinations were made of the bilirubin content in the meconium excreted during the first three days. The velocity constant of excretion of bilirubin was determined in 18 infants by the method of Weech et al. The relation of maternal and fetal isohemagglutinins to the development of neonatal hyperbilirubinemia was investigated in 50 other normal infants.

Evidence is presented which strongly suggests that physiologic hyperbilirubinemia is not purely, if at all, hemolytic in origin but due mainly to functional immaturity of the liver before and for a variable period after birth. The degree of hyperbilirubinemia could not be correlated with the magnitude of the fall in red cell count and packed red cell volume nor with mother-child ABO and Rh incompatibility. There was an inverse correlation between the amount of bile pigment in the first meconium and the height of the plasma bilirubin rise during the first week of life. Impairment of the bilirubin excretory capacity of the liver was demonstrated in infants with hyperbilirubinemia, whereas normal excretory function was found in infants whose plasma bilirubin levels had returned to normal.

H. W. B.