ABSTRACTS

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ABSTRACTERS

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ERYTHROCYTES AND ERYTHROCYTIC DISEASE


These investigators have found that a nonmotile, rod-shaped organism from hen feces, when grown aerobically on simplified media, produces appreciable quantities of the 'animal protein factor' as indicated by assay with chicks on diets deficient in this factor. Since it is known that refined liver extracts produce a growth response in chicks deficient in the 'animal protein factor,' concentrates of the microbial animal protein factor were tested for anti-pernicious anemia activity in two patients with pernicious anemia in relapse. The results indicate that the concentrates were active in inducing a hematopoietic response in such patients. Whether the active substance in the microbial concentrates is identical with the anti-pernicious anemia factor or the recently isolated vitamin B₁₂ is not known. The answer to this will have to await chemical identification of the various substances. The possibility exists that factor X, the cow manure factor, zoophenin, the animal protein factor, the microbial animal protein factor, vitamin B₁₂ and the anti-pernicious anemia substances are all similar, identical or related compounds.

G.E.C.


Examination of crystals of anti-pernicious anemia factor has shown the presence of cobalt. If each molecule contains one atom of cobalt the molecular weight of the compound is about 1,500. Allowance for loss on drying brings this in excellent agreement with that found on x-ray crystallography (1,550-1,750). The higher value (1,000) found by the diffusion method may be due to errors inherent in the method, the use of impure material in earlier experiments, or that association occurs in solution. Analytic figures indicate that the molecule contains three atoms of phosphorous. Reference is made to the fact that the Merck workers have found cobalt and phosphorous in their vitamin B₁₂.

S.T.C.

ABSTRACTS

Reference is made to previous work on cobalt as an essential factor in ruminant nutrition. Observations on three sheep with rumen fistulae are described. Sheep A was given a seeds hay diet (0.27 p.p.m. cobalt in dry matter). Sheep B and C, bred originally on a cobalt deficient pasture, were maintained on a hay diet containing only 0.07 p.p.m. cobalt. C was given 1 mg. added cobalt daily. After 6 weeks, rumen contents were collected, fractionated, examined microscopically and for cobalt content. The data make it apparent that rumen micro-organisms concentrate cobalt from their external environment and that the cobalt concentration of the microbial population is related to cobalt content of the diet.

It is suggested that absorption of cobalt by the host may deprive micro-organisms of an essential factor, the host in turn being deprived of essential bacterial products; or if cobalt is an essential metabolite for the host alone, concentration in the micro-organisms may reduce its availability. Again host and alimentary micro-organisms may both require cobalt for metabolic activities, the competition being important on cobalt deficient diets.

Although this work is superficially remote from hematology the finding of cobalt in the crystalline anti-pernicious anemia factor indicates that it may be important in helping to elucidate the problem of megaloblastic anemias, especially those of intestinal origin. It may also link up with the experimental macrocytic anemia in rats (Watson et al., Lancet 2: 404, 1948) in which a gross change of microbial population of the intestine is probably produced.

S.T.C.


The response to crystalline vitamin B₁₂ of 3 patients with pernicious anemia exhibiting acute neurologic manifestations is reported briefly. No data is presented other than that included in the one representative case report. The case is that of a 48 year old male with pernicious anemia who lapsed in treatment and presented a three weeks' history of glossitis, weakness, and inability to walk unsupported. Blood studies revealed a moderate slightly macrocytic anemia. Four parenteral injections of 25 micrograms each of vitamin B₁₂ were given at forty-eight hour intervals. Within the first forty-eight hours pain and tenderness of the legs and soreness of the tongue had disappeared, and by the fourth day the patient could walk without support. Improvement in, although not disappearance of, abnormal neurologic signs (other than the return of a normal plantar response) was noted on the fifth day. A reticulocytosis of 14 per cent occurred on the fifth day followed by elevation of the red cells, white cells, platelets and hemoglobin (no figures given). Reference is made to the relief from neurologic symptoms noted in three previously reported cases following a single injection of 15 micrograms of vitamin B₁₂ (Postgrad. M. 1: 89-95, 1948).

As the authors admit, insufficient time has elapsed to evaluate the effectiveness of vitamin B₁₂ as maintenance therapy for patients with pernicious anemia with or without neurologic complications. Certainly the experience with folic acid has shown that one must be extremely cautious in drawing conclusions from an initial neurologic improvement of several days.

H.W.B.


Two cases of tropical macrocytic anemia occurring in Bombay showed a good response to single injections of 80 μg. each of Lester Smith's crystalline anti-pernicious anemia factor. This appears to be an interesting observation in view of previous suggestions that such cases are deficient in 'Will's factor' rather than the anti-pernicious anemia factor.

S.T.C.


Anemia resembling pernicious anemia sometimes develops in association with intestinal lesions. This suggested a method for producing macrocytic anemia in rats. Two operations were devised. In operation
A, the intestine was divided, the lower part tied off, and the upper part was anastomosed to the gut some 12 inches below the blind end. One hundred and eighteen rats survived operation and 21 developed macrocytic anemia six weeks to one year later. As anemia followed only when there was some stenosis at the anastomosis or dilatation of the loop, operation B was devised. Here the lower part was anastomosed to the gut 12 inches above the division; later modified to 3 inches. Peristalsis then filled the loop which always became dilated. Seventeen of 24 rats survived the 3 inch operation and 13 developed progressive anemia after an average of eight weeks.

The anemia is normo- or hyperchromic with an increase in red cell diameter and irregular reticulocytosis. The bone marrow shows an increase in proerythroblasts and basophil erythroblasts. Treatment with liver extract (total of 0.1 to 0.8 ml. Anahaemin) suggests that the anemia responds unless there are complicating infections. One rat injected with 15 mg. of folic acid also showed a good response. Further work is in progress to determine how specific are these responses to treatment.

Such experiments may provide the long sought test animal for the therapeutic potency of liver extracts, although further advances in the research on crystalline anti-pernicious anaemia factor may render this unnecessary. More important is the fact that the technic opens up a new field for the investigation of the pathogenesis of macrocytic anemia.

S.T.C.


Determinations of the average life span of red cells from 4 patients with pernicious anemia in relapse were performed using the method of differential agglutination (Ashby technic). It was found that the survival time of the red cells when injected into normal individuals was markedly decreased (27 to 75 days). After adequate treatment, the life span of the cells from the pernicious anemia patients became normal. These observations, as the authors conclude, are evidence for the concept that pernicious anemia is a true hemolytic syndrome caused by an intracorpuscular mechanism. The shortened life survival time of the cells would seem to account for the increased pigment production observed in this disease but is difficult to correlate with the observations of London, Shemin and Rittenberg, using labeled glycine, which indicate that a considerable portion of the pigment production is derived from sources other than hemoglobin. It is likely that this problem is somewhat more complicated than it appears to be.

G.E.C.


This paper deals with cross determinations of the survival time of sickle cells. Trait cells were transfused into patients with sickle cell anemia and anemia cells into healthy recipients displaying the sickle cell trait. It was found that the trait cells survived normally when transfused into patients with sickle cell anemia, whereas the patient's own cells continued to be hemolyzed at a faster rate. Cells from patients with sickle cell anemia, when transfused into trait carriers, had a shortened life span with an average of about one-fourth of the normal. Therefore the pathogenic principle operating in sickle cell anemia would appear to reside within the red cells themselves rather than in an extracorpuscular mechanism. The authors conclude that the sickling process is by itself not a satisfactory explanation of the pathogenesis of the anemia. They speculate that sickle cell anemia develops because of an additional alteration in the cytoskeleton which is qualitatively different from the structural anomaly responsible for the sickling phenomenon.

G.E.C.

A simple and rapid method of producing sickling of the red blood cells in wet cover slip preparations of the blood of patients with sicklemia is described. The principle on which the test is based is the production of reduced hemoglobin in the red cells by the addition of a reducing agent. In order to perform the test, a drop of a five-fold aqueous dilution of Cevalin (approximating a 2% per cent solution of buffered ascorbic acid and also containing a per cent sodium bisulfite) on a drop of 1 per cent sodium bisulfite, Na₂S₂O₅, is added to a small drop of the patient's blood on a glass microscope slide. After mixing, a cover slip is dropped on the preparation and excess blood is expressed by gentle pressure in order to produce a film of blood sufficiently thin to permit inspection of individual red cells under the high-power objective of the microscope. With the diluted Cevalin solution, sickling of the blood usually appeared within an hour, and with the 1 per cent bisulfite solution it was often present within fifteen minutes at room temperature.

G.E.C.


On blood samples from 11 male and 10 female subjects, hemoglobin determinations were made by means of iron analyses, oxygen and carbon monoxide capacities. Various hemoglobin derivatives were tested by several types of photometer, photoelectric colorimeter and in one series of experiments with a Hilger medium quartz spectrophotograph. For visual instruments, the "true reading" was taken as the mean of 20-50 readings obtained by several observers. The readings were compared with the "base line" values obtained from the iron analyses and gasometric determinations respectively. Analysis of the results showed that the neutral grey wedge photometer (King, E. J., Biochem. J., 41, Suppl. 32, 1947) compared favorably with the standard photoelectric and visual instruments. The single cell photoelectric colorimeter proved more reliable than the two celled absorptiometer. Of the hemoglobin derivatives, oxyhemoglobin and cyanhematin gave the least variable results.

Most hematologic laboratories now use photoelectric colorimeters for hemoglobin estimation, but where such instruments are not available the grey wedge photometer seems to provide a simple and accurate instrument.

S.T.C.


The purpose of this work was to determine the nature of the anemia which accompanies pregnancy in the adult female rat of the Long-Evans strain. Calculations were made on the total erythrocyte count, hematocrit, hemoglobin level, whole blood and plasma specific gravities, and blood volume. Studies were made at three stages of pregnancy and on the second day postpartum. A significant decrease in whole blood and plasma specific gravities occurred during pregnancy, but the total blood volume increased. Calculations of the total circulating erythrocytes and hemoglobin in pregnant rats showed a sharp rise in both elements. The author concludes from this evidence that the anemia which accompanies pregnancy in the rat is due to a hemodilution.

R.C.C.


Using supravital examinations of bone marrow in pernicious anemia the author advances the theory of origin of megaloblasts from undifferentiated reticulum cells. He considers megaloblastic blood formation as a mesenchymatous process in contrast to the normal parenchymatous erythropoiesis. Furthermore, he points out the necessity of accepting a second factor in the genesis of megaloblasts. He considers this factor to be the loss of the mitotic heteroplastic properties of the cells and assumes this to be the effect of the absence of the antipernicious principle.

The peculiar megaloblastic nuclear structure is considered as the persistence of mesenchymatous nuclear properties.

C.M.
292.  ABSTRACTS


Studying the mitosis of megaloblasts gained from the bone marrow in pernicious anemia the author observed a singular granular structure of the nucleus, which he was able to stain with the Giemsa method and which is called paramitotic granulation because of its temporary appearance during mitosis. This granulation has been formerly described by Rohn (and others) who, however, thought it identical with the basophilic stippling of the erythrocytes. The author believes that the phenomenon has to be differentiated from the former. Apart from the megaloblasts, the paramyototic granulation was also observed in normal maturing erythrocytes and leukocytes.

The author believes that the granulation belongs to other mesenchymial elements as well. The described structures are looked on as mitotic-formed agglomerations of the basophilic substance. A relation to the basophilic stippling of the erythrocytes is probable.

C.M.


Basing conclusions on his electron-optic studies this author deduces that erythrocytes possess a genuine membrane made of protein and containing hemoglobin inside. The membrane is covered on its surface by a lipid layer. The inside is formed by a spongelike stroma made of protein. This latter is easily denatured, causing a change in permeability properties and leading to hemolysis. The author studied the influence of different salts and of hemolytic substances. He considers the "Heinz-bodies" a sign of degeneration. They are composed of coagulated parts of the cells which are more easily stained and not really located in the inside of the cells. They have no relation to methemoglobin.

C.M.

THROMBOEMBOLIC DISEASE


The prothrombin activity, using Quick's one stage method, was determined preoperatively and followed daily through the sixth postoperative day in 68 patients, most of whom were considered likely candidates for venous thrombosis. In nearly all 38 postoperative patients who did not develop thrombosis, there was a progressive decrease in prothrombin activity during the first three days, followed by a gradual return to normal about the sixth day. All of the 10 patients who developed thrombosis, on the other hand, showed a rise to above normal on either the second or third day. This hyperprothrombinemia was interpreted as evidence of impending thrombosis, although the prothrombin activity was usually normal by the time thrombosis was clinically evident. No satisfactory explanation was offered for the fact that the hyperprothrombinemia was more uniformly apparent in the undiluted than in the diluted plasma determinations. The authors suggest this test as a practical method of early detection of postoperative thrombosis and as a basis for selection of patients to receive prophylactic anticoagulant therapy.

The pathogenesis, diagnosis and prevention of thrombo-embolism are discussed. In their comparison of the relative merits of prophylactic vein ligation and anticoagulants, the authors present more convincing evidence for the latter.

The whole problem of the relation of prothrombin activity to the occurrence of intravascular thrombosis has yet to be defined, although there are fewer conflicting reports on changes in prothrombin activity in postoperative than in nonsurgical patients (coronary thrombosis, etc.) who develop thrombosis.

H.W.B.


It was concluded from a study of 31 cases of acute coronary occlusion that there were: (1) no constant
changes in blood coagulability as measured by the Waugh-Ruddick test, prothrombin time (diluted and undiluted plasma) or coagulation time; (2) no constant changes in the Waugh-Ruddick test during prolonged bed rest; (3) no constant variation in plasma protein levels during convalescence; (4) a high percentage of patients with prolonged circulation times due to shock and/or myocardial weakness; and (5) that the variance in blood volume studies depended on the presence or absence of shock and/or cardiac failure.

This study is of interest because of the present controversial issue of whether or not there is a concurrent increase in clotting tendency to account for the appreciable incidence of thrombo-embolism in myocardial infarction. The prothrombin studies support the work of Cotlove and Vorzimer (Ann. Int. Med. 24: 648, 1946) but are at variance with that of others; e.g., Peters et al. (J. A. M. A. 130: 398, 1946). The findings of normal or decreased blood coagulability by the Waugh-Ruddick test in 77.4 per cent of cases on admission with a low incidence (0.14 per cent) of increased clotting tendency during hospitalization in half of the group which did not receive dicumarol varies considerably from the results obtained by Ogura et al. (J. Clin. Investigation 25: 586, 1946).

The answer to this problem awaits a more complete understanding of the clotting mechanism and its relation to intravascular thrombosis as well as a greater refinement and uniformity in our laboratory tests. However, convincing evidence is accumulating in large series of cases to justify the cautious prophylactic use of dicumarol in patients with coronary occlusion.

H.W.B.

EFFECT OF HEPARIN AND DICOUAROL ON SLUDGE FORMATION. H. Laufman, W. B. Marvin, and C. Tanturi.


The mesenteric vessels of dogs were studied, using the Kniseley technics. Sludging was produced by venous occlusion. Dogs were divided into four groups. Group 1: Control dogs. After venous occlusion sludge formation developed, followed by adherence of sludged masses to the endothelium of the vessels. This was followed by the piling up of more cells to the agglutinated mass until the vessel was finally completely occluded. The thrombosis remained in many vessels after the venous circulation had been released. Group 2: Heparin was given after the appearance of sludge formation. Group 3: Heparin was given before venous occlusion. Group 4: Dicoumarol was given before occlusion. In the last three groups, although sludge formation did occur, no thrombosis developed in any animal.

R.C.C.


The specific prophylactic or therapeutic measures used in 1,600 postoperative patients, some of whom received a combination of methods, are evaluated. With few exceptions these were patients over the age of 30. Prophylactic treatment by small doses of dicumarol was given to 496 patients. None of these died of pulmonary embolism although there were two fatalities associated with hemorrhage. Four of 871 patients who had prophylactic bilateral superficial femoral vein interruption died subsequently of pulmonary embolism, whereas, in this particular group of patients deemed likely to develop thrombosis, 37 deaths from embolism might have been expected had specific measures not been used. Treatment for 1,166 patients was by phlebotomy, thrombectomy and femoral vein interruptions after clinical evidence of thrombosis occurred. There were six deaths in this group from further emboli compared to an estimated sixty had therapy been withheld.

This paper includes a good discussion of the factors predisposing to venous thrombosis. Emphasis is laid on the fact that despite the progress made since the advent of specific measures in the prevention and treatment of thrombo-embolism, a statistically significant percentage of patients still die from massive pulmonary embolism.

The authors do not share the general enthusiasm of many for the prophylactic use of dicumarol in postoperative patients. They stress its hazards and condemn its empiric use without adequate clinical and laboratory control. It is their opinion that vein ligation is the safer and more feasible measure in the older, debilitated or very ill patient.

H.W.B.
HEMORRHAGIC DISEASE AND BLOOD COAGULATION

THROMBOCYTOPENIC PURPURA; THE FAILURE OF DIRECT BLOOD TRANSFUSION TO RAISE THE PLATELET LEVEL.

This work was undertaken with the purpose of determining if massive direct transfusions of blood given to patients with thrombopenic purpura would raise the level of circulating platelets significantly. A patient with aplastic anemia was given 1500 ml. of whole blood within a short period of time. A second patient was given approximately the same amount of blood on two different occasions. Theoretically, this amount of blood should have raised the circulating platelet levels about 100,000 per cu. mm. However, in only one of the three experiments reported was a significant increase noted in the recipient, and in this case it was so small as to be of little practical importance. The reasons for the unsatisfactory results are not evident, but the results suggest that either the life span of platelets is exceedingly short or that they are unusually rapidly utilized in thrombocytopenic conditions.


A haemophiliac boy of 16 months developed complete paralysis of both legs and retention of urine. Cisternal myelogram showed complete arrest of the opaque medium at T-9. Laminctomy was performed and a large subdural clot removed successfully. Convalescence was complicated by secondary haemorrhage from the wound but general progress was excellent and a high degree of functional recovery took place. Throughout the course in hospital the prolonged clotting time was controlled by repeated small transfusions of fresh blood (62 in the 66 days in hospital). Larger volumes of blood were used only to replace blood lost.

This case illustrates a rare complication of haemophilia and also shows clearly that major surgery may be safely undertaken with adequate control by transfusion.

Studies on a Proteolytic Enzyme in Human Plasma. III. Some Factors Controlling the Rate of Fibrinolysis. O. D. Ratnoff. From the Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland. J. Exper. Med. 88: 401-416, 1948.

The phenomenon of fibrinolysis has long been recognized and it is now well established that the blood contains both a proteolytic enzyme system and inhibitors of this system. However, the factors responsible for rapid clot dissolution under certain conditions remain a subject of controversy.

The author, in this well controlled in vitro study of factors governing clot lysis, has observed certain interesting phenomena. Caseinolysis was used as a measure of fibrinolytic activity and his methods for the determination of proteolytic and inhibitory activity of plasma are described in detail. He was unable to demonstrate that there was any correlation between the clot lysis time of recalcified plasma clots and the amount of proteolytic activity, either spontaneously developed or activated by chloroform or streptococcal filtrate, in a globulin precipitated from the same plasma. Furthermore, a constant relationship between the inhibitory activity of fresh plasma, serum or albumin against plasma proteolytic enzyme and clot lysis time could not be shown. Following the discovery that this inhibitory activity was unstable and decreased during incubation, however, it was possible to correlate clot lysis time with the deterioration of inhibitory activity occurring during incubation of recalcified plasma at 37 C. This inhibitory activity decreased until a minimal stationary level was reached and fibrinolysis occurred. The nature of the labile component of the inhibitory activity of plasma is now under investigation.
ABSTRACTS

The fundamental importance of the process of fibrinolysis and its relation to other physiologic processes involving the mechanism of blood coagulation, protein metabolism, and the body's response to various stimuli have been appreciated only recently. The significance of such relationships are discussed in an excellent review of the subject by MacFarlane and Biggs (Blood 3: 1167, 1948).

H.W.B.


A simple method for assaying the concentration of the labile factor of the prothrombin complex in blood is presented. This method is based on the principle that tricalcium phosphate when added to plasma removes components A and B of the prothrombin complex thus leaving fibrinogen and the labile factor as the only known plasma constituents playing a role in the process of clotting. On adding fresh plasma thus treated to stored human, dog or rabbit blood the prothrombin time was found to be shortened strikingly. By determining the amount of plasma that had to be added to a fixed amount of stored plasma in order to reduce the prothrombin to an arbitrarily selected value (30 seconds), the relative concentration of the labile factor could be calculated. By this procedure it was found that the prothrombin time was reduced to a markedly shorter value when the labile factor was added to stored plasma than when added to fresh plasma, thus suggesting that something is elaborated in stored plasma which enhances the activity of the labile factor.

G.E.C.


Five patients were injected with nitrogen mustard (methyl-bis (beta-chloroethyl) amine hydrochloride) as follows: 2 were given 0.1 mg./kg. on four successive days, 1 received the same dose and four injections at twelve hour intervals, 1 was given the same dose and four treatments at seven hour intervals, and 1 was given 0.3 mg./kg., two doses, at six hour intervals. Within two weeks, all 5 patients developed a moderate anemia, severe leukopenia, thrombocytopenia, prolonged bleeding time, cutaneous petechiae, and ecchymoses. Coagulation time was prolonged. Intravenous injections of toluidine blue or protamine brought the coagulation time back to normal. The author points out that nitrogen mustard treatment may induce serious or fatal complications due to the presence of an anticoagulant in the blood.

G.E.C.


A method is described for the measurement of electric resistance of blood and other fluids. Lightly platimined platinum electrodes were placed in tubes of blood. An audiofrequency oscillator was used to generate power. An oscilloscope was used instead of the conventional telephone bridge balance indicator. By means of a selector switch and parallel circuits, six different samples could be studied at one time. All determinations were made in a constant temperature water bath set at 37°C.

Determination of resistance changes during the coagulation of blood make possible the determination of clotting time with elimination of inconsistencies caused by motion and offer a quantitative means for the study of clot retraction. By means of the ratio of blood resistance to plasma resistance, the cell volume fraction of a sample of blood may be calculated. It was found that the centrifuge hematocrit was 7.7 per cent too high (average), a value comparable to that obtained by Chapin and Ross by entirely different technics (Am. J. Physiol. 137: 447, 1946).

The authors report the prophylactic use of serial infusions of normal human plasma in hemophilia. It was found that the intravenous injection of 10 cc. of plasma into a hemophiliac was capable of reducing the coagulation time of the blood to normal levels; the effect, however, began to disappear within a few (eight) hours. When 100 to 190 cc. of plasma was used, the effect was still present in twenty-four hours, was beginning to disappear in thirty-six hours, and was completely gone in three days. The use of larger amounts of plasma—up to 750 cc.—did not cause prolongation of the effect. It was further found that the administration of plasma intramuscularly was of little effect, 30 cc. of plasma having less of a coagulant power than 1 cc. given intravenously.

A schedule was therefore devised, in which 100 to 180 cc. of reconstituted, freshly processed, frozen, normal human plasma was administered intravenously three times a week to patients with hemophilia. Four patients with long histories of bleeding tendency and increased coagulation time were treated in this manner for from ten to twenty months. It was possible to maintain the coagulation times of these patients at high normal levels (15 to 20 minutes), and there was striking clinical improvement with elimination of serious hemorrhages. The only relapse occurred when, for various reasons, the schedule of plasma infusions was temporarily interrupted. The patients were able to work or go to school, indulge in sports, and even, in one case, undergo a surgical operation (tendon transplantation). There was no refractoriness to the plasma; on the other hand, there was no permanence of effect. The incidence of transfusion reactions was 1.2 per cent; and one patient developed mild serum hepatitis.

The clinical results in these cases are so striking as to endorse the authors' schedule of therapy as a beneficial and practical one, at least until fractionation of normal plasma provides a consistently potent product for use in hemophilia.

INFLUENCE OF SULFONAMIDES ON BLOOD COAGULATION. M. Kubias. From the City Hospital, Prague. Čas. lek. čes. 86: 291, 1947.

Clinical observations seemed to indicate that the sulfonamides affect the blood coagulation. Therefore, experiments were made to test this effect in patients treated for gonorrhea with various sulfa drugs: blood coagulation, bleeding time and osmotic resistance of red blood cells were systematically followed. In 10 patients treated in this way, the acceleration of blood coagulability was very marked; it appeared immediately following the first day of treatment and lasted for about six to nine days.

BLOOD PROTHROMBIN LEVEL IN PATIENTS SUFFERING FROM DISSEMINATED SCLEROSIS. J. Louný and L. Poláček. From the Clinic of Nervous Diseases, Charles University, Prague. Čas. lek. čes. 86: 1569, 1947.

Blood prothrombin has been determined in 53 patients suffering from disseminated sclerosis; 34 patients (65 per cent) were a little higher than normal in prothrombin content (over 120 per cent); some of these were very high (150 to 180 per cent). The arithmetical mean value of blood prothrombin was 120.6 per cent.

LEUKEMIA AND MALIGNANT LYMPHOMA


The authors studied the hemogram of 56 cases of Hodgkin's disease. The leukocyte count was subject to important fluctuations and, specially in the terminal phase of the disease, leukopenia was more common than leukocytosis.

Lymphopenia was the most frequent symptom; the authors give figures of 60 per cent initially and 90 per cent terminally in the illness. Eosinophilia was less frequent (12 per cent); the same was so for the frequently described monocytosis.

Anemia was seldom seen at the beginning, and always developed sooner or later during the course of the disease.

Thirty-one cases of Hodgkin's disease were treated with a total of 44 courses of methyl-bis (3-chloroethyl) amine hydrochloride. Beneficial results were observed in 20 patients receiving twenty-four courses. Indirectly, 3 other patients benefited through an apparent resensitization to roentgen rays. Improvement was characterized in most instances by an immediate disappearance of fever, itching and pain. Brownish pigmentation of the skin was observed to decrease in several cases as did Hodgkin's skin lesions, splenomegaly, hepatomegaly, and adenopathy. A regeneration of lymphocytes and a return of the monocyte-lymphocyte ration toward normal was the most consistent laboratory finding associated with a clinical remission. Bone marrow hypoplasia proceeding to aplasia and followed in every instance by complete regeneration to the previous level and in some cases to a more normal level within a few weeks after therapy was observed.

G.E.C.


This experiment was performed to determine the effects of nitrogen mustards on the leukemia of fowls. Chicks of 1 to 2 weeks of age were injected with the Beltville strain "A" leukemia virus either intravenously or intraperitoneally. After the leukemia had become established (four to six weeks), chicks were treated with HN3 or HN2. Optimal dose of HN3 was found to be 1.0 mg/Kg.; for HN2, 2.0 mg/Kg. Of 14 birds treated with HN3, 2 made clinical recoveries lasting from three to six months. Of 19 birds treated with HN2, 11 made complete recoveries. With treatment early in the disease, the recovery is greater. This work indicates that two nitrogen mustards have a profound action upon the immature cells, called hemocytoblasts, retard the mitotic activity both of the blood and the bone marrow, and have a lethal effect upon the virus which causes the disease as indicated by the failure of blood drawn from the treated animals to infect a normal host.

R.C.C.


This paper was a study on the effects of urethane on pulmonary capillaries in the mouse. The mice used were F-NH hybrids transplanted with myelogenous leukemia. Urethane was administered intraperitoneally after the leukocyte counts were in the neighborhood of 100,000 cells per cu. mm. Doses of urethane varied from 0.5 mg./Gm. daily to 1.0 mg./Gm. daily. Pulmonary edema was present in all treated animals. Giving graded doses produced edema in all cases in which the dose of urethane was sufficient to have an effect on the leukemia. If death did not result from the edema, a subsequent development of pneumonia did produce death. Although the edema was restricted to the lungs, evidence was found of capillary damage in other regions of the body. The authors point out the toxic effects of urethane when used over a long period of time.

R.C.C.


Urethane has been used in the treatment of leukemia. This substance has been reported as inducing a lymphopenia as well as other effects. Urethane treatment also induces an adrenal hyper trophy. In view of the work of Dougherty and White where a lymphopenia was induced by adrenal cortical extracts, this work was done to determine whether urethane induces the lymphopenia via the adrenal cortex. Adult male rats of the Sprague-Dawley strain were used.

A lymphopenia and an absolute lymphopenia were induced by urethane by these authors in both normal and adrenalectomized rats. The adrenals would, therefore, not seem to be the factor which induces lymphopenia under urethane treatment. The authors discuss the theory that urethane acts as a mitotic poison.

R.C.C.
ABSTRACTS


Leukemia was induced in mice by injections of leukemic material. A few days to a few weeks later the mice were injected subcutaneously with 1-2 mg. of leukocytosis-promoting factor (obtained from canine exudates as previously described by the author). Injections were daily at first and, after several weeks, three times per week. This material induced a shift in the differential leukocyte formula with a rise in the percentage of mature polymorphonuclear leukocytes. Several children with leukemia were injected with this material. The only positive effect was a frequent drop in the total leukocyte level.


This experiment was performed in an attempt to determine whether the effects of alcohol on lymphosarcoma were due to a direct effect or to effects mediated by the adrenal cortex. C3H mice bearing 6B1HED tumors were used. One group of mice was treated with 19 per cent ethyl alcohol and another group was treated with various amounts of 95 per cent alcohol. The 19 per cent alcohol produced no toxic symptoms and no tumor regression, while the 95 per cent alcohol did produce toxic symptoms and showed a definite tumor regression. Diffuse cell necrosis was seen in the tumors treated with the 95 per cent alcohol. The results did not answer the original question as to whether the adrenal cortex was involved. The authors suggest that the results obtained were not due to the alcohol itself but were due to the toxic effects obtained.


Three cases of systemic aleukemic nonlipid reticuloendotheliosis are reported with a brief discussion of the disease. The usually accepted criteria of this disease are: (1) its occurrence, neither hereditary nor familial, in infants and young children, of unknown etiology and fatal prognosis; (2) hepatosplenomegaly; (3) generalized lymphadenopathy; (4) hemorrhagic diathesis; (5) localized skeletal changes or tumors; (6) progressive secondary anemia, usually with a normal leukocyte count; (7) general hyperplasia of the cells of the reticuloendothelial system which may assume focal tumor-like proliferation; and (8) an acute onset unrelated to infections. The authors take issue with this last criterion as their cases, like many others reported in the literature, were associated with, although not necessarily caused by, infection. Emphasis was also placed on the presence of cutaneous lesions similar to sebaceous dermatitis which so frequently occur in the systemic reticuloendothelial diseases.

Certain authors, including Siwe, have made a distinction between this disease and so-called infectious reticuloendotheliosis, which in all other respects appear to be similar. The very frequency of infections in young children as well as those occurring coincidentally in malignant disease make such a distinction extremely tenuous. One wonders about the precise relationship of this disease to Schüller-Christian disease, leukemic reticuloendotheliosis, reticulum cell sarcoma, etc., and whether it should be rightly considered a separate disease entity. Certainly, our whole concept of the reticuloendothelial disorders is confusing and badly in need of clarification.


The purpose of this experiment was to determine the effect of adrenal cortical extract (ACE) on the lymphocyte content of the spleen under in vitro conditions. Rabbits served as the source of the spleens and the blood. A perfusion apparatus was used, the details of which are given. ACE administered to the isolated rabbit spleen, under conditions of constant pressure and bathed by whole blood, produced a
significant rise in the lymphocyte content of the blood. This rise occurred rapidly, (15 minutes). The lymphocytes then dropped below normal levels. This secondary decrease in the circulating lymphocytes appears to be due to accelerated lymphocyte breakdown by the spleen, in the presence of ACE. These reactions to ACE were not dependent on changes in pressure or splenic blood flow. They could not be elicited with the thymus, lung, or liver. Glucose, epinephrine, desoxycorticosterone acetate, and estradiol propionate had no effect on the circulating lymphocytes.

R.C.C.

**Solenic Lymphocyte Discharge Induced by Adrenal Cortical Hormones Under in Vivo Conditions.**


In a previous paper it was noted that adrenal cortical extract (ACE) produced a discharge of lymphocytes into the circulation from the spleen under in vitro conditions. This work was done to study the spleen under in vivo conditions. Rats were used for the experiment and a stress was obtained by making the rats swim. A lymphocytosis resulted from this stress in normal animals. This rise was significantly decreased by adrenalectomy or splenectomy. Injections of ACE to adrenalectomized swimming rats produced a lymphocytosis. ACE injections had no effect on adrenalectomized-splenectomized swimming rats. Desoxycorticosterone acetate had no effect. ACE, then, would seem to induce lymphocyte discharge from the spleen under in vivo conditions as well as under in vitro conditions. This work is interesting when compared to the lymphopenia obtained by ACE in previous reports by Dougherty and White. Is the breakdown of the lymphocyte in lymph nodes greater than the discharge from the spleen when animals are injected with ACE?

R.C.C.

**Lymphopenia Following Electrically Induced Convulsions in Male Psychotic Patients.**


The object of this experiment was to determine if the stress of an electrically induced convulsion would produce a lymphopenia in psychotic patients. A significant lymphopenia was found in the third hour following both the grand mal and petit mal reactions. The relation of these results to the lymphopenia found after other stresses and after injections of adrenal cortical extract or adrenocorticosteroid hormone are discussed.

R.C.C.

**IMMUNOHEMATOLOGY**

**Preliminary Note on Influence of Heterospecific Immunization on Production of Rh Antibodies.**


Volunteers were given repeated intravenous injections of red cells in an attempt to induce anti-Rh agglutinins. When, after 15 to 41 injections, no antibodies were found, mixed typhoid, paratyphoid vaccines were given simultaneously.

The relatively weak antigens C and E were used. Rh- antibodies appeared in 4 of 17 volunteers; 2 of these only after vaccine injections. One of the others showed a striking increase in titer after the vaccine. In general, only those who showed a clinical response to the vaccines and who produced antibodies to nearly all the injected typhoid antigens showed a satisfactory Rh antibody response.

If this observation can be confirmed on a larger scale the technic should prove most useful both for producing anti sera and, as the author suggests, for screening for potentially good antibody producers, only those who react clinically to vaccine being used for Rh immunization.

S.T.C.

**Genetic Transmission of Two Rare Blood Group Genes.**


This note records the phenotypes and genotypes of four families, three of whom show transmission of the gene R′ and one the extremely rare r.

S.T.C.

At the author's institution, the frequency of post-transfusion febrile reactions has been reduced from 7.9 per cent in 1936 to only 1.2 per cent in 1947 as a result of the perfection of methods of eliminating pyrogenic materials from blood transfusion apparatus. This virtual elimination of pyrogenic reactions has served to make more prominent mild hemolytic reactions occurring in Rh-positive patients as a result of Hr sensitization by repeated transfusions given over a long period of time. In a series of 23 Rh-positive patients having febrile reactions and at the same time showing evidence of posttransfusion hemolysis, 17 were Hr negative. Among 10 patients with febrile reactions but without evidence of hemolysis none were Hr negative. The author suggests that one should investigate every febrile reaction for evidence of hemolysis. If hemolysis has occurred even though the patient is Rh positive, Hr tests should be done, and if the patient is found to be Hr negative, only Hr-negative blood of a compatible blood group should be used for future transfusions. If Rh-negative patients have reactions despite transfusions of type rh blood, one should search for other sensitizations, particularly against the M factor.

G.E.C.


Sheep's erythrocytes, sensitized with extracts of human tubercle bacilli or products of their culture filtrate, were agglutinated by sera of rabbits previously injected with BCG and by sera of patients with active pulmonary tuberculosis. At least one material capable of sensitizing the red cells was shown to be heat stable and present in the polysaccharide fraction of the tubercle bacillus. Evidence for the specificity of this hemagglutination was obtained from the negative or insignificant reactions observed when the sensitized red cells were tested against sera of experimental animals immunized with other bacteria and against sera of nontuberculous individuals. It was of particular interest that there was no cross-reaction with Wassermann-positive sera.

Inhibition of the specific hemagglutination reaction was accomplished by adding the soluble reactive antigen to the serum before the red cells were introduced into the system. Utilization of both the inhibition test and the agglutination test permitted the detection and quantitation of small amounts of the sensitizing antigen.

The authors have suggested the possibility that this method may be of aid in the detection of a specific antigen circulating in vivo and that there may be even some correlation between the degree of activity of tuberculosis and the titer of the patient's serum in the hemagglutination test.

H.W.B.

ERRATA


Page 8, second line from bottom, "the Rh0 factor" (instead of "the Rh1 factor").
Page 12, third line from bottom, "A1MRh1rh" (instead of "A1MRhrh").
Page 35, first word of second line of reference 24, "patent" (instead of "patent")