ANTICOAGULANTS

ANTICOAGULANT THERAPY. C. H. Jaimet. From the Hamilton General Hospital, Hamilton, Ontario.

The prophylactic administration of dicumarol in patients with myocardial infarction and in surgical and obstetrical patients is briefly discussed. Of particular interest is the author’s experience with preoperative and antepartum dicumarolization. Surgical patients with venous thrombosis were operated on with a prothrombin time between 30 and 40 seconds. In none of these was there excessive bleeding; embolism did not occur and the phlebitis was cured after a normal postoperative hospitalization. There were 90 obstetrical patients in the group (15 of these are described in more detail in the previous paper in this journal). Those with phlebitis were dicumarolized (prothrombin time between 34 and 40 seconds) prior to delivery, and those with a history of previous phlebitis or embolism were started on dicumarol immediately following the onset of labor. Dicumarolization was maintained for approximately fourteen days postpartum. None of the patients experienced abnormal intrapartum or postpartum bleeding; embolism did not occur and there was marked improvement in existing phlebitis.

The author considers properly controlled earlier anticoagulation therapy a safe and more effective means of reducing the incidence of thromboembolism in surgical and obstetrical patients.

No mention is made of the infants whose mothers were dicumarolized prior to delivery and one wonders whether hemorrhagic manifestations were encountered. Without further knowledge it would seem that a maternal hypoprothrombinemia of this degree might well constitute a potential hazard to the infant.

H. W. B.

ANTICOAGULATION THERAPY IN DISSEMINATED SCLEROSIS. I. Lesnj and L. Poldéek. From the Clinic of Nervous Diseases, Ch. U., Prague, Čas. lék. čes. 83: 115, 1949.

The treatment of disseminated sclerosis by anticoagulant drugs seems to be justified by two facts: the rare occurrence of this disease in yellow races where, as a rule, a longer coagulation time is observed, and the relatively high prothrombin level in the blood of patients suffering from disseminated sclerosis (see Blood 4: 296, 1949).

When heparin was used as anticoagulant, 12 patients out of 17 were improved. A dicumarol preparation (trade mark Pelentan) proved to be equally effective; of 40 patients treated with this preparation, 34 were substantially improved. This improvement was not only subjective but also objective: disappearance of nystagmus and pyramidal tract signs, reappearance of abdominal reflexes, improvement of gait, etc. Not only recent cases showed improvement but even patients who had been paraplegic for years started to walk again when treated with Pelentan.

In 8 patients, the dicumarol therapy has been continued for fourteen months and the prothrombin level has been kept constantly at about 10 per cent; no bleeding has been witnessed which could not be stopped by simply interrupting treatment with Pelentan for one or two days.

In spite of these successes which were considerable, the authors do not claim that Pelentan is a specific remedy of disseminated sclerosis or that it is related to the cause of the disease. Further studies are necessary to clear up this problem.

M. N.

In an effort to throw further light on the pathogenesis of venous thrombosis in postoperative patients, the thrombin inactivating capacity of the blood was investigated by means of heparin cofactor assays. Determinations were performed on 67 normal fasting individuals, 6 patients with hypoalbuminemia, and on 22 surgical patients, preoperatively and daily during the postoperative course. Details of the test are described and the results are expressed as percentage of thrombin destroyed compared to normal.

The average value of thrombin destruction in the group of normal individuals was 92.6 per cent, whereas that in the hypoalbuminemic patients was 83.1 per cent. The finding of a consistently reduced cofactor activity in this latter group bears out previous observations of the close association of thrombin inactivating agents and the serum albumin.

Twenty surgical patients had no thromboembolic complications and showed little change in their heparin cofactor activity. The 2 patients with postoperative venous thrombosis, however, demonstrated appreciable reductions in cofactor activity several days prior to clinical recognition of the thrombosis.

It is impossible to determine at the present time the precise relationship of the operative procedure, the reduction in thrombin inactivating substances and the development of venous thrombosis. It would be of interest, however, to know the level of serum albumin in those patients who developed thromboembolic complications.


This report is a summary of the authors' experiences with naturally-occurring hypercoagulable and anticoagulant substances in human blood. The presence of these substances and their effect on the prothrombin and coagulation times in thromboembolic diseases is demonstrated.

Heparin exerts a maximal effect upon the whole plasma prothrombin time and a slight effect on the more dilute prothrombin times when compared with normal plasma. The effect of heparin on the prothrombin time is immediate and is usually not detectable four hours after its administration parenterally. Dicumarol produces a moderate prolongation of the whole plasma prothrombin time and a marked prolongation of the dilute plasma prothrombin time.

The effect of an anticoagulant-like substance present in diseases associated with thrombosis, inflammation or necrosis is detected in the whole plasma prothrombin time but is usually undetectable in the 1:5 per cent plasma since the substance is generally rendered ineffective by diluting 1:8.

In patients with myocardial infarction, phlebitis and pulmonary embolism the prothrombin determination of whole and 1:5 per cent plasma is of definite diagnostic value. During the early thrombotic period the prothrombin times of either whole plasma, dilute plasma or both were shorter than normal (accelerator phase). This is followed shortly by a prolonged plasma prothrombin time (auto-anticoagulant phase).

IMMUNOHEMATOLOGY


A family is described in which, following 3 normal children, the Rh negative mother had 3 Rh positive children, all of whom in later life developed hepatosplenomegaly of the Banti type. Injection of 5 ml. of the Rh positive father's blood stimulated the production of antibodies in the mother's serum. This was in favor of the idea that isoimmunization had played a part in this familial Banti syndrome. Reference is made to two families described by Drummond in which Rh immunization may also have been responsible for familial cirrhosis.
ABSTRACTS


Anti-A was thought to be responsible for the development of hemolytic disease in 2 newborn infants. In neither case could an atypical antibody be found in the mother's serum, but there was an unusually high anti-A titer. In one infant, A cells were rapidly eliminated after transfusion, whereas O cells survived normally. In the other, anti-A antibodies were detected in eluates from the tissues at necropsy.

This type of investigation seems to leave little doubt that ABO incompatibility may be responsible in some cases of hemolytic disease of the newborn.

S. C.


Multiple transfusions for an anemia, possibly due to myelosclerosis, in a woman of 51, induced the formation of anti-S as well as anti-D. The anti-S was responsible for several hemolytic reactions. Later, although Rh negative S-negative red blood cells were compatible in vitro, such cells were rapidly eliminated after transfusion on two occasions, indicating that present in vitro tests cannot detect all cases of sensitivity to foreign erythrocytes.

S. C.

LEUKOCYTIC DISEASE


A clinical syndrome in young children characterized by long persistent eosinophilia, hyperleukocytosis and hyperglobulinemia is described. Although the condition is in general benign and self-limited and the patient may be asymptomatic throughout much of his course, the common manifestations encountered were hepatomegaly, pulmonary infiltrations, upper respiratory symptoms, joint symptoms, urticaria and convulsions. Study of the pathologic lesions in the liver of 4 cases, obtained by biopsy specimens or at autopsy, demonstrated a common pathologic process despite the variability in the clinical picture. Essential histopathologic features were focal necrosis, granuloma formation with histiocytes and giant cells, and widespread eosinophilic infiltrations without demonstrable micro-organisms or parasites.

Although definite proof is lacking, the clinical and laboratory evidence presented strongly supports the concept that the underlying condition is an allergic tissue response to an undetermined antigen. The similarity of this syndrome to Loeffler's syndrome in older children and adults is pointed out. It is conceivable that this syndrome in young children with predominantly hepatic localization and Loeffler's syndrome with pulmonary localization are merely two of a large group of related allergic disorders in which the variability in the clinical picture depends on the severity of the condition and the organs involved.

This study is interesting and should serve as an incentive for more complete investigation of the, at present, poorly defined group of conditions associated with persistent eosinophilia.

H. W. B.


The circulating eosinophil count by the chamber method has been studied, using two diluents. With an eosin-acetone mixture, there is a large and rapid decrease in cell count with passage of time after
dilution of blood and with aging of the oxalated blood. A diluent composed of phloxine in propylene glycol and water provides more consistent results and no evidence of destruction of eosinophils.  

G. E. C.

FURTHER STUDIES ON ENHANCEMENT OF HETEROPHILE AGGLUTINATION TITERS BY MEANS OF SERUM DILUENT. A. Milter and S. Nathan. From the Department of Bacteriology and Virology, Medical Research Institute, Michael Reese Hospital, Chicago, Ill. J. Lab. & Clin. Med. 34: 1014-1016, 1949.

Heterophile agglutination titers of both unabsorbed and guinea pig kidney absorbed serum obtained from patients were significantly enhanced by the use of human serum or acetic fluid diluent instead of saline. Horse serum, bovine serum, 10 per cent bovine albumin, 10 per cent human albumin, 10 per cent human gamma globulin, and human albumin and gamma globulin mixtures failed to enhance heterophile agglutination titers.

G. E. C.


Four cases of polycythemia and definite multiple myeloma are reported. All 4 cases were first studied and followed because of polycythemia, and the myeloma was an unexpected development or finding.

Some interesting questions suggested by these cases are discussed: the relation of myeloma to polycythemia and their etiologies; response of polycythemia to radioactive phosphorus; radioactive phosphorus as a therapeutic agent in myeloma, and the latent period of myeloma.

A review of the literature by the authors has revealed that there are two reports of polycythemia associated with possible myeloma. Two cases of polycythemia with Bence-Jones proteinuria have also been described in the literature.

G. E. C.

THE BONE MARROW IN GLANDULAR FEVER. A. C. P. Campbell. From the Department of Pathology, Edinburgh University, Edinburgh, Scotland. J. Path. & Bact. 60: 63-63a, 1948.

The blood picture of glandular fever (infectious mononucleosis) has been adequately investigated and described and to a lesser degree so have the lymph nodes. However, the reports of bone marrow studies in this disease, although quite numerous, have been contradictory or negative. In the present study, marrow sections and smears from 15 cases were obtained at the peak of the disease or shortly thereafter. In sectioned material, foci composed chiefly of undifferentiated reticulum cells and medium-sized lymphocytes were found. The former resembled endothelioid cells. Although Campbell has not observed a similar picture in the marrow of other conditions, Sundberg and Spink (Blood, Special Issue No. 1 Morphologic Hematology 7, 1947) described a similar formation in brucellosis. Campbell was unable to demonstrate the participating cells (endothelioid) in marrow smears. He believes this was due either to the sparsity of the foci or the lability of the cells concerned. The foci of lymphoid reaction are similar to those found in lymphatic tissue throughout the body in this disease.

O. P. J.


In normal rabbits, the intravenous injection of nitrogen mustard in a dose of 3 mg. per kilogram of body weight produces a modest anemia and a severe leukopenia and reticulocytopenia. Nitrogen mustard in similar dosage, when given to animals in which an anemia, reticulocytosis and hyperplastic marrow are already present by virtue of prior phenylhydrazine administration, produces further anemia, a leukopenia and a reduction of the reticulocyte value. In the normal rabbit, HN2 produces a marked depletion of lymphatic tissue, atrophic bone marrow and a temporary decrease in mitotic activity. In
animals previously treated with phenylhydrazine and then given HN₂, the usual destructive effects in the hemopoietic tissues were observed but large numbers of hemocytoblasts and erythroblasts in the bone marrow survive which are immediately capable of proliferation. Mitotic activity continues at a greater than normal rate under these conditions. Thus, the production of a hyperplastic (erythroblastic) marrow protects the marrow from the destructive effects of HN₂ by virtue of increasing the population of hemocytoblasts and basophilic erythroblasts which are less sensitive to this chemical agent than the more mature derivatives of these cells.

G. E. C.

CLINICAL EXPERIENCES WITH NITROGEN MUSTARDS. F. Černík, P. Lukí, J. Procházk a K. Roubík. From the Medical Clinic, University in Hradec Králové. Čas. lék. čes. 88: 339, 1949.

The results obtained in 18 cases of various forms of leukemia, treated with nitrogen mustards (tris-form of Czech origin) were very much like those seen after x-ray treatment. In chronic myelogenous leukemia (5 cases), the average length of the remission was two months; in chronic lymphatic leukemia, it was a little longer (3.5 months). The toxic effect on the bone marrow was much more pronounced and sudden than with x-ray therapy, could not be predicted and persisted one to five weeks after the end of the treatment. The results of the treatment were somewhat better in chronic lymphatic leukemia than in the myelogenous form but the danger of thrombocytopenia and neutropenia was here more pronounced. Subacute leukemia is not considered a contraindication to this treatment.

M. N.

HEMATOPOIETIC FACTORS


The observations here reported show that in nutritional macrocytic anemia and sprue, as in pernicious anemia, something of the order of 30 to 60 times the effective parenteral dose is required to give any response by the oral route. In all, 16 cases of pernicious anemia, 17 cases of nutritional macrocytic anemia, 14 cases of tropical and 2 cases of nontropical sprue were observed. Nine illustrative cases are summarized in the paper.

S. C.

VITAMIN B₁₂ IN PERNICIOUS ANAEMIA. M. F. Beard, M. Nataro and L. H. Layman. From the Medical Service, Veterans Administration Hospital, Louisville, and the Department of Medicine, University of Louisville School of Medicine, Louisville, Ky. South. M. J. 42: 677-684, 1949.

Six patients with pernicious anemia in relapse were studied to determine the minimal effective intramuscular dose of vitamin B₁₂ and the effect of this vitamin on neurologic manifestations of the disease. Initial injections varied between 0.025 and 0.100 mg.; additional doses were given as needed; and the total dosages during the one to four months of observation were between 0.80 and 0.110 mg. All patients showed satisfactory clinical and hematologic responses. Reticulocyte peaks were reached between the third and ninth day. Serial bone marrow studies revealed that the reversion to a normoblastic marrow started as early as six hours and was almost complete in forty-eight to seventy-two hours after therapy was instituted.

Observations on 4 patients indicated that initial injections of 0.025 and 0.050 mg. of vitamin B₁₂ produced hematologic effects comparable to injections of 25 and 50 U.S.P. units of refined liver extract respectively. It was suggested, however, that much larger initial injections of vitamin B₁₂ be given, prior to the monthly maintenance doses, in order to correct the depleted reserves of the liver.

The patients with minimal peripheral neuritis showed moderate improvement within four to six weeks and the 2 cases of combined system disease experienced marked subjective improvement, although little change was noted in their objective neurologic signs. Since this study was primarily designed to establish the minimal effective dose of vitamin B₁₂ and these patients with combined system disease were
followed for only one and three months, conclusions as to the effect of vitamin B₁₂ on neurologic manifestations of the disease are hardly warranted.

H. W. B.


The common deficient vitamins in the sprue syndrome are all essential growth factors for the usual intestinal bacteria. Large numbers of these bacteria have been shown by intubation to be present in the upper part of the small intestine in the sprue syndrome instead of being confined to the lower parts of the gastrointestinal tract. It is suggested that they compete with the host for common essential nutrients producing avitaminosis in the host. Evidence is given to support this hypothesis.

S. C.


Powers and Murphy showed that liver extracts produced a neutrophil leukocytosis when given to a normal person. The substance concerned was found in a fraction soluble in phenol-butanol, but was absent from a pinkish fraction isolated by Laland during the purification of liver. This paper shows that crystalline anti-pernicious anemia factor, like Laland’s fraction, fails to produce a leukocytosis in normal persons.

S. C.


Nine cases of typical Addisonian pernicious anemia were treated with a simple aqueous extract of whale liver, 1 ounce of extract being equivalent to 25 ounces of whole liver. The results confirmed observations of Aylward et al. (1941) that the whale liver is hematopoietically active. Complete remissions were obtained in 3 cases with ½ ounce of extract daily. The other patients received either ¼ ounce or 3 ounces daily; only one showed a suboptimal response. It appears that whale liver is at least as potent as whole bovine liver as a source of hematopoietic factor.

S. C.


Five patients with pernicious anemia were given a folic acid antagonist and then treated with adequate doses of liver extract. In none of the patients was an optimal response to liver extract observed. A sixth patient was treated with 200 mg. of methyl pteroxic acid for fourteen days. On the third and eleventh days of therapy he was given 10 and 15 µg of vitamin B₁₂ respectively and 5 mg. of 4-amino 10-methyl pteroylglutamic acid intramuscularly. There was no clinical remission or reticulocyte response; the hemoglobin, red cell and white cell count did not rise; and four sternal aspirations done during the period of observation revealed a megaloblastosis of 11 to 13 per cent.

The results would seem to indicate that pteroylglutamic acid is necessary for the proper function of the anti-pernicious anemia factor of liver.

G. E. C.