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JOSEPH F. Ross, M.D., Editor

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ANEMIA

SURVEYS OF NUTRITION OF POPULATIONS: IRON AND ANEMIA. J. B. Youmans, E. W. Patten, R. Kern, R. Stein-
kamp, H. Johnson and C. Ball. From the Departments of Medicine and Biochemistry, Vanderbilt Uni-

The results of a study of the nutrition of a rural population of some 1,000 persons in middle Tennessee, in respect to the intake of iron, signs and symptoms of anemia and type of anemia, are reported.

The daily intake of iron as determined from a study of the diet was found in a large percentage of the population to be below the levels commonly recommended. An anemia was found in approximately 24 per cent of the population. The incidence was greatest in females at the age of puberty and beyond. A decreased mean cell volume was found in 8 to 2.2 per cent of those 16 years of age and older. An increased cell volume was found in over one-third of the population. In 166 individuals the macrocytosis was marked. Five of these subjects were given folic acid therapy and responded with a slight but definite reticulocytosis.—G.E.C.


An investigation into the iron content of the two staple foods, wheat and pulses, was undertaken to throw some light on the common occurrence of iron deficiency anemia in North West India. The content was assessed by dietary survey and iron analyses and was found to be 22-27 mg. per day for male adults. The availability of the iron was tested by incubation of Chapattis and cooked dahl with HCl and pepsin. Forty per cent of the iron could be extracted in a soluble form, i.e., an available iron intake of 9-11 mg. per day. Though this is an adequate intake for men in Europe, factors such as malaria, dysentry and achlorhydria probably influence the intake adversely in India and make it insufficient for normal hemolytosis.—S.C.

DIAPHRAGMATIC HIATUS HERNIA. WITH SEVERE IRON-DEFICIENCY ANEMIA. S. O. SCHWARTZ and S. A. BLMENTHAL. From the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Ill. Am. J. Med. 7: 501-510, 1949.

Twenty patients with severe iron-deficiency anemia associated with diaphragmatic hiatus hernia are presented. Gastrointestinal symptoms were minimal but cardiovascular symptoms, in part due to anemia, were quite prominent. The authors briefly review the literature and comment on the pathogenesis of bleeding in hiatus hernia. The importance of suspecting a hiatus hernia in a patient, particularly a female past middle age, who has an iron-deficiency anemia without a history of bleeding, localizing symptoms or significant physical findings is stressed.—H.W.B.


A severe hemolytic anemia developed in a patient with Hodgkin’s disease. Splenectomy appeared to slow down but not to arrest the hemolysis. X-ray treatment was followed by remissions in the anemia but later the hemolytic process reappeared and the patient died.—S.C.
VITAMIN B₁₂


This is a useful review of the steps leading up to the isolation of the crystalline antipernicious anemia factor. The more outstanding contributions to the chemical fractionation of liver are mentioned, starting with the work of Cohn, Minot and others in 1928. The achievements of Laland and Klem in introducing new technics and isolating an active reddish-yellow fraction in 1936 are given due emphasis, and the progress made by Lester Smith's own group following the use of partition chromatography is described. Since the initial isolation of the crystalline factor by the Merck and Glaxo teams, it has become apparent that there are probably not one, but three red factors active in pernicious anemia. The molecule of vitamin B₁₂ contains cobalt and some readily hydrolysable group essential to its microbiologic activity. There is evidence to suggest that there may be some structural relationship with chlorophyll and heme pigments. The isolation by Rickes et al. of vitamin B₁₂ from the metabolism fluid of Streptomyces griseus has shown the possibility of the industrial production of a purified B₁₂ concentrate from fermentation liquors.—S.C.


Seventy-three responses to single intramuscular injections of vitamin B₁₂ were observed in 53 patients with pernicious anemia in relapse, the doses being graded logarithmically from 2.25 to 160 micrograms. The increase in red blood cells in fifteen days was thought to be a better measure of response than the reticulocyte rise. Two and five-tenths micrograms was the lowest dose which gave a small but definite response. The mean response to various doses was roughly proportional to the logarithm of the dose in the range of 5 to 80 micrograms and possibly even to 160 micrograms. A formula was devised from this which the expected response to any dose could be calculated.

Eighteen of 21 patients were maintained satisfactorily on 10 micrograms of B₁₂ every two weeks for six to fifteen months, but the author recommends larger doses for routine treatment to cover individual variation in requirements. Eight patients with neurologic changes showed significant improvement on being treated with B₁₂ (usually 40 micrograms per week). They were observed over a period of at least ten months.—S.C.


The authors applied bioautographic methods to the study of vitamin B₁₂ and substitute growth factors for L. leichmannii 333 and revealed marked similarities among such diverse materials as parenteral liver preparations intended for treatment of pernicious anemia, a fermentation A.P.F. (animal protein factor) and condensed fish solubles. However, their findings suggest that all studies on the apparent vitamin B₁₂ content of natural materials determined in the usual form of tube assay should be checked by a bioautographic study to ascertain the types of growth factors present.—P.F.W.


Lambs suffering from a cobalt deficiency showed a loss of appetite, an anemia, loss in body weight, and eventual death. These lambs quickly improved when they were fed 1 mg. of cobalt each day. Injections of the same amount produced no improvement. It thus seemed possible to the authors, considering vitamin B₁₂ as a necessary metabolite for sheep, that cobalt is changed to vitamin B₁₂ by the rumen flora. According to this idea, cobalt deficiency is essentially a B₁₂ deficiency, and if this vitamin is furnished via injection a favorable response should follow. Daily injections of B₁₂ in amounts up to 125 μg gave no response.

The authors conclude that these limited observations give no support to the theory that vitamin B₁₂ is an important intermediary in cobalt metabolism in lambs.—R.C.C.
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The effect of crystalline vitamin B₁₂ on the excretion of tyrosine metabolites in pernicious anemia was studied by fractionating the ether-soluble urinary phenols into a fraction containing the hydroxyphenyl acids (A) and a fraction containing ether-soluble phenols not soluble in sodium bicarbonate (B). Three of the 4 patients studied were noted to have elevated pretreatment phenol fraction ratios (A: B) which decreased after the parenteral administration of crystalline vitamin B₁₂. In 2 of these patients the decrease in ratios was noted to precede the reticulocyte response. The one patient who did not have elevated pretreatment ratios was a Negro man who responded to vitamin B₁₂ therapy with an increase in ratios which preceded reticulocytosis. Crystalline vitamin B₁₂ in the very small amounts needed to produce remission in pernicious anemia was found to have a prompt effect on tyrosine metabolism as indicated by these variations in the excretion of tyrosine metabolites.—G.E.C.

Liver Extracts, Vitamin B₁₂ and Thymidine. K. Hausmann. From the Department of Internal Medicine, St. Georg General Hospital, Hamburg, Germany. Lancet 2: 961-963, 1949.

The author reports briefly investigations into the relationship of different hemopoietic factors and makes a number of interesting points.

Cobalt-containing red compounds isolated from cow dung and broth cultures of Streptomyces griseus were ineffective in treatment of pernicious anemia, until digested with hog stomach mucosa or pancreatic enzyme. They then showed hemopoietic activity. A second group of cobalt-containing red pigments present in purified liver extracts was clinically active and precipitable by saturated ammonium sulfate. Thirdly, cobalt-containing red pigments were found in autolyzed liver and in urine, these being clinically active but soluble in ammonium sulfate. It is suggested that enzymatic digestion converts these forms of B₁₂ from one to the other and that the amounts in liver vary with the degree of autolysis.

Purified liver extracts prepared from postmortem livers of patients with megaloblastic anemia treated with folic acid showed clinical activity due to their B₁₂ content.

Two patients with pernicious anemia treated with purified Thymidine showed a good hematopoietic response, 100-200 mg. daily being given.—S.C.

Blood Coagulation and Hemorrhagic Disease

The Biochemistry and Clinical Application of Vitamin P. B. A. Levitan. From the Department of Physiology, Faculty of Medicine, McGill University, Montreal, Canada. New England J. Med. 241: 780-789, 1949.

Papers on the biochemistry, metabolism, pharmacology, toxicity, and suggested mechanisms of action of flavones are reviewed. The possible clinical significance of vitamin P therapy in so-called capillary-fragility states is discussed. Of the studies on various diseases possibly benefited by treatment with vitamin P preparations, that on the hemorrhagic tendency following experimental radiation exposure seems the most convincing although it is not conclusive. It is obvious in reviewing several of the papers mentioned here that measurements of capillary fragility have not been well standardized.—P.F.W.


The authors summarize their work as follows: Normal platelets were not seen to initiate fibrin formation in normal plasma, enclosed in silicone-coated surfaces. The platelets did serve as foci of formation of the fibrin network. Part but not all of a complex of factors which favor rapid conversion of prothrombin to thrombin is concentrated in or on the platelet.—R.C.C.

Changes in the Coagulability of the Blood After Radiation Therapy. The Results of Studies Using the Modified Waugh-Ruddick Test for Increased Coagulability. S. B. Silverman. From the De-
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Department of Pathology, Division of Surgical Pathology and Haematology, McGill University, Montreal, Canada. Am. J. Roentgenol. 62: 541-546, 1949.

Using the modified Waugh-Ruddick test, studies of blood coagulation were done on a series of patients receiving radiation therapy for neoplastic disease. The coagulability was found to be decreased and this trend was roughly proportional to the total irradiation received. The possible causes of this change are reviewed.—F.F.W.

Studies on Thrombocytopenia. I. A Reliable Test for This Principle in Organ Homogenates and in Urine. K. Singer and R. Rotter. From the Department of Hematologic Research, Medical Research Institute, Michael Reese Hospital, Chicago, Ill. J. Lab. & Clin. Med. 34: 1336-1351, 1949.

When organ homogenates were injected into rats with a high degree of liver cell damage produced by carbon tetrachloride, a significant decrease in the platelet count was observed. The same organ suspensions did not reduce the platelet count of normal animals. The platelet-reducing agent was found in spleen, lung, heart, kidney and brain of dogs, cattle and sheep. Normal as well as pathologic human spleens were found to be active. Spleens from patients with thrombocytopenic purpura were also active but no more so than spleens from patients without thrombocytopenia. This factor was also found in human urine.

The authors postulate that thrombocytopen, like many of the known steroids, is inactivated in the liver and excreted in the urine. No evidence is presented which would support the hypothesis that thrombocytopen is involved in the pathogenesis of thrombocytopenic purpura.—G.E.C.


This is a report of a patient exhibiting a hemorrhagic tendency associated early in the clinical course with a qualitative defect of the platelets. Despite a normal platelet count there was a prolonged recalcification time and a high serum prothrombin activity. This could be rectified completely by the addition of normal platelets to the patient’s deplateletized plasma, whereas the patient’s platelets could not correct the abnormality induced in normal plasma by removal of its platelets. The authors point out qualitative differences in platelets may be more important than suspected. The degree of thrombocytopenia necessary to induce clinical and laboratory manifestations of purpura does seem to vary from patient to patient. A procedure for the measurement of the functional capacity of platelets is proposed. The patient subsequently developed thrombocytopenia.—P.F.W.


The diagnostic features of and diagnostic tests for various hemorrhagic diseases are presented. Such topics as vascular changes, clot retraction, role of platelets, “prothrombin accelerators,” “recalcification time,” prothrombin activity, prothrombin consumption and fibrinolysins are very ably discussed.—P.F.W.


This paper is a report of the results of a one and one-half year study of blood coagulation in 45 patients with polycythemia vera, 18 patients with leukemia and 16 patients with various other diseases. Two new tests for blood coagulation were used. These two methods are the clot retraction rate which is a quantitative measure of the clot retraction obtained by electric resistance measurements and a modification and simplification of the heparin tolerance test which measures the effect of added heparin upon the clotting time of blood.
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In chronic leukemia, one-half of the patients showed a coagulation defect characterized by a prolongation of the heparin clotting time, decreased clot retraction rate, and a slight thrombocytopenia between 110,000 and 180,000. The severity of this defect was closely related to the degree of hemorrhagic symptoms.

Of the untreated patients with polycythemia vera, 33 per cent showed increased clot retraction rates and platelet counts above 400,000.—G.E.C.


In the course of twelve months, 5 cases of purpura occurring in association with pulmonary tuberculosis were seen at a general medical out-patient clinic. In addition to skin lesions, gastrointestinal hemorrhage occurred in two, renal hemorrhage in one, and arthritis in one. There was no thrombocytopenia and the condition was thought to be due to a sensitivity rather than a toxic effect on the bone marrow.

Two patients deteriorated rapidly and died, but the other 3 showed a spontaneous recovery from the purpura.—S.C.


A case is reported of a 67 year old female with polycythemia vera, previously treated with phlebotomies and x-irradiation, who received approximately 8.4 mc. of radioactive phosphorus intravenously and five weeks later developed hemorrhagic skin manifestations, nasal bleeding, marked thrombocytopenia (platelets below 5,000) and increased capillary fragility. Bone marrow study revealed megakaryocytes in normal numbers but with unusual cytologic changes which were quite different from those seen in idiopathic thrombocytopenic purpura. Spontaneous clinical recovery occurred within six weeks. Sternal marrow at five months showed essentially normal megakaryocytes with a minimal number of bizarre forms. The platelet count at this time, however, had risen to only 55,000. Capillary fragility remained slightly increased.

Although thrombocytopenia has been previously reported as a complication of radioactive phosphorus therapy, this patient illustrates the potential danger of instituting treatment when there is already a mild or moderate thrombocytopenia. The peculiar alterations in the megakaryocytes were attributed to radioactive phosphorus although this could not be proved since an examination of the marrow was not made prior to treatment. Further study of megakaryocyte changes in irradiation-induced thrombocytopenia is indicated.—H.W.B.


The first case reported is a member of a hemophilic family. After a series of blood transfusions an anticoagulant was demonstrated in his blood.

The second case is a 58 year old male, with herpetiform dermatitis. For the first time in his life a series of acute hemorrhages was observed, alternating with the recurrence of the skin disease. The greatly delayed clotting time was found to be related to a lack of prothrombin consumption. An anticoagulant was found in the blood which acted on the first stage of the clotting mechanism and had no antithrombin effects. This anticoagulant appeared to interfere with the interaction between thromboplastinogen and platelet enzyme and did not modify the Quick prothrombin time. The electrophoretic study showed an increase in the globulins, most marked in the γ globulins. Fractionation showed the anticoagulant activity to be associated with the γ globulins. Different therapeutic approaches were tried: blood transfusions, thrombin, washed red cells. Their efficacy is discussed. The etiologic part played by pemphigus and allied disorders in such hemorrhagic diatheses is considered.—J.P.S.
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A series of cases diagnosed as Laennec's cirrhosis and Banti's syndrome treated by portal shunt operations is reported. There was an operative mortality of 35 per cent in the first group and no deaths in the last. It is of extreme interest that 4 of the 7 deaths occurred within a few hours of uncontrollable hemorrhage from the site of operation due to a state of incoagulability of the blood. The preoperative prothrombin times were normal in all these patients and for the first two hours of the operation in each case there was no evidence of the failure of the blood to clot. However, after varying periods from two to three hours after the operation was commenced, blood began to ooze from all cut surfaces. Samples of blood collected in test tubes failed to clot for many hours.—P.F.W.

SPORADIC HEMOPHILIA IN SWITZERLAND. A. Fonio. From the Medical Department of the University of Berne, Switzerland. Schweiz. med. Wchnschr. 79: 827-828, 1949.

Aside from the many known family histories of hereditary hemophilia, the author found in Switzerland twenty-four families with so-called sporadic hemophilia. Cases with a single sporadic bleeder are described, but in eight instances there was also a bleeding tendency with the mother being a conductor. In two instances there was a bleeding tendency of the grandmother, and in one even of the great-grandmother. In five families there were several siblings with bleeding. In one instance a bleeding tendency of both mother and grandmother was found.

The clinical symptoms of sporadic hemophilia are exactly the same as those in hereditary hemophilia, as far as its nature and also its severity are concerned. Sporadic hemophilia may be diagnosed when there are (1) single bleeders in pedigrees that have not shown bleeders for several generations, (2) several sons of the same sibling group who are bleeders.

There can be found the same bleeding tendency in conductors as in family histories with hereditary hemophilia. Etiologically, there is probably a hemophilic hereditary predisposition handed down latently through several generations. An occurrence for the first time, by mutation, is less likely.—C.M.


By means of experimental investigations the author proves, in agreement with Quick, that the normal plasma contains a coagulation factor which acts independently from thromboplastin, prothrombin and fibrinogen. This factor is thermolabile, belongs to the fraction of the euglobulins and is responsible in these cases for the occurrence of hemophilia.—C.M.


It is well known that dicumarol can inhibit intravascular clotting if given in sufficient dosage to depress the prothrombin level markedly. There is not general agreement, however, as to the effectiveness in clot inhibition of clinically safe levels of dicumarol-induced hypoprotrombinemia. The many clinical studies indicate that, while the drug is not 100 per cent effective, the incidence of thromboembolic complications in postoperative conditions, myocardial infarction, etc., has been appreciably lowered by properly controlled use of dicumarol. The data obtained from experimental animal studies, on the other hand, has been confusing and contradictory.

In the present study in which a total of 41 dogs and 113 veins (traumatized by a surgical clamp) were used, the incidence of thrombosis was not significantly reduced by a degree of dicumarolization considered therapeutically safe. There was marked inhibition of thrombosis at lower levels of prothrombin but an alarmingly high incidence of hemorrhagic complications. Results are tabulated with daily prothrombin determinations and coagulation times.—H.W.B.
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**THE PRODUCTION AND PREVENTION OF THROMBOSIS AND EMBOLISM.** E. C. Mason and S. P. Harrison. From the Departments of Physiology and Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla. Surg., Gynec. & Obst. 39: 640-642, 1949.

The mechanism of production and prevention of thrombosis was studied by means of a simple artificial circulatory system. Freshly heparinized blood was circulated through the system, the rate of flow being regulated by a stopcock, and thrombus formation was initiated by the addition through a side arm of controlled amounts of lung tissue extract.

From their observations the authors conclude that tissue extract is the most potent agent in the production of thrombosis; that the clinical value of heparin in the prevention and treatment of thrombosis lies in its ability to neutralize thromboplastin (tissue extract), and that whether or not an intravascular clot forms at the point where tissue extract is introduced depends mainly upon the rate of blood flow and also upon the rate at which the tissue extract is introduced. The authors appear adequately to have demonstrated, by means of this apparatus and a histologic study of the blood clots, that the factors involved in extravascular and intravascular coagulation are similar except for the single mechanical factor of the streaming action of the blood. —H.W.B.

**LEUKOCYTES AND LEUKEMIA**


Many cases of congenital leukemia have been reported, but few have stood the test of critical evaluation. The 3 cases here reported must be accepted as congenital. In 2, clinical and hematologic changes were found immediately after birth, in the third case two weeks later. The clinically leading sign was always hemorrhagic diathesis. All 3 cases were acute myelocytic leukemias, 2 of them with predominance of paramyeloblasts and tendency toward formation of monocytoid forms, the third with micromyeloblasts. All 3 cases proved fatal within a short time; in two instances the diagnosis was ascertained by autopsy. The blood of the mothers was normal.—C.M.


A micromethod is described which allows the determination of the nucleotid content of even small blood samples. The blood is centrifuged, the plasma discarded, and the layer of leukocytes fixed in formalin. This pellicle of leukocytes is then worked up with a special method. It was found that in leukemic patients the increase of the nucleotid content does not parallel the increase in number of white cells; in other words, apparently the cells are defective in this respect.—C.M.


The authors investigated, with the Warburg apparatus, the respiration and glycolysis of leukemic blood. In chronic myelocytic leukemia there was found a metabolism typical for tumors, which could be normalized by the use of urethane. Myeloblastic and lymphatic leukemias did not show this alteration. In successfully treated cases there was found an increase in oxygen consumption.—C.M.

**EOSINOPHILIC LEUKEMIA AND FAMILIAL EOSINOPHILIA.** Two Illustrative Cases. J. D. Gray and S. Shaw.

From the Belgrave Hospital for Children and Royal Eye Hospital, King's College Hospital Group and the Charing Cross Hospital Medical School, London, England. Lancet 2: 1131-1134, 1949.

The literature on eosinophilic leukemia and familial eosinophilia is reviewed, together with 2 cases of eosinophilia. The first, a boy of 1 year 4 months, was thought to have leukemia on the basis of a shift to the left in the granulocytes in the marrow, the presence of an unusual type of early myelocyte and absence of a family history. The second child, aged 2 years 4 months, was classed as a familial eosinophilia as his mother and other members of her family also showed eosinophilia.

The existence of eosinophilic leukemia as an entity has been debated but the authors believe that there is sufficient evidence to justify such a diagnosis in some cases. Eosinophilic infiltration and the relation of allergy to familial eosinophilia are also discussed.—S.C.
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