ABSTRACTS

HEMATOPOIETIC TISSUES

OLIVER P. JONES, PH.D.


The results of studying growth of lymphoid tissues in 474 rats from birth to 19 months of age are very interesting, but most important for the hematologist are the data collected on the output of lymphocytes. Thoracic and cervical lymph ducts in 33 adult female rats were cannulated for varying periods and the lymph collected for cell count and volume studies. The total number of lymphocytes delivered to the blood stream per hour is about 9 million. This means that approximately 10 per cent of the total lymphocytes in the blood stream are replaced hourly. The entire lymphocyte population in the blood is replaced 2.05 times per day and the average life span of a lymphocyte in the blood stream is 12 hours. In this connection, it should be noted that following transfusions of cells labeled with acriflavine hydrochloride lymphocytes were found chiefly in the bone marrow (Farr: Anat. Rec. 94: 460, 1946).

BLOOD TRANSFUSIONS AND BLOOD SUBSTITUTES

EUGENE L. LOZNER, M.D.


It is obvious from this and previous reports of Madden and his various co-workers that the ten essential amino acids may be given by mouth, vein, subcutaneously, or intraperitoneally and may maintain nitrogen and weight equilibrium in the dog. The observations reported herein include those on 3 patients in which amino acids were given intravenously, subcutaneously, and orally with favorable clinical results. Madden feels that amino acid mixtures are better tolerated parenterally and more palatable orally than protein hydrolysates. However, he points out that amino acids offer practical problems in large scale production and as yet are expensive. At the present moment they cannot be considered a significant therapeutic agent except in research laboratories.


Evans and Rafal in this article provide additional data in support of the increasingly evident conclusion that gelatin is a very useful substitute for plasma in situations where decreased plasma volume is present or is imminent. They have used both "lightly and heavily" degraded gelatin in traumatic shock and burn shock, and in these situations the lightly degraded gelatin appeared to be superior in that it was retained longer in the blood stream. They discuss the advantages and disadvantages briefly, and it may be well to repeat the disadvantages here. These consist of pseudo-agglutination of the red cells complicating blood grouping and cross matching (this may now be abolished by using a drop of 1 per cent glycine in the erythrocyto-serum-gelatin suspension); high viscosity which renders the gelatin solutions impossible to administer when cold (a 6 per cent gelatin solution must be kept at approximately 35°C.); and the fact that gelatin does not supply any oxygen-carrying capacity, which may be important both in proper management in shock due to trauma and in burns. Thus, they point out that gelatin (as well as plasma) cannot be used as a true substitute for whole blood.

This reviewer desires to call attention to two additional disadvantages, one the nutritional inferiority of gelatin as a protein and the other the fact that these gelatin solutions require especially careful preparation in order to produce a nonpyrogenic and uniform material.
HEMOSTASIS AND HEMORRHAGIC DISEASES

ABSTRACTS

HEMOSTASIS AND HEMORRHAGIC DISEASES

Marilyn T. Schitbone, M.D.


The author presents a study of 30 cases of thrombocytopenic purpura and attempts to show that increased eosinophils in sternal bone-marrow puncture preparations represent a favorable prognosis for spontaneous recovery while the presence of relatively few such cells suggests a chronic course with probable necessity for splenectomy. He believes that marrow eosinophilia under such circumstances represents an allergic state and that the thrombocytopenia represents a "sensitization reaction" involving the megakaryocytes. An arbitrary base line of 50 eosinophils per 1000 leukocytes of the metamyelocyte and polymorphonuclear series was chosen because eosinophils presumably arise from the same stem cell and because specific stimulation or decrease of granulocytes does not occur in this disease. Those patients showing more than 50 eosinophils per 1000 granulocytes in bone marrow had a relatively benign course followed by complete hematological and clinical recovery without splenectomy. Those with fewer than 50 eosinophils per 1000 granulocytes tended to have protracted courses without cure except by splenectomy. Blood transfusions were felt to hasten recovery in the first group. Correlation was not found between marrow and peripheral eosinophilia.

The author is aware of the limitations necessarily inherent in attempting to make a prognosis based on the numerical evaluation of a single cell, but suggests that certain correlations exist which may be helpful in considerations of prognosis and treatment.

Case Analysis: 12 cases: 50 or more eosinophils per 1000 granulocytes in marrow, had short courses with spontaneous recovery. 1 case: Less than 50 eosinophils, spontaneous recovery (the author feels the marrow was examined too late and after platelets had increased). 2 cases: Few eosinophils and chronic course. 5 cases: Few eosinophils, and responded to splenectomy. 3 cases: High eosinophils, and responded to splenectomy ("allergic" thrombocytopenia apparently can do well with splenectomy). 4 cases: Few eosinophils, and death of patient. 3 "equivocal" cases.


A case is presented of a 6 year old Italian male who was first seen because of uncontrollable, nontraumatic epistaxis occurring one week after the onset of an upper respiratory infection. Examination revealed pallor and hemorrhagic areas over the eyes, forehead, lips, and lower extremities. Laboratory data disclosed a mild normochromic anemia, leukocytosis, and marked thrombocytopenia with normal bleeding and clotting time. Two weeks after onset of illness, he suddenly developed failing vision. A diagnosis of left corneal infiltrate and left retinal hemorrhage was made. Under therapy the infiltrate healed but subsequently optic atrophy developed. Splenectomy, performed 7 weeks after onset of illness and during an apparent quiescent phase, produced an almost immediate return of the blood picture to normal but the eye findings are still unchanged 20 months after onset of the disease. The bilateral optic atrophy is attributed to hemorrhage into the nerve sheath and probably into the orbit. A review of the literature tends to show the rather infrequent observation of a "choked disk" and of 2 cases of optic atrophy which did not respond to splenectomy.

This case emphasizes the necessity for the consideration of early splenectomy in cases of idiopathic thrombocytopenic purpura, especially when massive or uncontrollable bleeding occurs. Prolonged observation may result in a serious and irreversible complication or even in death from hemorrhage into a vital organ.


The authors present the case of a 37 year old Negro male who was treated for rheumatoid arthritis with a total of 44 grains of sodium salicylate over a period of one month without response. Treatment was reinstituted 3 weeks later for 9 days with a daily dosage of ½ gram a day following which a severe epistaxis occurred. Treatment was continued two days more, with the development of hematuria, hemate-
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given and after a prolonged course of illness, followed by most of scarlet fever’s complications, the patient recovered. The authors could find no references in the literature to the development of purpura following scarlet fever only.


The authors present 2 cases of hereditary hemorrhagic telangiectasis with the characteristic triad of multiple telangiectases, hemorrhage or anemia, and a history of familial occurrence. The extreme fragility of the lesions and the time of their appearance largely determine symptomatology. As the nasal mucous membrane is usually involved first, epistaxis occurs with increasing frequency from late childhood onward. In middle life, the skin and visceral lesions appear and add to the blood loss. The resulting anemia is often severe but the hemoglobin is seldom below 50 per cent. Skin lesions occasionally disappear after a period of years but the anemia persists. As the patient ages, the quantity of blood lost increases and nasal hemorrhages of 1000-1500 cc. are not uncommon. The 6 per cent mortality of the disease is associated with these conditions. Over 500 cases occurring in 100 families have been described in the literature. The hereditary factor seems to be transmitted as a simple dominant by and may affect both sexes. Atavism may occur.

Although various forms of treatment have been advocated, none seems to be satisfactory. However, cauterization, radium packs, iron, and transfusions are used.

The authors’ patients—men of 51 and 70—both had hemoglobin levels lower than those usually described and lesions in the skin, mucous membranes, upper respiratory tract, and colon. One case had microscopic hematuria on several occasions.

The authors make the point that in cases of recurrent epistaxis or chronic anemia for which no cause can be ascertained, hereditary hemorrhagic telangiectasia should be considered and a search made for the lesions in the nasal, oral, and pharyngeal mucosa. The presence of telangiectases in the skin and a familial history of similar lesions or epistaxis complete the diagnosis.

(Recently the use of thrombin-fibrin foam has been of value in controlling local bleeding, particularly from the nose.)


The author reports a case of a 36 year old white male with hemorrhagic telangiectasia (probably similar to the atavistic type of atypical cases without positive familial history) who had suffered from repeated epistaxis from age 14 and in later life from gastro-intestinal hemorrhage severe enough to produce an incapacitating anemia. Multiple gastric telangiectases were seen by gastroscopic examination. An aneurysm of the pulmonary artery was present which did not increase appreciably in size during 7 years of observation. Aneurysm of the pulmonary artery had not been previously reported. A unique feature at autopsy was the presence of multiple hazelnut-sized aneurysms of the splenic artery.


A case of congenital afibrinogenemia in a boy of 11 is presented, and 6 other cases recorded in the literature are reviewed. The principle features of the disease are its hereditary character, a high incidence of consanguinity in the parents, the susceptibility of both sexes, a total absence of fibrinogen in the blood, complete incoagulability of the blood, a usually prolonged bleeding time, a great reduction in capillary resistance, a low erythrocyte sedimentation rate, and in some cases intermittent thrombocytopenia. The absence of fibrinogen is regarded as the principal cause of the hemorrhagic diatheses, but diminished capillary resistance may be a contributory factor. The principle distinctions between congenital afibrinogenemia and hypofibrinogenemia are discussed. The greatest differences occur in the clotting time; it is normal in the latter condition whereas no clotting occurs in the former. The authors conclude that from the literature it would appear that congenital fibrinopenia is caused probably by some hereditary defect of fibrinogen formation whereas the acquired type is caused by some toxic or neoplastic interference with fibrinogen formation. When acquired, the condition is sometimes transitory. It is thought that the liver and bone marrow are concerned with the function of fibrinogen formation.
Hemophilia-like Disease in the Female (with a note on the clotting time of the recalciﬁed plasma).
A case of a 30 year old female resembling hemophilia both clinically and in laboratory findings is presented showing bleeding into muscles, intermittent hematuria, normal bleeding and clot retraction times, prothrombin concentrations and platelet counts with terminal hemorrhage at base of tongue. Coagulation was markedly delayed (17–51 minutes by Lee-White method). Madison and Quick compare this case and true male hemophilia and ﬁnd them alike except for age of onset and clotting time of recalciﬁed plasma. Oxalated hemophilic plasma subjected to high centrifugation clots signiﬁcantly more slowly on recalciﬁcation than that obtained by spontaneous sedimentation or slow centrifugation. This case did not show that difference. Armand J. Quick (in Am. J. M. Sc. 201, 1941) showed that the test was consistently positive in a small series of true hemophilia cases but negative in one other atypical or hemophilia-like condition. The signiﬁcance of the test is not yet known. In the newly discovered hemorrhagic disease of swine the coagulation time of recalciﬁed plasma is positive just as it is in human hemophilia which this so closely resembles. Tourniquet tests were positive on several occasions and spontaneous nontraumatic hemorrhages occurred. The coagulation defect, however, appears to be the primary factor and the authors consider the term “hemophiloid” an appropriate one.

Differential Diagnosis of Hemophilia and Hemophilia-Like Diseases

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<th>Heredity</th>
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<td>Spontaneous</td>
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<td>Clotting time of recalciﬁed plasma</td>
<td>Positive</td>
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The authors present the case and familial history of a patient with a hemorrhagic diathesis symptomatically resembling hemophilia.

Case Report: A 39 year old soldier of Greek birth suffered his fourth attack of hematuria in 3 months. The sequence of events was the same in each instance—in the course of his work he lifted a heavy weight and about 4 hours later passed bloody urine with considerable pain. The past history revealed that he had been severely incapacitated from birth to the age of 14, with skin, mucosal, visceral, muscle, and even on one occasion cerebral hemorrhages and for the next 10 years bled profusely and for long periods from minor cuts and wounds. Examination revealed a large submucosal hemorrhage centered at the left ureteral orifice, hyperextensibility of the joints, rudimentary toe nails, and undue glossiness of the finger nails. It was otherwise negative. In spite of the severe bleeding there was no anemia. Coagulation time, prothrombin time, and platelets were normal. Bleeding times done by the Duke and saline methods were normal but bleeding began again spontaneously about 5 minutes after the completion of each test and continued for a further two minutes.

Investigation indicated that the family suffered from similar and often fatal hemorrhagic tendencies affecting 37 of 62 males and females for at least 4 generations. The tendency seemed to be inherited as a Mendelian dominant and was inbred through marriage between cousins twice removed. Although the patient could not remember exactly, he suggested that rudimentary toe nails and hyperextensibility of the joints were associated with the tendency to bleed in his family history. The authors propose that this association may well be due to some hereditary anomaly of collagen condensation. The capillaries could not be examined for distortion and evidence of defective power of contractility.

The authors studied the effect of quinine sulfate on the prothrombin time of normal subjects. Five normal males ranging in ages from 18 to 43 years, whose nutritional state was satisfactory and whose prothrombin times were normal, were given single grain doses of quinine sulfate by mouth daily for periods ranging from 6 to 16 days. In all cases the drug produced a significant increase in the prothrombin time, varying from 5 to 11.8 seconds. The times promptly regressed on discontinuation of the drug. On repeat testing, the concurrent administration of vitamin K afforded full protection in all individuals from this quinine sulfate-produced hypoprothrombinemia. Neither the minimal hypoprothrombinemic dose of quinine nor the optimal vitamin K dose has been established yet.

The authors urge the prophylactic administration of vitamin K to troops receiving quinine sulfate for the purpose of eliminating the danger of prolonged bleeding from wounds.


Various investigations indicate that the synthesis of prothrombin probably occurs in the liver. Rats with large primary hepatic tumors were used for the testing of prothrombin activity before and after the administration of dicoumarol. Simultaneous observations were made on normal rats and on those bearing tumors in other parts of the body. The rats with spontaneous mammary tumors, induced skin tumors, or inoculated Flexner-Jobling tumors did not show a prolongation of the normal prothrombin time. On the other hand, the presence of primary hepatic tumors may cause a mild hypoprothrombinemia. Dicoumarol in standard doses (1.5 mg.) usually caused a more severe hypoprothrombinemia in rats with primary hepatic tumors than in the other rats. The extent and duration of the hypoprothrombinemia is probably influenced by the amount of normal hepatic tissue present. Vitamin K protected normal rats from this dicoumarol effect, but the protective action is either lessened or abolished in those with primary hepatic tumors.


A case of hypoprothrombinemia is presented. The patient, a 56 year old white male, presented with massive hemorrhages into various muscles, from mucous membranes, the gastro-intestinal and genitourinary tracts, and a marked anemia, with remissions and exacerbations leading to death in a few months. Laboratory data revealed normal bleeding time, increased coagulation time, poor clot retraction, normal platelets, and a negative tourniquet test. The patient was Rh negative but no evidence of an anti-Rh agglutinin was found. The prothrombin time was markedly prolonged, prothrombin concentration low, blood calcium and fibrinogen were normal. A sternal puncture revealed normal marrow. Autopsy revealed scattered hemorrhages and granuloma (questionably tuberculous) of the lungs, liver, and nodes. The possibility that this might be Hodgkin's disease or sarcoidosis was considered. However, the authors do not feel that there was a causal relationship between the hypoprothrombinemia and other conditions. Causes for secondary hypoprothrombinemia were ruled out. There was no evidence for K avitaminosis and there was a lack of response to various vitamin K preparations. Autopsy showed minimal liver damage and liver function tests were negative after fully developed bleeding tendencies were established. Therefore there was no evidence for vitamin K fastness secondary to liver damage. There was no dicoumarol administration. The authors had previously reported 4 other cases of idiopathic (questioned) hypoprothrombinemia and realize that this case differs from the others in certain fundamental differences (i.e., age of onset, familial history, course, coagulation time, clot retraction and bleeding, and tourniquet tests) and conclude that cases thus termed represent more than one disease.


Shortly after hydroxycoumarin was discovered as the causative agent of hemorrhagic sweet clover disease, it was observed by Field, Overman, and Baumann that pregnant and lactating rats tolerate higher levels of the anticoagulant than normal females, and in an extension of this study it was noted that continuous feedings of the anticoagulant to female rats with suckling pups caused hemorrhages to appear...
in the young. The authors demonstrated that the drug fed lactating rats produced a hypoprothrombinemia in the sucklings and the suckling pups are subject to hemorrhages. It is not known whether the drug passes directly through the milk or whether a metabolite from it is the cause of the hypoprothrombinemia and hemorrhage in the young. Vitamin K afforded a greater protective action in the pup than in the mother, but it cannot yet be stated whether the protective action is due to the transmission through the mammary gland of the intact vitamin K or an active metabolite. Hypoprothrombinemia can also be induced in suckling rats by giving large quantities of acetylsalicylic acid to the mothers. Dairs and Porter in the British Medical Journal, May 27, 1944, reported on the favorable clinical results of the treatment of puerperal thrombosis with dicoumarol.

It would appear that removing the suckling from the mother or administering vitamin K prophylactically to the baby would be advisable.


The authors conducted experiments to show that the methylxanthines (caffeine, theobromine, and theophylline) induced in the dog, rat, and rabbit a state of hyperprothrombinemia as reflected by shortened plasma prothrombin times and indicate that, as a result of the induced hyperprothrombinemia, the hypoprothrombinemic action of the anticoagulant dicoumarol is lessened.

The hyperprothrombinemic effect was not exhibited by other purines, pyrimidines, and related compounds. The action from a single dose of methylxanthine persisted 4 to 5 days in the dog. Through repeated small doses, the action was maintained for periods up to 30 days. When the methylxanthines were given either with or 24 hours after the anticoagulant they not only reduced the intensity of the hypoprothrombinemic response but also shortened its duration. Single doses of the methylxanthines protect a standardized dog against repeated doses of dicoumarol for periods up to 14 weeks. Continued ingestion of caffeine and theobromine prolonged the survival time of rats fed the anticoagulant daily. The authors suggest that the methylxanthines provide a functional stimulation of hepatic tissue which accounts for the hyperprothrombinemia in normal animals and for the protective action against the anticoagulant. They caution that their prolonged use in cardials might augment the tendency for thrombus formation which is a frequent complication.


The authors present 2 cases of proved bacterial endocarditis which showed early improvement following penicillin therapy but fatal termination from hemorrhage. One patient, a 37 year old female, was treated with penicillin only, with a total of 700,000 units and died with extensive cerebral hemorrhage. The other, a 22 year old white pregnant female, received 54 grams of sulfamerazine and 1 month later delivered a viable 7 months baby. At this time, a course of 1,400,000 units of penicillin and 1.1 Gm. of heparin was given. The patient died 1 month later. Autopsy revealed widespread intraperitoneal, mesenteric, and pleural hemorrhages. This prompted the authors to investigate the effect of penicillin on heparin tolerance. Studies of prothrombin times, platelet counts, and heparin tolerance curves were made on 10 cases before, during, and after penicillin treatment. Two patients showed a spectacular delay in coagulation time occurring after administration of 10 mgm. of heparin with a 1 to 7-fold increase over the normal levels, in 5 cases mild increases of 1 to 2 minutes were noted, and in 3 cases no changes occurred. No changes in the other determinations (platelets, prothrombin time, R.B.C., Hgb.) were noted. The tendency to this change in the tolerance is important in the treatment of bacterial endocarditis if penicillin is used with adjuvant heparin therapy, and the authors suggest that it is advisable to run heparin tolerance tests as a precautionary measure when both drugs are used at the same time.


Twenty normal subjects were administered penicillin by oral and intramuscular routes and its effect on blood coagulation was studied. After having first established base lines, determinations on the penicillin level, clotting, bleeding, and prothrombin times were made at 15 and 30 minute intervals after administration of the drug. The patients were found to show a marked fall in the clotting time which occurred
in inverse ratio to the penicillin concentration, and it persisted at a depressed level even after penicillin had completely disappeared from the blood, in some cases for as long as 1 hour. Bleeding times also fell, but the effects were not marked and were transient. Prothrombin times did not show a unidirectional change. A striking alteration in the blood as the penicillin levels rose was the production of a nonretractile clot.

The authors maintain that penicillin is conducive to thrombus formation and suggest investigative studies to test the value of the drug as a coagulant in hemorrhagic disorders. This paper contradicts the results obtained in the previous paper abstracted here, and further investigation is indicated to establish the effect of penicillin on coagulation.


The authors have prepared two protein fractions from cell and calcium-free human plasma both of which have a definite effect in lowering the coagulation time of hemophilic blood. One of these protein fractions requires the presence of both calcium ion and prothrombin to exhibit its activity, while the other acts as a true thrombin since it can covert fibrinogen to fibrin in the absence of calcium and prothrombin. Fibrinogen is the plasma protein coagulating on the addition of thrombin only. Prothrombin was detected by a modification of Quick's method, using 0.1 cc. of the plasma fractions rather than of whole plasma. Several fractions of plasma containing varying amounts of albumin, alpha, beta, and gamma globulin, and fibrinogen were tested for antihemophilic activity. The greatest activity occurred with that fraction called Fraction I by the authors—which contained the largest amount of fibrinogen (61 per cent) and which also appears to contain the antihemophilic fraction. These investigators hope to subfractionate a highly potent injectable material from Fraction I for use in the treatment of hemophilia.


Some preliminary observations on the in vivo effect of the administration of "Fraction I" of plasma to hemophiliacs are presented. This fraction contains 60-70 per cent fibrinogen together with smaller amounts of the other globulins. The intravenous or intramuscular administration of doses varying from 11.5 to more than 125 mg. of "Fraction I" of pooled human plasma reduced the coagulation time of hemophilic blood toward or to normal values in 15 of 16 cases in which it was employed. Fibrinogen is not the active antihemophilic principle in this fraction. The dosage for therapeutic use has not yet been established. It was found that 300 to 600 mg. of the globulin have an effect equal to that obtained by 80 cc. of fresh plasma or 100 cc. of fresh whole blood. The only undesirable reaction observed was a slight sclerosis of the injected vein in one case, and this was thought to be probably due to the high concentration of the injected material. There was no change in prothrombin times. Injections of this active globulin fraction had no influence on the effectiveness of subsequent injections of the material.

The work of these investigators suggests that soon a substance may be available whereby hemophiliacs may be maintained in a relatively normal state by the injection of maintenance doses of the effective plasma protein.