ABSTRACTS

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ABSTRACTERS

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SPECIAL ARTICLE

THE CONTRIBUTIONS OF GEORGE RICHARDS MINOT TO EXPERIMENTAL MEDICINE. W. B. Castle. From the Thormdike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass. New England J. Med. 247, 585-592, 1952.

This is a beautifully written resume of some of Minot's contributions to medicine. The unmentioned role of the author in so much of the work described also adds interest to the article. The paper will be a source of stimulation to anyone interested in experimental medicine.—P.F.W.

ERYTHROCYTES


This paper reports experiments devised to measure the permeability of the human erythrocyte to sodium and potassium. It determines the temperature coefficient of these two permeabilities and investigates the relationship between external concentration of sodium and potassium and their relative permeabilities.—O. P. J.

POTASSIUM AND SODIUM OF RED BLOOD CELLS IN SICKLE CELL ANEMIA. D. C. Tosteson, E. Shea, and R. C. Darling. From the Department of Medicine, College of Physicians and Surgeons, Columbia University; and the Presbyterian Hospital in the City of New York, New York, N.Y. J. Clin. Investigation 31: 406-411, 1952.

Previous investigators have reported that red cell potassium (K) in sickle cell anemia is 10 per cent less than the 100 mEq./l of potassium in normal red cells. The authors then observed an elevation of the serum (K) in three patients with sickle cell anemia. These observations led to the present investigation of the effect of varying oxygen concentration on red cell potassium in this disease. Their studies revealed that in the de-oxygenated but not in the oxygenated state, red cells from patients with sickle cell anemia begin to lose K and gain Na almost immediately and continue to do so for at least 24 hours. This does not occur in de-oxygenated normal red cells. This exchange may be reversed, at least during the first half-hour, by reoxygenation and can be prevented if carbon monoxide is present in addition to the absence of oxygen. The explanation for this K-Na exchange is not established. Two hypotheses offered are (1) that the exchange is due to an abnormality of sickle cell anemia plasma, or (2) that the exchange is due to an abnormality in sickle cell anemia red cells. The available evidence suggests that the red cell K-Na exchange is probably related to the second hypothesis.—R. B. C.

Under controlled conditions, including complete bed rest, serial determinations were made of the concentration of $^{32}$ tagged red cells in the blood following intravenous administration. A semilogarithmic plot of the radioactivity per unit volume of whole blood as a function of time produces a biological decay curve which is a straight line for at least 48 hours in subjects with unchanging blood volumes. On the basis of this exponential relationship, it is possible to make serial whole blood and plasma volume determinations by relating the observed radioactivity to the predicted radioactivity at a given time after initial blood volume determinations have been carried out. Reinjection of additional tagged red cells is not necessary. Utilizing this method, the authors have evaluated acute changes in blood volume that occurred after (1) the intravenous infusion of salt-free albumin, (2) phlebotomy (3) paracentesis, (4) mercurial diuresis, (5) digitalis and (6) change in position from recumbency to ambulancy.—R. B. C.

HEMOGLOBIN and IRON METABOLISM


When one oxygen molecule combines with heme, it greatly increases the likelihood that a second oxygen will be attached to an oxygen-combining center. Apparently the sulfhydryl (-SH) groups play a part in this heme-heme interaction. This has been supported by experiments devised to block the -SH groups with p-chloromercuribenzoate and to attack them by dialysis. The effects of blocking and dialysis were reversed by the addition of glutathione.—O. P. J.


Enzymatic hydrolysis of hemoglobin by crystalline pepsin and trypsin was increased in the presence of an aqueous alcohol-treated extract of beef spleen. The substances responsible for this increased proteolytic activity have not been identified.—P. F. W.

CONTRIBUTION TO THE FORMATION OF HEMOGLOBIN IN THE NUCLEI OF ERYTHROBLASTS. F. Hřmanský. From the first Medical Clinic, Charles University, Praha. Časop. lék. česk. 90: 988, 1951.

This article describes a new staining method giving similar results in erythroblasts as the modified Lepehne method for hemoglobin although it is based on quite different principles. Both methods demonstrate a peculiar filamentous reticulum in the nucleus of the erythroblasts and in the nucleated red blood cells of the lower vertebrates. By the new method chloroplasts are stained intensively. Comparing the results obtained by both methods a close relation between hemoglobin and the intranuclear reticulum is suggested as well as the formation of this pigment in the nucleus of the erythroblasts.

The following freshly prepared mixture was used for both fixation and staining (20 to 30 minutes): methyl alcohol 5 ml., 10 per cent Lugol’s solution 2 ml., 20 per cent aqueous solution of basic fuchsin, slightly alcalized by adding 3 to 5 drops of 10 per cent sodium carbonate.—M. V.

SERUM IRON AND THE TOTAL BINDING CAPACITY OF THE HUMAN SERUM FOR IRON IN SOME PATHOLOGICAL STATES. L. Donner and S. Daum. From the Third Medical Clinic, Charles University, Praha. Časop. lék. česk. 91: 393, 1952.

The total iron binding capacity of the serum was measured in 23 normal subjects. The
mean ± S.D. was 359 ± 30.8 μg per cent. The saturation of the iron binding protein with iron was found to be 33.8 ± 6.8 per cent.

The serum iron, the total iron binding capacity of the serum and the saturation of the iron binding protein with iron was measured in 55 patients.

Of 18 patients with epidemic hepatitis the total iron binding capacity was found to be significantly increased in 16 patients. The serum iron was increased in each instance. The maximal value appeared between the second and fourth month of the diseases. In 3 patients with cirrhosis of the liver the serum iron and the total iron binding capacity was found to be decreased.

In 7 hemorrhagic anemias the serum iron was decreased, whereas the total iron binding capacity was significantly increased. In 3 essential hypochromic anemias the total iron binding capacity was found to be decreased. In 5 untreated pernicious anemias the same value was also decreased.

A marked decrease in serum iron, total iron binding capacity and the saturation of the iron binding protein with iron was found in 10 patients with infections and 8 with malignant tumors.

The importance of the total iron binding capacity of the serum for the regulation of iron metabolism is stressed and its use for differential diagnosis is suggested.—M.N.


Four hundred and twenty three unselected Negro hospital patients were fed a standard dose of reduced iron tagged with radioactive Fe^{59}. Hematologic determinations were made immediately prior to iron ingestion and again eight days later when an activity assay was carried out.

The patients were classified into eight clinical groups. The control or reference group was composed of patients who had ailments not expected to alter iron metabolism to any notable degree. While there was some variation in iron utilization within this group (range 0.24 to 9.20 per cent), the mode value of utilization was 1.50 per cent. Little correlation could be found between hematologic findings and the actual per cent utilization in these individuals. As might be anticipated, the largest mean utilization occurred in the pregnancy group (26.28 per cent) and the lowest mean value in acute infections (0.60 per cent). Values for patients with cardiovascular disease and for the traumatic cases with acute blood loss varied little from those of the reference group. Of particular interest was the lack of significantly depressed utilization in the groups with chronic infection and malignant neoplasm. Also not completely explained was the finding of elevated utilization values in all the patients with benign neoplasm.—H.W.B.

IMMUNOHEMATOLOGY


The authors report some very interesting data relative to their experience with the use of cortisone in Rh incompatibilities. Seventy Rh negative women without antibody were treated with cortisone during labor and for seven days postpartum. It was estimated that 5.5 sensitizations could be expected in this particular group. None of these patients, however, showed evidence of sensitivity when tested at four weeks postpartum.

Perhaps not as impressive but nonetheless definitely encouraging were the results of treatment during the last trimester of 12 sensitized Rh negative women in whom the expectation of a healthy baby was poor. With a few exceptions, the infants of these women were delivered in a satisfactory condition. The most striking example in this group was the strongly sensitized mother who had 3 Rh positive children, the last one being hydropic, and who on this occasion gave birth to a normal appearing Rh positive infant.
ABSTRACTS

Cortisone or ACTH was combined with exchange transfusion in the treatment of several severely erythroblastotic infants with very good results. It is the authors' impression that the chances of survival of this group may be increased by use of the drug.

Attempts to prevent a postpartum rise in antibody titer in previously sensitized women met with failure.

While any conclusions may be premature at this time, it does appear that cortisone interferes with the antigen-antibody reactions of the Rh type and thereby opens up a new approach to the management of Rh incompatibilities and erythroblastosis fetalis. Further and most certainly cautious investigation of this problem seems warranted.—H.W.B.

BLOOD COAGULATION and HEMORRHAGIC DISEASE


Previous investigations have indicated that citrovorum factor (CF) is closely related chemically and metabolically to pteroylglutamic acid (PGA). The present study was undertaken to investigate the role of ascorbic acid in the metabolic relationship of PGA to CF in man. The urinary excretion of CF was determined after PGA was administered orally to 2 patients with scurvy and to a nonscorbutic subject, before, during and after ascorbic acid therapy. Pteroylglutamic acid was administered in 10 mg. doses and ascorbic acid in 1 Gm. doses. During the initial control period, a small amount of CF was excreted by patients with scurvy and by the nonscorbutic patient. When PGA was administered orally to the scorbutic patients, CF excretion increased slightly. On the other hand, maximal CF excretion occurred in scorbutic subjects after only adequate therapy with ascorbic acid. The data obtained indicates that PGA is closely related metabolically to CF in man. Furthermore, the authors conclude that ascorbic acid greatly facilitates the conversion of PGA to CF.—R.B.C.


The mechanism which initiates the coagulation of shed blood has not been definitely established. Some feel the platelets are necessary for the initiation of blood coagulation, while others consider platelets essential only for efficient coagulation. Previous investigations have been interpreted as providing evidence for the existence of a “plasma thromboplastin.” It was observed that the rate of clotting of platelet-free plasma was directly related to the area of surface glass to which it was exposed. Other similarly prepared platelet-free plasma in dogs was not successful. The present study attempts to elucidate the clotting properties of canine plasma. The results showed that canine platelet-free plasma clotted when exposed to glass surfaces and the rate of clotting was related to glass surface areas. In dogs such a preparation of plasma in silicone tubes at 37 C. remained fluid but clotted on contact with glass. The plasma of hemophiliac dogs did not clot even when stored in contact with glass. The authors conclude that their data supports the view that the clot-accelerating effect of glass surfaces is mediated by a “plasma thromboplastin.” It is the substance which is lacking in a case of hemophilia.—R.B.C.

STUDIES ON A PROTEOLYTIC ENZYME IN HUMAN PLASMA. VII. A FATAL HEMORRHAGIC STATE ASSOCIATED WITH EXCESSIVE PLASMA PROTEOLYTIC ACTIVITY IN A PATIENT UNDERGOING SURGERY FOR CARCINOMA OF THE HEAD OF THE PANCREAS. O. D. Ratnoff. From the Departments of Medicine, The Western Reserve University School of Medicine, and the Mount Sinai Hospital, Cleveland, Ohio. J. Clin. Investigation 31: 521–528, 1952.

Among the substances present in plasma there is a proteolytic enzyme which can digest
ABSTRACTS

fibrinogen and fibrin. It is postulated that, with excessive plasma proteolytic activity, a hemorrhagic state may result, due either to the destruction of fibrinogen or the lysis of fibrin.

The author presents a case of carcinoma of the pancreas who developed uncontrollable hemorrhage during an operation. Extensive studies of the coagulation process were performed. Appreciable amounts of fibrinogen were present. In spite of this, clotting failed to occur and the author feels that the failure to clot was associated with excessive plasma proteolytic activity.—R.B.C.


Of twenty-eight new dicumarine derivatives four substances were found which are more effective than the di-(4-hydroxycoumarinyl-3) acetic acid ethylester (pelentan). Their toxicity, with one exception, 1,1-di(4-hydroxycoumarinyl-3) propanone, was correspondingly more than the toxicity of pelentan. For its high activity and low toxicity this substance, coded FL 2, was recommended for clinical trials as a new anticoagulant drug.—M.N.


Clinical use of a fibrinolytic enzyme derived from bovine plasma in the treatment of 100 patients is described. Three groups were studied. Group I: 38 patients in whom blood clots were liquified. Group II: 32 patients in whom fibrinolysis was used for debridement of infected wounds, burns and draining sinuses. Group III: postoperative respiratory complications, 24 patients with atelectasis and 6 patients with annoying bronchial secretions. Results were favorable in all three groups but further evaluation is indicated.—C.E.R.


The formation of L. E. cells is enhanced by some substance active for a short period of time during the process of blood coagulation. A “two-hour blood-clot technic” is described. The authors feel that lysis of nuclear material is the fundamental process in the L. E. cell phenomenon.—P.F.W.


Trehuron is a synthetic heparin-like anticoagulant which prolongs the coagulation time of whole blood and has from one-third to one-fourth the potency of sodium heparin. It is therapeutically effective when given intravenously in doses of 200 mg. In one case reported in this small series, when 50 mg. of protamine sulfate was injected 30 minutes after an injection of treburon, there was a prompt decrease in the coagulation time. The coagulation time of the 3 patients who received treburon sublingually did not seem to be affected.—P.F.W.

MASSIVE GENERALIZED WOUND BLEEDING DURING OPERATION WITH CLINICAL AND EXPERIMENTAL EVIDENCE OF BLOOD TRANSFUSION REACTIONS. S. R. Friesen, W. N. Harsha and C. H. McCroskey. From the Department of Surgery, University of Kansas School of Medicine, Kansas City, Kansas. Surgery 32: 620–629, 1952.

This is a continuation of observations reported by one of this group relative to the bleeding tendencies developing in 7 patients following, and presumably due to infusion of incompatible blood. Six pure bred dogs were given repeated infusions of sterile pooled blood of mongrel dogs intravenously six times a week for four weeks. All the dogs in this
particular series developed a significant increase in the protamine titration. A gross bleeding tendency developed. Prothrombin times in all were unchanged. In addition, observations on 4 more patients receiving 250 to 500 cc. of incompatible blood and developing hemolytic transfusion reactions are reported. They all presented subsequent defects in coagulation. Toluidine blue dye (15 mg. per Kg. body weight intravenously) seemed to correct the bleeding tendency clinically in 2 patients. Marked fibrinolysis was observed in the coagulation of blood from 1 patient.—P.F.W.


An improved fibrin plate method for the estimation of plasmin and other fibrinolytic enzymes is described. The method is shown to have high sensitivity and specificity. Employing Armour crystalline trypsin, its sensitivity was 0.02 mg.—C.E.R.

LEUKOCYTES and LEUKOCYTIC DISEASE


This paper should be of value to all investigators interested in quantitating intracellular constituents. Although two methods may be used in maintaining homogeneous solutions, the resulting analyses are divergent. When the movement was such as to produce a sloshing motion of the liquid, the K content of the cells approached diffusion equilibrium in 12 hours. In contrast, when the motion of the liquid was that of a uniform flow, there was only a 6 per cent K loss for the same period.—O. P. J.

SOME STRUCTURAL REQUIREMENTS FOR THE PREVENTION OF LEUKOPENIA INDUCED BY NITROGEN MUSTARD. A. S. Weisberger, R. W. Heinle and B. Levine. From the Department of Medicine, Lakeside Hospital, and the School of Medicine, Western Reserve University, Cleveland, Ohio. J. Clin. Investigation 31: 217-222, 1952.

It has been shown that the administration of L-cysteine hydrochloride to animals prior to the injection of nitrogen mustard (HN₂) modifies the leukopenia characteristically produced by HN₂. If L-cysteine is administered after HN₂ is given, the leukopenia is not modified. The mechanism of L-cysteine protection was investigated by the authors by correlating the chemical structure of L-cysteine and related compounds with their ability to prevent HN₂-induced leukopenia. Of the compounds studied, only those with vicinal sulfhydryl, amino and carboxyl groups modified HN₂-induced leukopenia. L-cysteine with a free sulfhydryl, amino and carboxyl group on adjacent carbon atoms was most effective. D, L-Homocysteine and glutathione were less effective. Substitution or alteration of any of these free groups results in the loss of any protective effect against HN₂-induced leukopenia. The actual mechanism of protection was not established by the experiments. The authors feel that the protective action of L-cysteine and its homologues in vivo does not result solely from inactivation of HN₂, but rather that these substances protect some substance(s) essential for leukopoiesis, from destruction by HN₂.—R.B.C.

LEUKOPENIA AND GRANULOCYTOPENIA DEVELOPING DURING THE COURSE OF TREATMENT WITH CORTISONE. J. E. Stevens and E. C. Toone, Jr. From the Department of Medicine, Medical College of Virginia, Richmond. South. M. J. 45: 738-740, 1952.

A case of temporary bone marrow depression with leukopenia is reported in a patient with rheumatoid arthritis under treatment with cortisone. Various explanations for this were considered and the hypothesis offered that the hormone may have attenuated the response of the patient so that he developed a hypersensitive reaction to one of the agents in the vehicle or to the acetyl salicylic acid or codeine sulfate which were taken concur-
ABSTRACTS 193

Currently. From the data presented, however, it is somewhat difficult to definitely incriminate cortisol in this case.—H. W. B.


A case of fatal pancytopenia occurring in association with Nuvarone therapy is reported. The close similarity between the chemical structures of Nuvarone and Mesantoin is of interest.—C. E. R.


The laboratory findings, signs and symptoms are described in 7 children in a residential nursery who developed pronounced lymphocytosis. The etiology of the syndrome is discussed. No definitive studies were done but it is concluded that the syndrome is caused by an infection with a virus of low virulence closely allied to rubella.—C. E. R.

DIFFERENTIAL DIAGNOSIS OF VISCERAL LEISHMANIASIS (KALE-AZAR) IN BIOPIC EXAMINATION. B. Bednář. From the First Institute of Pathological Anatomy, Charles University, Praha and the Laboratory and the Medical Department of Military Hospital, Praha. Časop. lék. česk. 90: 1019, 1951.

The chronic form of kala-azar was diagnosed by means of biopsy from the spleen in a male student aged 22. In 1948 the patient had spent a fortnight in Yugoslavia (Dubrovnik); this was the only occasion when he had left Czechoslovakia. No acute illness had been noticed, but two years later the patient developed septic fever, anemia and leukopenia with hepatosplenomegaly. The biopsy made during exploratory laparatomy disclosed clusters of characteristic leishmanias in cells of the spleen pulp; the parasites were particularly well seen in sections stained by the Papp method for reticulum. Some difficulty may arise in differentiating the leishmania from histoplasma, but this is easily overcome.—M. N.


In 4 cases of unilocular swelling of the lymph nodes the clinical course as well as histologic findings were characteristic of benign viral lymphadenitis described by Mollaret et al.

In an additional 4 cases with involvement of the mesenteric lymph nodes, all in children, it was not possible to assess whether this was an identical, or akin, or a different disease.—M. N.

LEUKEMIA and NEOPLASTIC DISEASE


A case is reported of a 65 year old man with pernicious anemia who, after four years of irregular treatment, developed rapidly fatal myelogenous leukemia. Although the coexistence of the two diseases in this case is presumed to be coincidental, the question of possible abnormal granulocytic stimulation by liver extract, folic acid and vitamin B₁₂ is raised.—H. W. B.

REMISSION OF ACUTE LEUKEMIA BY EXCHANGE TRANSFUSION. J. Chropil and E. Kohn. From the Central Military Hospital, Praha. Časop. lék. česk. 90: 1020, 1951.

This is the report of a case of acute myeloblastic leukemia in a woman aged 39. After five to six months of clinical symptoms she developed a spontaneous partial remission, lasting
fifteen months. Afterward the patient relapsed in a more severe form and a fatal outcome seemed inevitable. Therefore an exchange transfusion (8 liters) was performed. The immediate effect was only that of the replacing red cells and hemoglobin, but within eight weeks a dramatic complete clinical and peripheral blood remission was observed, the bone marrow still containing 61 per cent myeloblasts. This clinical and hematologic remission has now lasted eighteen months; the whole duration since the onset of the first clinical symptoms is more than twenty-six months, the longest ever reported. It is difficult to decide whether the second remission was also spontaneous or whether it is an effect of exchange transfusion. Finally the technic of exsanguination transfusion used is described.—M. N.

CLINICAL EXPERIENCE WITH TREATMENT OF MALIGNANT DISEASES WITH NITROGEN MUSTARDS. F. Černík, P. Lukl, J. Procházka and J. Vička. From the Medical Clinic, University in Hradec Králové. Časop. 16k. česk. 91: 44, 1952.

Twenty-four cases of various malignant diseases were treated with nitrogen mustard (treatment form) of Czech manufacture. Most cases were advanced generalized forms of neoplasms, refractory to local treatment.

In 15 out of 24 cases some improvement was noticed. The most striking objective improvement, regression of tumorous masses, was observed in some cases of lymphosarcoma, reticulossarcoma and in one case of multiple myeloma. More frequently, the favorable results were transient, including only indirect symptoms such as dyspnea, pain and subjective complaints. According to our experience, nitrogen mustard must be regarded not as a substitute for existing therapy, but as its palliative supplement in cases of inoperable neoplasms. Nevertheless, the results of nitrogen mustard therapy definitely prove the potency of chemotherapy in malignant new growth.

The lines for further progress in the chemotherapy of malignant neoplasms are considered.—M. N.

OBSERVATION OF SIMULTANEOUS APPEARANCE OF HODGKIN’S DISEASE AND LEUKEMIC RETICULOSIS. O. Soyka. From the Third Medical Clinic, Charles University, Praha. Časop. 16k. česk. 90: 1191, 1951.

The possibility that one form of malignant lymphoma can revert to another is discussed. Such changes have often been reported in Brill-Symmers disease (giant cell follicular lymphoma), which reverts to lymphosarcoma, Hodgkin’s disease or lymphatic leukemia. A case of Hodgkin’s disease which developed into reticular leukemia is reported. It is, however, impossible to exclude that the patient was suffering from two tumors of the hematopoietic system simultaneously.—M. N.

MULTIPLE MYELOMA DIAGNOSED FROM HYPERPROTEINURIA. L. Donner, J. Pechar and J. Hrabčan. From the Third and Fourth Medical Clinic, Charles University, Praha. Časop. 16k. česk. 90: 1275, 1951.

A case of high proteinuria in which a multiple myeloma was diagnosed by the aid of electrophoresis is presented. The patient was treated with urethane for twenty-eight days in total dose of 84 Gm. Striking benefit was observed. Abnormal plasma cells decreased quantitatively in the bone marrow from 43 to 0.5 per cent. The cells underwent morphologic changes indicative of retarded growth. The proteinuria decreased from 30 Gm. of the excreted protein daily to 1 Gm. The elevation of serum globulin became less pronounced and decreased from 46 to 24 per cent. No benefit from urethane was noted in 3 other patients with multiple myeloma. One patient was treated with urethane in a total dose 46 Gm. for twenty-six days. The second was treated with urethane in a total dose of 60 Gm. for forty-three days. The third was treated with 72 Gm. of urethane over eighteen days. All 3 died without any improvement of the disease.—M. N.