HEMOLYTIC SYSTEMS and ERYTHROCYTE DESTRUCTION


Lysolipid, a hemolytic substance, produced by the action of snake venom on egg yolk, contains a mixture of the lysolipids, lysocephalin and lysolipid. The effect of various factors upon the hemolytic action of lysolipid with washed rabbit erythrocytes is described. Lysis was produced very rapidly at first, then ceased within a few minutes at room temperature. A given amount of lysin appeared to hemolyze a fixed number of cells, under specified conditions. The more dilute erythrocyte suspensions required relatively more lysin per cell, for 50 per cent hemolysis of the suspension. There may be an equilibrium between the lysin dissolved in the medium and that adsorbed on the cells.—O.P.J.


This paper reports two experiments that show cells are heterogeneous with respect to certain lysins and that after the lysin has initiated a process in the cell preceding hemolysis, it cannot be stopped by diluting the system.—O.P.J.


Oxygenated blood diluted 1 in 20, added at 20 C. to a glucose solution begins hemolysis when the concentration of the solution is 2.2 Gm. per 100 cc. and completes hemolysis when the concentration is 1.2 Gm. per 100 cc. After the addition of blood, there is a delayed hemolysis, or prolytic phase, which lasts 60 to 80 minutes. Without further manipulation this is followed by hemolysis to completion. Increases in temperature and decreasing ratios of blood to hemolyzing system accelerates delayed hemolysis. The addition of chlorhidin inhibits delayed hemolysis. Delayed hemolysis may be dependent on enzymic activity.—O.P.J.


Utilizing the technic of differential red cell agglutination applied to the enumeration of donor erythrocytes in the circulation of a recipient, the authors have studied the kinetics of red cell destruction. Studies were made of the destruction of normal erythrocytes in
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diseased persons and of defective erythrocytes in normal subjects. Equations were derived for the study of the kinetics of destruction of red cells. They confirmed the previously demonstrated fact that transfused normal erythrocytes completely disappear in 120 ± 15 days in a normal recipient and are lost in a manner that describes a straight line on rectilinear paper. This rate appears to be due to the age of the transfused cells. Defective transfused cells may survive a shorter time due to premature aging of the cells, the curve again being a straight line. In contrast, in a diseased recipient normal transfused erythrocytes may be decreased by a random destructive mechanism acting in addition to the normal aging process. This random destruction may occur at a constant rate, or it may occur at an increasing rate. Curves dependent upon this random destruction are logarithmic or exponential in character.—R.B.C.

ANEMIA

THE EFFECT OF SPLENECTOMY AND RETICULO-ENDOTHELIAL BLOCKADE UPON THE ANAEMIA OF LEAD POISONING IN GUINEA PIGS. R. Pirrie. From the Muirhead Department of Medicine, University and Royal Infirmary, Glasgow, Scotland. J. Path. & Bact. 64: 211–222, 1952.

This investigation was undertaken in order to gain further information about the relative importance of dyshemopoiesis and hemolysis in the production of anemia in chronic lead poisoning. Guinea pigs were splenectomized before and during experimental lead poisoning and the changes in the peripheral blood, bone marrow and weight and iron content of liver and spleen studied. Observations upon the effect of reticulo-endothelial blockade by trypan blue were also made. Lead seems to exert its hematologic effect primarily upon the red cell precursors in the bone marrow. The resultant defective erythrocytes are removed from the circulation by the spleen and reticulo-endothelial system in general. Dyshemopoiesis and hemolysis both appear to play a part in the production of anemia in chronic lead poisoning.—O.P.J.

CONTRIBUTION TO THE HEMOLYTIC CRISIS IN CONGENITAL HEMOLYTIC JAUNDICE. F. Heřmanůský. From the Medical Department, State Hospital Motol, Praha. Časop. lék. česk. 90: 15, 1951.

A case of congenital hemolytic jaundice, observed in a crisis, is reported, in which marked reticulocytopenia and a slight decrease in the white blood cells and platelets was present. There was also a definite arrest of maturation in the moderately hyperplastic erythropoietic tissue. At the end of the crisis a leukocytosis appeared at first, followed very soon by a rapidly increasing reticulocytosis and a return of the platelet count to normal. In the bone marrow, normal maturation reappeared with a preponderance of mature normoblasts. During the crisis there was no definite increase of the bilirubinemia. Neither the moderate spherocytosis nor the increased fragility changed significantly during the crisis. On the basis of this and similar observations, it is obvious that the arrest of maturation, especially in the erythropoietic tissue, plays an important part during a crisis. This can be explained as evidence of sudden overactivity of the spleen. This bone marrow inhibition is often, but probably not constantly, accompanied by an increase in splenic hematologic activity, which may in some cases be due to the production of atypical iso-antibodies, and which further accelerates the rapid destruction of the congenitally abnormal red blood cells.—M.N.


The author observed in most cases of pernicious anemia a striking reticulum reaction in the bone marrow with increase of plasma cells, mast cells, fibro- and histiocytes. In 50 per cent of the cases there were numerous faci lymphocytes in the sternal puncture. In relapse, there was an increase in osteoclasts; in remission, there was an increase of osteoblastic reticulum cells.—C.M.
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IRON METABOLISM


Estimations of the serum-iron level and the iron binding capacity in 7 patients with hemochromatosis are reported. All showed an elevated serum iron level and a saturated or almost saturated iron binding protein. Oral iron tolerance curves were flat except in 1 case. These data confirm those previously published for hemochromatosis. It is surprising that 3 of the patients did not have complete saturation of the iron binding protein. It is not recorded whether or not these patients were suffering from infection at the time. It is unfortunate that 2 of the 3 patients showed the unsaturated iron binding protein were not cases proven by liver biopsy. —C.E.R.


In this investigation the kinetics of intravenously injected Fe" globulin IV-7 tracer in doses were observed by external scintillation counting over marrow, liver and spleen as well as by in vitro analysis of plasma and erythrocyte radioactivity. For details of method, reference to the original article by those interested is recommended. Thirty patients with erythropoietic disorders and 7 normals were studied. In normals, the tissue of major importance in depleting the plasma of the tracer was the bone marrow. After transient accumulation in the bone marrow, the Fe" increased in the erythrocytes as it was discharged from the bone marrow. A minor initial transient accumulation in the liver occurred in the liver. In patients, abnormalities in the initial direction or destination, as well as the velocity, were observed. With known marrow hyperplasia without splenic or hepatic abnormality, the velocity from plasma to marrow was increased. With marrow hypoplasia and initial accumulation in the spleen, the velocity of transfer from plasma to spleen was also increased. A large spleen was not indicative of a particular type of iron kinetics. Two types of splenic curves were observed: (1) erythrogenic spleen curve in which the spleen accumulated a greater than normal amount of iron as the high initial plasma concentration fell and subsequent discharge of iron from the spleen as the red cell concentration of radioiron rose; (2) erythrolelastic spleen curve in which the spleen showed the ability to accumulate an abnormally great amount of radioiron concomitantly with a fall in marrow radioiron and a rise in red cell concentration. "Erythroleastic" indicates excessive cell destruction. The liver was never observed to be the major remover of iron from the plasma to discharge it into cells. When the liver was the major primary accumulator, it continued to maintain high levels for many days. In those patients in whom Fe" did not accumulate in the second major compartment, the circulating erythrocytes, variations in the preceding kinetics were observed. Several such variations are described. The authors conclude that in vivo studies with Fe" utilizing this approach, is of value in the study and diagnosis of various hematopoietic disorders. This report should be reviewed in detail by those interested in the pathologic physiology of anemias. —R.B.C.

VITAMIN B₁₂ AND FOLIC ACID


The hematopoietic effect of various agents was tested on male mice following the peak of anemia induced by intraperitoneal injection of phenylhydrazine hydrochloride. The red blood cell counts determined under these conditions were increased comparably by injec-
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The compounds thymidine, alpha-ribose, 5,6-dimethylbenzimidazole, 1-D-ribose, 5,6-dimethylbenzimidazole, and 1,2-diaminoo-4,5-dimethylbenzene exhibited little or no anti-anemic activity, while the synthetic analog (2,5-dimethylbenzimidazole) of these degradation products of vitamin B12 inhibited red blood cell formation to a level below that obtained on a folic acid-free diet.—C.E.R.


Although wild type E. coli does not require vitamin B12 as a growth factor, the organism will absorb a large amount of B12 from the medium. Extracts of pig stomach inhibit this absorption. Lysozyme is without effect. This may offer an explanation of the effect of "intrinsic factor" as it is known that in patients suffering from pernicious anemia large amounts of E. coli are found in the upper intestine and even in the stomach.—C.E.R.


Cells of a vitamin B12 deficient mutant strain of E. coli are capable of absorbing radioactive vitamin B12, labeled with Co60 in excess of amounts required for growth or oxidation. This observation agrees with the finding of Koditschek and Hendlin using Lactobacillus lactis that these bacteria take up considerably more vitamin than is required for growth. In the presence of glucose, the absorption rate of deficient cells was decreased. No exchange of intracellular B12 in respiring cells could be demonstrated.—C.E.R.


The results are interpreted as indicating the involvement of vitamin B12 or of its physiologic derivative in the synthesis of serine from glycine. Folic acid or its physiologic derivative is involved in the synthesis of both moieties of choline from serine, and, through serine, from glycine.—C.E.R.

LEUKOCYTE PHYSIOLOGY and PATHOLOGY


Morphologic hematologic alone has definite limitations when the problem of determining the relationship of cells containing acidophilic spheroid cytoplasmic bodies is undertaken. Russell body cells, erythropoietic cells, eosinophilic leukocytes and globule leukocytes or Schollenleukozyten. However, when these four cell types are subjected to cytochemical analysis, certain of the reactions seem to have cytotoxicologic significance. The globule leukocytes of the sheep are for the most part located throughout the mucous membrane of the alimentary canal. They arise from small lymphocytes and migrate through the epithelium. The globules contain iron but do not give the hemoglobin reaction. They contain phosphatase but not stable oxidase and labile peroxidase. Milon and xanthoproteic reactions were negative, but the biuret reaction for peptide linkage was weakly positive and the reaction for argenine positive. The metachromasia obtained with aqueous toluidine blue was not abolished by digestion with hyaluronidase. Although the globules of the globule leukocyte are sudanophobic, the cytoplasm contains small sudanophilic particles which appear to be either Golgi material or mitochondria. Globule leukocytes in the sheep are distinct from eosinophilic leukocytes, Russell body cells and erythropoietic cells. They may arise as a reaction to the diffusion of substances of various origins into the mucous membrane.—O.P.J.

Macrophages do circulate in the blood stream under certain conditions and large numbers of them have been shown to move through the liver. The problem of determining their origin and the pattern of their sequestration has been attacked by studying mice after thorium dioxide was injected into the tail vein. Both histologic observations with measurements of the quantity in various parts of the body, and measurements of radioactivity were made.

The red bone marrow, spleen, gut, adrenals, kidneys, ovaries or testes, etc. liberate loaded macrophages which accumulate in the liver more rapidly than they are eliminated from the body. Some macrophages have at least one passage through the capillaries of the lungs, before reaching the liver. The observations and data indicate that this occurs, but they also indicate that a macrophage which has passed through the liver is somehow distinguished from one which has not, since the lungs eliminate primarily those macrophages which have come from the liver. Normal liver structure may not only be favorable for macrophage function, but may as well alter the character of such macrophages as enter the liver, in such a way as to account for their sorting out in the lungs.—O.P.J.


Experiments were devised to determine whether or not some agent in extracts of Ascaris could, on a single injection, stimulate the bone marrow to produce eosinophil leukocytes. Two extracts of Ascaris serum were made. One contained polypeptides with other protein break-down products and the other contained polysaccharides. When tested in rabbits and guinea pigs, the first extract was a more powerful eosinophilogenic agent than the second. The administration of antihistamine drugs prevented the eosinophilogenic action of the second extract. The ability of histamine alone to produce a transient eosinophilia was demonstrated. By using a substance possessing surface active properties, it was concluded that the second extract owed its properties to the adsorption of material during the process of separation. The temporary inhibition of the parasympathetic nervous system by atropine produced no changes in the eosinophil level. The stimulus for eosinophil production seems to be a direct action on the bone marrow by some substance derived from the material injected, or from some chemical reaction in which the injected material takes place.—O.P.J.


A man, age 73, was admitted to the University Hospital of Hradec Králové with generalized eczema. He had been given 650 mg. of an antihistaminic drug (phenergan) per os. The drug was discontinued because of increased fatigue and somnolence. On the sixteenth day after the withdrawal of the drug the white cell count dropped to 1000 with 7 per cent granulocytes, but without clinical symptoms of agranulocytosis. Treatment with penicillin was followed by a cure of the granulocytopenia in course of 10 days.

Since no other medication had been used, agranulocytosis is considered to be the consequence of phenergan therapy. The importance of blood smear examination during treatment with antihistaminic drugs is stressed.—M.J.

NEOPLASTIC DISEASE


Observations on 18 splenectomized patients with leukemia, generalized myeloid metaplasia, Hodgkin’s disease, lymphosarcoma and giant-follicle lymphoma are reported. Hemoly-
tic anemia, pancytopenia, thrombocytopenia and a large spleen causing pain were the indications for splenectomy in such patients. This is a form of therapy of very questionable value and as the authors mention in their summary is at most applicable to a very small percentage of such types of cases.—P.F.W.

**Multiple Myelomatosis Treated with Chlorothylamine. O. Zwetschke. From the Medical Clinic, University of Plzeň. Časop. lék. česk. 90: 585, 1951.**

A case of multiple myelomatosis treated with chlorothylamine is described. The patient remained in good condition for two years and three months. The treatment was repeated eight times at different intervals during this period and the total dose of chlorothylamine (TS 160) amounted to 126 mg.

A pathologic fracture of spine improved, the patient put on weight, lost his pains and was able to walk. The treatment is recommended for its simplicity and favorable effect.—M.Y.

**Chloroleukemia. L. Donner, A. Stieda and J. Vaněk. From the Second Medical Clinic and the First Institute of Pathological Anatomy, Charles University, Praha. Časop. lék. česk. 90: 278, 1951.**

The clinical picture, radiography and autopsy findings in a girl of 10, suffering from chloroleukemia are described. The patient was under observation for about six months and the clinical picture was that of an aleukemic paramyeloblastic leukemia. There was a marked osteoporosis with destruction of the internal part of the corticalis in some flat bones.—M.Y.

**The Incidence of Splenic Metastasis of Carcinoma. H. Abrams. From the Montefiore Hospital, New York, N. Y. California Med. 76: 281-282, 1952.**

The incidence of metastasis to the spleen in a series of 1000 consecutive cases of malignant neoplasm of epithelial origin was 9 per cent. In a group of malignant neoplasms of nonepithelial origin, the spleen was involved in 45 per cent. These data do not support the contention that metastasis to the spleen is rare or that the spleen possesses anti-neoplastic properties.—C.E.R.

**Gaucher’s Disease: A Review, and Discussion of Twenty Cases. C. Reich, M. Seife and B. J. Kessler. From the Hospital for Joint Diseases, New York, N. Y. Medicine 30: 1-20, 1951.**

The authors review the literature of Gaucher’s disease and present the clinical, x-ray, laboratory and pathologic features of this disease. They emphasize the importance of sternal marrow examination in establishing a diagnosis. Other methods of diagnosis are discussed. Treatment is unsatisfactory but fortunately, since the advent of antibiotics, patients with the onset of this disease after childhood may survive for many years. Much of the authors’ data is based on 20 cases they reviewed of their own.—R.B.C.


After experimental work on guinea pigs given subcutaneous injection of 100 microcuries, using autoradiography and Geiger radiocounter, the authors appreciate the repartition of AS\(^\text{14}\) in the organs (in per cent of what is fixed by the bowel), the skin comes next after the bowel (42 per cent), then spleen (25 per cent), liver (18 per cent), kidneys (17 per cent). In man, AS\(^\text{14}\) is given by mouth, 2 to 8 millicuries. Four cases were treated: 2 with Hodgkin’s disease; 1 with skin localization (cured now for 15 months); 1 generalized form, resistant to X-rays, where only skin lesions were affected by AS\(^\text{14}\).

There were two observations of treatment of mycosis fungoides. The first case had been treated without result by radioactive phosphorus and by nitrogen mustard. Ten days after the ingestion of AS\(^\text{14}\), the skin was cured and pruritis disappeared but prompt recurrence was observed which was only partly relieved by new AS\(^\text{14}\) administration, and finally inefficient.
The second case was a terminal radioresistant mycosis fungoides. After 6 millierys, in spite of a transitory arsenical erythrodermia, the improvement was striking, but lasted only one month. AS75 was without action against the recurrence of the disease.

Thus AS75 is especially active against skin lesions of malignant hemopathies. But the effect is short.—J.P.S.


R 48 was given to 6 patients with polycythemia vera, and a good hematologic remission was obtained in 5. The sixth patient also improved though the effect was not so striking. One patient felt well and still had a normal blood count fifteen months after treatment was stopped.—S.T.C.

**HEMORRHAGIC DISEASE and BLOOD COAGULATION**

**THE HEMORRHAGIC PHASE OF THE ACUTE RADIATION SYNDROME DUE TO EXPOSURE OF THE WHOLE BODY TO PENETRATING IONIZING RADIATION. E. P. Cronkite, C. J. Jacobs, G. Brecher and G. Dillard. From the Naval Medical Research Institute and the National Institutes of Health, Bethesda, Md. Am. J. Roentgenol. 67: 796-804, 1952.**

Although hemorrhage not due to trauma was one of the major causes of death in the Japanese casualties at Hiroshima and Nagasaki such bleeding was prominent only after a period of two weeks elapsed following the radiation exposure. This is a report of observations made on dogs following radiation injuries. Evidence points to there having been after radiation exposure adequate amounts of prothrombin, plasma accelerator factors, serum prothrombin converting accelerator, antihemophilic factor and fibrinogen. There was some correlation between the hemorrhagic tendency and decrease in platelet concentration. However, all thrombopenic dogs did not become purpuric. A second phase anticoagulant of the hemorrhagic type was not demonstrated in these radiated dogs. Apparently the erosion of vessels in ulceronecrotic lesions created occasionally such vascular damage that the thrombopenic animals' hemostatic mechanism was inadequate and fatal hemorrhage resulted.—P.F.W.


Utilizing a flavonoid preparation from citrus fruit, these investigators were able to decrease the capillary permeability induced in rabbits by leukotaxine. Five mg. of this material administered orally for 30 days, 5 days prior to the exposure and 25 days post radiation, gave a considerable but not complete protection against a total body, near-lethal dose of x-ray radiation, administered to rats. Clinical administration of this flavonoid compound in oral doses of 300 to 600 mg./day for 5 days prior to radiation treatment and during exposure to deep x-ray radiotherapy, resulted in diminished radiation erythema of the skin and in some cases to a complete absence of such erythema. Nausea and vomiting persisted in some patients.—R.B.C.

**THE USE OF ANIMAL CHARCOAL IN THE ESTIMATION OF THE PROTHROMBIN LEVEL. J. Novák. From the Medical Department, State Hospital Motol, Praha. Časop. lék. česk. 93: 120, 1951.**

The end-point of the Quick test for prothrombin level is made more exact by the addition of 5 per cent animal charcoal to the n/40 CaCl2. This addition does not affect the reaction in any way.—M.N.

**THE SITE OF INHIBITION OF BLOOD Clotting BY Soy BEAN Trypsin Inhibitor. M. B. Glen- dening and E. W. Page. From the Division of Obstetrics and Gynecology, University of
Previous investigations have demonstrated that a trypsin inhibitor isolated from soy beans delays coagulation by inhibiting the first phase of coagulation. It has no activity on thrombin. The present study was undertaken to elucidate the manner in which soybean trypsin inhibitor (SBTI) affects prothrombin conversion. The data obtained suggests that SBTI delays the coagulation of blood by forming a dissociable complex with the substrate, prothrombin, or a derivative of that substrate. It does not exert its effect upon the enzyme of the first phase (thromboplastin), nor upon the co-factor (accelerator globulin), nor upon the product (thrombin). At present there appears to be no clinical application for this substance.—R.B.C.

BLOOD VOLUME

VENOUS CONGESTION OF THE EXTREMITIES IN RELATION TO BLOOD VOLUME DETERMINATIONS AND TO MIXING CURVES OF CARBON MONOXIDE AND T-1824 IN NORMAL HUMAN SUBJECTS. E. Brown, J. Hopper, Jr., J. J. Sampson and C. Murdock. From the Division of Medicine, University of California School of Medicine, San Francisco, Calif. J. Clin. Investigation 30: 1441-1450, 1951.

This investigation was designed to determine the influence venous congestion of the extremities may exert on blood volume measurements dependent upon the carbon monoxide and T-1824 methods. Congestion was imposed on three limbs of healthy human subjects by means of pneumatic cuffs. Measurements revealed that one-fifth to one-fourth of the total blood volume was contained in the congested extremities. However, if a mixing time of 20 minutes or longer is allowed after delivery of CO gas, the CO-available volume is the same whether or not venous congestion is present. Although the contour of time-concentration curves for CO was slightly different when determined in the presence of venous congestion, the changes were not sufficiently striking to permit use of such curves for estimating the presence or degree of venous pooling. However, the variation lent additional support to the use of sampling periods at least 15 to 20 minutes after the CO or dye is administered. The authors conclude that the presence of massive congestion of the extremities does not interfere with complete admixture of CO or T-1824, with the entire blood volume within 20 minutes, and, that with the CO method, total rather than “effective” blood volume is measured.—R.B.C.

NEWS AND VIEWS

Hemophilia Foundation

The Hemophilia Foundation, a nonprofit New York organization operating on a national basis and located at 60 East 42nd Street, New York, N. Y., announces conclusion of plasma processing arrangements with the Blood Transfusion Association of New York.

Commencing May 5, 1952, the Blood Transfusion Association will process classified human plasma for direct transfusion to hemophilia cases by their own physicians or hospitals. Distribution will be through the Foundation’s administration and medical staff, but for the time being will be limited to hemophilia victims residing in New York State. Distribution on an interstate basis will begin immediately following authorization by the National Institute of Health. Nationwide processing by other institutions will be encouraged.