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HEMOSTASIS

EXPERIMENTAL PRODUCTION OF MICROANGIOPATHIC HEMOLYTIC ANAEMIA IN VIVO. M. L. Rubenberg, B. S. Bull, E. Regoecci, J. V. Dacie and M. C. Brain.

Acute defibrination was produced in rabbits by injection of Malayan pit-viper venom and lysis of microemboli was inhibited with epsilon amincaproic acid and soya-bean trypsin inhibitor. This treatment resulted in prolonged hemolysis with presence of fragmented red cells in the peripheral blood. During defibrination, the blood contained microclots with red cells adherent to fibrin strands. Similar fibrin aggregates containing red-cell fragments were seen in small blood vessels in histological sections. Hemolysis was enhanced when the experiments were performed on thrombocytopenic rabbits. It was suggested that red-cell fragmentation and hemolysis resulted from the physical interaction of red cells and intravascular fibrin and that in thrombocytopenia the lack of platelets in the fibrin clots rendered them more permeable to red cells and permitted continued interaction between red cells and fibrin. Red cell interaction with fibrin may account for the hemolysis of microangiopathic hemolytic anemia and of other conditions associated with intravascular coagulation.—A. B.

THE HEMORRHAGIC SYNDROME OF EARLY CHILDHOOD. V. A. Lovric and R. J. Jones.

Twenty-five children aged 4-24 weeks showed an abnormal hemorrhagic tendency, chiefly GI bleeding and oozing from transfusion sites, associated with deficiencies in the prothrombin complex and resolving after vitamin K therapy. In 12 chronically ill children, the cause appeared to be malabsorption of K, but no predisposing factors were found in the others. Prophylactic vita-
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Vitamin K therapy was recommended for surgical patients in the first 4 months of life.—F. W. G.


Two cases were described. In the first, a hemorrhagic diathesis developed after 0.5 G of aspirin and in the second after ingestion of rat poison.—M. K.


An increase in the erythrocyte and thrombocyte count in capillaries was found in the early stages of hemodynamic shock. Lower levels of fibrinogen were observed in capillaries than in venous blood. Simultaneously, activation of fibrinolysis was higher in capillary blood. Disturbances in the coagulation system and of fibrinolysis in the capillary vascular bed were seen earlier than any others changes in circulating blood.—M. K.


Administration of estrogens in the pre-delivery period caused an increase in fibrinogen level. Administration of estrogens by intravenous drip did not decrease bleeding in the third stage of labor, bleeding thought to be connected with a pathologic drop in fibrinogen.—M. K.


Daily IV injections of ethionine into dogs induced prolongation of prothrombin time and lowering of activities of Factor V and VII. These changes may have been due to liver injury. The drop in Factor VII activity was observed much earlier when liver cell damage was minimal, while Factor V declined only when numerous foci of necrosis and extensive fatty degeneration of the liver had appeared.—M. K.


Levels of Factors I, II, V, VIII, IX, X, XI were studied in mothers in labor and in newborn infants. Levels of Factors II, IX, X, XI were low in infants. Because many normal infants had prolonged prothrombin times, a new normal range was suggested for infants. Normal colored infants had significantly longer prothrombin times than either whites or Bantus.—T. H. B.


Survival of Cr51 labeled isologous platelets was studied in 10 healthy subjects and in 16 cases of thrombocytopenia. External measurements of radioactivity over spleen and liver were included. Shortened survival was observed in 9 cases of ITP. In 7 cases of secondary thrombopenia with impaired production of platelets, results were not uniform. The index of spleen-liver Kr51 platelet sequestration may be of value for predicting the effects of splenectomy.—M. K.


Twenty seven cases of primary thrombocytopenia were studied. Incomplete platelet
antibodies were detected in the sera of 18 patients. Complete antibodies were present in only one.—M. K.


Acute activation of fibrinolysis after excision of the prostate in 5 cases of carcinoma was observed. A beneficial effect of inhibitors of fibrinolysis, EACA and trasyrol, on bleeding was described.—M. K.


Muscular exercise caused an increase in plasminogen activator in blood. This increase was proportional to the work load. The time required for disappearance of 50 per cent of the increase after exercise (15,000 Kg.) averaged 43 minutes.—M. K.


In 8 cases of arterial thrombosis of the lower limbs treated with streptase, thrombosis had appeared after operative restoration of patency of an atherosclerotic artery. In 5 cases, therapy was completely successful, but in one only partial patency was attained. In two cases, mechanical obstacles other than thrombosis were found during operations performed after unsuccessful treatment with streptase.—M. K.


Castration caused prolongation of r and k values, slight increase in clot retraction and enhanced fibrinolysis.—M. K.

**IMMUNO-HEMATOLOGY**


The positive direct antiglobulin test observed during treatment with methyldopa usually became negative within six months of stopping the drug. The length of time for the test to become negative was related to the strength of the antiglobulin test while on the drug. In three patients, methyldopa was reintroduced, but the antiglobulin test became positive again within six months in only one. Antinuclear factor was demonstrated in the serum of 14.6 per cent of patients on methyldopa, but the frequency of this finding was not related to age, dose, or incidence of positive direct antiglobulin test. None of the patients with positive antinuclear factor had clinical features of disseminated lupus erythematosus.—A. B.


In a terminal case of acute granulocytic leukemia in a 28-year-old female, the blood group was essentially type B, but part of her cells were modified and reacted like type O.—K. F.


A statistical evaluation of the occurrence of blood groups O, A, B, AB, M, N, Kell, P, and Rh was made. Only the constellation A, MN, Kell-, D+, Rh+ appeared more frequently among chronic schizophrenics than among healthy people.—M. K.

**A Case of Multiple Myeloma with Polyclonal Gammopathy.** T. Ogawa, K. Toyama, K. Nakamura and M. Hasegawa.
A 65 year-old male had a myeloma with peculiar immunoglobulin findings. Serum electrophoresis revealed two components of K type gamma G myeloma protein. Bence-Jones proteins in the urine consisted of type K and type L. Myeloma cells aspirated from the marrow were of two types on light- and electron-microscopic observation; one had chromatin-rich nuclei with prominent nucleoli and parallel endoplasmic reticulum, the other had scattered chromatin in the nucleus and distended endoplasmic reticulum. These two cell types could be compatible with the two types of Bence-Jones protein.-K. F.


The sera of 40 patients with complete transverse lesions of the spinal cord were studied after 3 to 30 transfusions. Antibodies to erythrocytes were not found, but anti-leukocyte antibodies occurred in two patients. Comparison with the control group of hematologic patients who had received a similar number of transfusions permitted the conclusion that lesions of the spinal cord may induce some inhibition of post-transfusion isoimmunization.—M. K.

ERYTHROCYTES


Red cell fragments were produced when normal red cells were forced at arterial flow velocity through a loose mesh of fibrin in a side chamber or through a mesh of fibrin or glass fibers of a nylon filter disc in a ring circuit. Fragments formed when membrane tears occurred in an arrested cell subjected to buffeting from other rapidly flowing cells. The shape of the fragments depended upon the position in which the cell was arrested and the site of the membrane tear. The fragments were morphologically indistinguishable from those found in microangiopathic hemolytic anemia.—A. B.


Two cases of favism in siblings of Polish origin were described. Transfusion of washed erythrocytes and corticosteroid treatment was followed by dramatic improvement.—M. K.


A patient developed methemoglobinemia and severe Heinz-body anemia while receiving 2 Gm. of Sulamin daily. Activity of erythrocyte G-6-PD in this patient and in 3 members of the family was moderately decreased, while in 5 other members it was just below the lower limit of normal. Of 390 patients treated with Sulamin, only this patient developed Heinz-body hemolytic anemia.—Z. R.


A beneficial therapeutic effect of glucocorticosteroids in a case of Cooley’s syndrome with hypersplenism was described. Hemolytic crises became shorter and less severe and spleen size decreased markedly.—M. K.

Hb G-Taegu was the only abnormal hemoglobin variant found in 6700 clinically normal Korean subjects. The overall incidence of this variant was 0.06 per cent. Preliminary structural analysis revealed a change in the βT3 peptide. No examples of Hb E, common in southeast Asia, were found in the Korean population tested.—T. F. N.


This variant of hemoglobin A, found in two generations of a Japanese family living in Hiroshima, had a higher anodal electrophoretic mobility than Hb A; a gain of two negative charges per molecule was indicated. Fingerprinting and amino acid analysis showed the biochemical anomaly to be in the β chain at residue 120 with lysine replaced by glutamic acid. In the heterozygote carrier, there was no apparent association with clinical or hematologic abnormalities. Hb Hijiyama was present in concentrations of 58 per cent of the total hemoglobin.—T. F. N.


Hemoglobin Rainier had several interesting properties: 1) increased alkali resistance and 2) abnormal heme-dissociation curve with a normal Bohr effect. In the proband and in several members of her family, this hemoglobinopathy was associated with erythrocytosis and increased urinary erythropoietin levels. Electrophoresis on starch gel at pH 7.0 or 8.6 failed to differentiate Hb Rainier from Hb A. Separation could, however, be achieved on agar gel at pH 6.2. Hb F values were not elevated by either starch or agar gel electrophoresis, despite elevated levels by alkali denaturation. Structural analysis revealed a substitution of a histidine for a tyrosine residue in the 145th position of the β chain. Tyrosine in this position, one of the "invariant" amino acids, was present in all of the myoglobins and hemoglobins studied thus far. This residue appeared to stabilize a portion of the β chain and may indirectly stabilize the attachment of the heme iron.—T. F. N.


Two types of hemoglobin are present in erythrocytes of adult hens, Hb I (73.67–77.34 per cent) and Hb II (22.66–26.33 per cent). Hb II has a markedly higher affinity for oxygen. The ratio of Hb I to Hb II is not changed by repeated bleeding and anemia.—M. K.


Infarcted bone marrow has been aspirated from 3 patients with Hb SC, SD, and SS disease. The histologic changes after marrow infarction do not differ from those seen in other tissues after infarction. One to 3 days after the onset of bone pain, cellular detail is indistinct. Cellular debris is often present. An inflammatory reaction is present 3–7 days after the onset of pain and marrow is infiltrated by normal neutrophils. This change is followed by a period of hypocellularity 1–2 weeks after the crises began. The marrow may then either become fibrotic with typical features of myelofibrosis, or become repopulated with normal marrow elements. Bone marrow infarction is probably a relatively common event in the painful crises of the sickle cell disorders. Patients most likely to develop this complication may be those who also develop aseptic necrosis of the femoral head and radiolucent bone lesions.—T. F. N.

Therapeutic Considerations in Acquired Pure Red Cell Aplasia in Adults. S. Kramer, L. Kaplan and J. Metz. From South African Institute for Medical Re-

Two cases apparently responded to treatment. The first, associated with a malignant thymoma, responded to prednisolone and the second to cobaltous chloride.—T. H. B.


Absorption after oral administration of 180 mg. of iron (ferrous gluconate) was higher in chronic pancreatitis (37.5 per cent of cases), diabetes mellitus (25 per cent), chronic gastroileitis (11.3 per cent) and peptic ulcers (12.5 per cent) than in normal persons. In all cases, increased iron absorption appeared to depend on disturbed pancreatic function. Administration of pancreatic enzymes decreased abnormal iron absorption.—M. K.


The mean iron content of foodstuffs was raised by 55 per cent when they were cooked in used iron pots and by 282 per cent when cooked in new iron pots.—T. H. B.


A 63 year old Japanese male was admitted to hospital in March, 1966, and peripheral blood showed moderate normochromic anemia with hypersideremia. Examination of bone marrow revealed normoblastic hyperplasia with defective hemoglobin formation. Sideroblasts were markedly increased and over half of them were ringed. On electron-microscopic study, a large quantity of iron was demonstrated in swollen mitochondria surrounding nuclei of erythroblasts. Although the life span of the patient’s erythrocytes estimated by the radiochromium method was moderately reduced, neither signs nor laboratory data suggested hemolytic anemia. Erythrocyte coproporphyrin content was normal, but the amount of protoporphyrin exceeded the normal. ALA synthetase, ALA dehydrase and heme synthetase activities in erythroblasts were normal. A disturbance in iron incorporation into heme in erythroblast mitochondria might have been responsible for this type of anemia.—K. F.


The interaction of heme, hemoglobin and albumin was studied under various conditions. In aqueous solution, heme transferred readily from hemoglobin to albumin, forming methemalbumin. The rate was increased by oxidation of the iron from the ferrous to the ferric form. A rise in temperature, alteration in pH from acid to alkaline and the presence of linoleate or arachidonate also increased the rate. The experiments indicated only a single binding site for heme on the globin.—T. H. B.


Eighteen patients with primary polycythemia were subjected to repeated phlebotomy and autologous plasma reinfusion. With only one exception, a patient who died from mesenteric thrombosis, remissions lasting from 1 to 19 month were obtained. This favorable effect led to the postulate that plasma of the patient with primary polycythemia might contain increased amounts of an inhibitor of erythropoiesis. This postulate was tested by measuring red cell utilization of Fe59 in rats injected with plasma of the patients. Evidence was presented that plasma of polycythemic patients exerted an inhibitory effect.—Z. R.

Two patients had erythrocytosis with normal white cell and platelet counts in association with primary carcinoma of the liver. In one patient, increased levels of erythropoietin were demonstrated in the plasma. No activity was demonstrated in tumor tissue obtained at necropsy, possibly due to post-mortem changes or insensitivity of the bioassay.—A. B.


An increase in serum erythropoietin levels soon after a high protein diet was started occurred concomitantly with a rise in the serum albumin. The reticulocyte count similarly rose to a mean maximum of 4.4 per cent; mean hemoglobin, serum iron, serum B12, and serum folate levels all fell during the 21 days of study.—T. H. B.


Inhibition of erythropoiesis in rats with post-transfusion polycythemia was studied without and after partial blockade of hemoglobin by CO. The results indicated that hyperoxemia cannot be the main factor inhibiting erythropoiesis. Hypervolemia, as well as augmented destruction of erythrocytes, should be taken into consideration as contributing factors.—M. K.


Seven ulcer patients were given L-hyoscyamine. Intrinsic factor in gastric secretion was assayed with radio B12 and by blocking with IF-antibodies. IF-output increased after histamine, most initially and more if patients were not pre-treated with the inhibitor, L-hyoscyamine. IF, like pepsin, may be stored in the mucosa and may be "washed out" by histamine.—P. G. R.


Follow-up study of 61 patients with pernicious anemia treated continuously for up to 63 months with an intrinsic factor-B12 preparation (Biofac) was reported. Complete remission was achieved in all patients after an average period of 7 to 8 weeks. No undesirable side-effects were observed. In 10 patients, however, 10 to 32 months after onset of therapy, hematologic relapse occurred. Increasing dosage failed to overcome resistance to this preparation. In all of these patients, complete hematologic remission was again induced after parenteral administration of B12.—Z. R.


Of 115 mental hospital patients on anticonvulsants, 14.6 per cent had red cell macrocytosis and 36.1 per cent had mean serum folate levels of 2.2 mg./ml., compared with 4.1 in 48 mental hospital patients not on anticonvulsants and 7.4 in 94 normal controls. Megaloblastosis in patients on anticonvulsants may result from a combination of a diet low in folate and the action of the drugs. There may be subnormal absorption of folates in patients on anticonvulsants.—F. W. G.


Activity of phosphohexose isomerase, aldolase and G-6-PD, content of inorganic phosphorus and GSH and the stability of GSH were determined in erythrocytes be-
fore and after storage in liquid nitrogen. No differences between control and frozen erythrocytes were found.—M. K.


Using Mortensen’s method, the authors showed that children with cyanotic congenital heart disease have lowered osmotic resistance of erythrocytes in comparison with control healthy children and with cases without cyanosis. The significance of a qualitative alteration in erythrocytes for possible hemolytic and fibrinolytic complications after heart operations was discussed.—M. K.


Erythrocytes of such children had a lowered osmotic resistance when hemolysis was examined at 20-37° C.—M. K.


Erythrocytes of children with cyanotic congenital heart disease had a lower osmotic resistance at slightly alkaline pH than did cells of healthy children and of patients with congenital heart disease without cyanosis.—M. K.

**Leukocytes**


A controlled trial of cyclic and noncyclic therapy for the treatment of acute leukemia in children was reported. In all cases analyzed, remission was induced with prednisolone and vincristine. In one group, treatment was continued with courses of vincristine, 6-mercaptopurine, cyclophosphamide and methotrexate given singly and sequentially in a cyclical regimen. In the noncyclic group, each of these drugs was given singly and continuously until relapse occurred when treatment was changed to the next drug. At the time of analysis (1966), there was no difference between the two groups in terms of survival curves and morbidity, including need for blood transfusion, time spent in hospital and episodes of CNS leukemia. Later analysis (1967) suggested that the median survival was likely to be approximately 22 to 25 months in each group and that the mortality rates two years after starting vincristine showed a favorable trend in the noncyclic group which will need to be confirmed in a later analysis.—A. B.


Patients suffering from untreated chronic granulocytic leukemia were admitted to a trial designed to compare the efficacy of busulphan treatment with that of radiotherapy. Patients in the radiotherapy group were treated mainly by intermittent external irradiation of the spleen. In the busulphan group, treatment was more continuous because it was designed to stabilize the white count at 10,000/mm³. The patients treated with busulphan survived significantly longer than those treated with radiotherapy and their hemoglobin concentrations were restored and maintained more effectively. Busulphan and radiotherapy were equally effective in controlling the size of the spleen. Death resulted from blast-cell transformation in 70 per cent of the fatalities. The incidence was the same in both groups, but transformation occurred earlier in the radiotherapy group.—A. B.

Peripheral blood leukocyte counts in four patients with chronic granulocytic leukemia were found to undergo periodic oscillations similar to, but longer than, those seen in healthy individuals. The platelet count was also found to oscillate in two patients for whom data were available. The findings suggested that normal control of granulopoiesis may be partly retained in this disease. — A. B.


The incidence of familial leukemia was 0.67 per cent in 446 leukemic patients. Fifty two families in Japan were studied and the kinships were: 17 pairs of siblings, 10 pairs of parent and child, and 25 other pairs of distant relatives. Type of leukemia was 72 per cent acute (49 myelogenous, 7 lymphatic, 4 monocytic, 12 unknown), 24 per cent chronic (19 myelogenous, 5 lymphatic) and 4 per cent erythroleukemia. Twenty nine per cent of pairs showed the same leukemic pattern. Forty six per cent of the pairs had time lags of less than one year. Among 7 families of sibling leukemia, four consanguineous marriages were found. These results might suggest the presence of recessive genes in the etiology of leukemia. — K. F.


Bone marrow from a patient with chronic myeloid leukemia was cultured in the presence of radioactive iron and chromosome preparations were made. Autoradiograms demonstrated cells in metaphase containing both radioactive label and the Ph1 chromosome. There was no radioactive labeling of cells of the myeloid, lymphoid or megakaryocyte series. The results provided direct evidence of the presence of the Ph1 chromosome in the erythroid cell series. — A. B.


The 233 cases consisted of 169 of acute erythroleukemia (including 18 of acute erythremia complicated by monocytic leukemia), 20 of subacute erythroleukemia, 34 of acute erythremia, 9 of subacute erythremia, one of acute erythrothrombocytopenia, and one of acute erythroleukothrombocytopenia. Sex incidence was somewhat higher in males, 60 per cent. There were 3 cases of erythroleukemia and one of erythremia with a familial incidence of leukemia or erythroleukemia. One case of acute erythroleukothrombocytopenia developed about 17 years after exposure to the atomic bombing at Nagasaki and 2 cases of erythroleukemia developed after radiation therapy. Most of the cases of acute erythroleukemia showed predominantly myeloblastic proliferation in blood and bone marrow before death, but some cases had characteristics of erythremia. The existence of megaloblastoid cells was evidence to support the diagnosis and PAS positive material was seen in these cells in 31 of the 32 cases. According to autopsy statistics, the frequency of acute or subacute erythremia and erythroleukemia was 2.6 per cent of all leukemias. Median survivals from onset to death were: 5 months in acute erythremia, 6 months in acute erythroleukemia, one year in subacute erythremia and one year and 10 months in subacute erythroleukemia. Median survival of cases receiving chemotherapy was 2 months longer than that of cases without antileukemic therapy in acute erythroleukemia, and 3 months longer in acute erythremia. — K. F.


The clinical and hematological findings in patients with advanced cancer, with or with-
out multiple metastases, were similar to the wasting syndrome in neonatal thymectomy or runt disease. Among 42 patients, almost all cases of advanced cancer with multiple metastases and cancers of parenchymatous organs showed lymphocyte counts below 1,000/mm³. In cases of gastric cancer without metastases, the lymphocyte count was less than 1,500/mm³ in about one half. Severe lymphocytopenia was observed in some cases of renal failure and encephalitis japonica, and in a few of leukemia and aplastic anemia, while moderate lymphocytopenia occurred in pulmonary tuberculosis, collagen disease and cirrhosis. In one patient with hypochromic anemia, cancer was suspected because of lymphocytopenia, and a diagnosis of cancer of the colon was finally made. In another case which seemed to be tuberculosis pleurisy, the search for the diagnosis of pulmonary cancer began with the lymphocytopenia. Thus, lymphocytopenia had diagnostic value for carcinoma in an early stage. The cytotoxic action of lymphocytes on HeLa cells in tissue culture was noted with peripheral lymphocytes of healthy persons. A similar effect was observed with the lymphocytes of cancer patients with lymphocytopenia. Peripheral lymphocytes were cultured according to the method of Moorehead and blast transformation and mitotic index were evaluated. In most cancer patients, blasts were below 20 per cent, while normal control cultures showed 0–80 per cent blast cells with a similar mitotic index. At autopsy of cancer patients, the mesenteric lymph nodes were generally small and lymphocyte depletion was observed in the lymph follicles and medulla. From these observations it was clear that the peripheral lymphocyte count was decreased in cancer patients. Although cytotoxic action toward other cells was maintained, the ability for blast transformation from the so-called rest cell was reduced or the number of these lymphocytes was decreased.—K. F.

MISCELLANEOUS


Naskapi and Montagnais families with segregation for albumin Naskapi gave evidence for close linkage of the Ge and albumin loci with high probability. One possible case of crossover was included.—H. H. F.


Unirradiated rats lived 113.2 ± 2.5 weeks, those injected with saline twice weekly 89.7 ± 4.8 weeks, and those given cysteamine 72–85 weeks. Groups of rats given 80–160 rad once or twice weekly lived 2–89 weeks without and 3–106 weeks with cysteamine, which protected against long term radiation effects. (Abstracter’s comment: Traumatic effect of repeated intraperitoneal saline, handling, etc., shortened life span as much as, e.g., an accumulated dose of 640 R in 80 R doses.)—F. G. R.