IRRADIATION EFFECTS


Spleen cells transferred from normal animals have been shown to counteract the lethal effects of ionizing radiation in mice, presumably through a humoral agent. On the other hand, it has been argued that the irradiated host tissue is repopulated by the transplanted cells. In the present paper, the fate of normal spleen cells injected into irradiated mice was traced. In some cases the injected cells were identified in the hosts by their iso-antigens. In other cases, injections were made of spleen cells which had been immunologically activated by intravenous injection of a bacterial antigen into donors. The production of antibody by the cells in their hosts then served as a method of identification. Spleen cells identified by iso-antigens were transplanted into irradiated mice. The iso-antigens were detected in the host lymph nodes and spleen up to 51 days after transplantation by their ability to induce transplantation immunity. Irradiation of the host enhanced the production of antibody by spleen cells transplanted from immunized donors.—O. P. J.


Ankylosing spondylitis was diagnosed in 28 patients. The bone marrow was considered to be hypercellular in 17 cases; 10 patients were considered to have an increase in plasma cells in the marrow, and 4 to have marrow eosinophils increased. These findings could not be correlated with previous radiotherapy.—R. H. G.


A 67 year old woman with a bilateral nodular goiter was given 17 mc of I\(^{131}\) in September 1953. In May 1955 she died of acute myeloid leukemia. This is the second such case to be reported.—R. H. G.


Studying the thermal fragility of red cells, an early diminution was found in guinea-pigs after x-ray irradiation. This disappears in 24 hours after a 50 per cent lethal dose and per-
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The blood of a 5 year old boy with chronic methemoglobinemia was investigated. It was found that the erythrocytes contained a pathologic pigment (Singer’s hemoglobin M). Respiration, methemoglobin reduction, and hemoglobin oxidation in the erythrocytes were measured. While the time of methemoglobin reduction was the same as in normal cells, the oxidation of hemoglobin to methemoglobin took place in about half the normal time. This is the cause of the abnormal high concentration of methemoglobin in the blood of the patient. Absorption spectra of the pathological blood pigment were measured.—M. H. H.


Two patients are presented having a congenital hemolytic anemia characterized by macrocytosis, basophilic stippling, neonatal icterus, and hepatosplenomegaly. The disease had its onset soon after birth and persisted in spite of splenectomy in one patient. That the hemolytic process is due to an intracorpuscular defect of the erythrocytes was demonstrated using Cr41-labelled patients’ erythrocytes. The slightly shortened circulating half-life of labelled erythrocytes from a normal donor into these patients suggested the presence of a secondary extracorpuscular component in the hemolytic process. Some macrocytosis and basophilic stippling of the erythrocytes were the most noteworthy findings in the peripheral blood smears. The onset of this disease in the early neonatal period demands that nonspherocytic hemolytic anemia be considered with hereditary spherocytosis, isoimmune hemolytic disease, and hemolytic anemia secondary to a variety of infections in the differential diagnosis of hemolytic anemia in early life.—N. J. S.


This paper is one of a most interesting series dealing with various aspects of sickle cell disease in childhood. Total plasma volumes were determined using T-1824 (Evan’s Blue) dye in 16 patients during sickle cell crises. The total circulating hemoglobin mass was determined from hematocrit observations. Increases in the total plasma volume and total hemoglobin mass were found 24 hours after transfusion and were greater than could be calculated on the basis of the transfused blood alone. These changes were accompanied by some relief of clinical symptoms. To simulate these changes without the use of whole blood 9 patients were given infusions of 6 per cent dextran in 5 per cent fructose. Six of the 9 patients showed clinical improvement and an increase in circulating hemoglobin mass and in 3 patients the plasma volume was elevated 24 hours after the infusion. Certainly these
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interesting observations warrant confirmation and might profitably be extended to larger series.—N. J. S.

NEONATAL ANEMIA


This paper discusses post-hemorrhagic anemia in the early neonatal period, with special reference to feto-maternal transfusion, three cases of which are described.—G. C. de G.


The last-born twin or triplet usually has a higher hemoglobin and erythrocyte content of the peripheral blood during the first two weeks of life than twin no. 1 (or triplets 1 and 2). This is assumed to be due to an extra "blood transfusion" to the last-born twin or triplet from the placenta and umbilical vessels after birth, before the clamping of the cord, caused by the more complete contraction of the uterus when the last fetus is delivered. The last-born twin or triplet therefore is likely to have a somewhat greater iron reserve at birth.—M. S.


An account is given of the results of the first experiments with model experimental fetal erythroblastosis in rabbits. It proved possible to produce experimental fetal erythroblastosis by the passive transmission of a serum with an extremely high titer of agglutinating antibodies of an opposite blood group to that of the fetus. Administration of the serum in a single dose and prolonged injection in pregnant rabbits resulted in damage to the fetus, abortion, premature birth of dead young or of young which died shortly after birth.—M. N.


Data obtained from one- and two-vessel exchange transfusions in puppies is presented. The procedure was done in a manner to simulate exchange transfusion as done in the therapy of erythroblastosis fetalis. By direct measuring of the venous and arterial pressures and by electrocardiogram various alterations in the customary technique were evaluated. The puppies were subjected to two times total blood volume exchange in as brief a period as five minutes with minimal untoward effects. Narcosis and previous shock appeared to make the animals particularly susceptible to untoward reactions from the procedure. The authors are justly cautious in correlating this experience with the clinical procedure as it is carried out in newborn infants, emphasizing the need for individual constant control of the infants.—N. J. S.

PLASMA PROTEINS


Within an 18-month period the authors observed 4 infants with marked irritability, edema, pallor, and severe anemia. The anemia was characterized by severe hypochromia,
microcytosis and absence of any evidence of hemolysis. The serum iron was low. The serum copper level was markedly reduced. The serum proteins were all uniformly reduced to very low levels with gamma globulin being absent on the Tiselius patterns. The disease appeared to be self-limited and unrelated to diet or other environmental factors. All infants spontaneously recovered by seven to nine months of age. Of the very elaborate laboratory studies carried out, of greatest interest were data obtained by injecting C14-phenylalanine intravenously and quantitatively measuring the rate of production and disappearance of plasma proteins from the circulation. The rate of protein formation was normal but the half life of plasma proteins was much less than that of the controls. The authors postulate that some undefined, transient defect is present in the plasma proteins of the patients accounting for their rapid disappearance from the circulation and the resulting hypoproteinemia. They do not feel dietary deficiency played any role in this new entity.—N.J.S.


Three years’ experience with electrophoretic investigations concerning 140 patients affected by varying blood diseases has led the authors to discriminate:

1) Minor dysgobulinemias, as observed in the course of leukosis or malignant reticulopathy; there are mild alterations of the protein ratio varying during evolution and difficult to define with regard to each type of affection; the change frequently observed was a low γ-globulin occasionally associated with low β-globulin and with a relative rise in albumin in the course of chronic lymphatic leukemia. This abnormality is to be found also in those affections resembling leukosis in which lymphoid hyperplasia predominates.

2) Major dysgobulinemias, of which the commonest type is multiple myeloma, a condition showing well-known electrophoretic alterations. One should distinguish myeloma from Waldenström’s macroglobulinemia. There are also other isolated conditions which are not clearly defined yet. In certain cases of dysgobulinemia nothing more than detection of an abnormality should be expected from electrophoresis. One must then have recourse to further means of investigation (ultracentrifugation, curves of “relargage”).—J.D.


A case is reported of purpura associated with essential cryoglobulinemia. The following abnormalities found in the patient’s serum are reported: (a) A precipitate formed on cooling to room temperature. (b) The serum showed an abnormal increase in viscosity on cooling. (c) Electrophoresis showed an abnormal protein pattern, with a high peak in the γ-globulin position. Ultracentrifugation gave anomalous results, in that with undiluted serum there was an abnormal fast component, whereas with diluted serum this component disappeared and there was an increase in the region of the albumin peak. This indicates a dissociating system. The cryoglobulin was isolated and characterized. From a survey of the literature the clinical significance of cryoglobulinemia is discussed. The commonest underlying disease is multiple myelomatosis, but it may also occur in other conditions and sometimes without any apparent pathologic basis, as in this case. The presence of cryoglobulins in high concentration is usually associated with a characteristic clinical picture, the main features of which are an hemorrhagic tendency and circulatory impairment, particularly on exposure to cold. The mechanism of these features is discussed, and it is concluded that they may be produced either by increased viscosity on cooling or by blocking vessels by precipitated protein.

Administration of cortisone (100 mg. daily for three weeks) failed to influence the level of the cryoglobulin.—G.C.deG.

Purified cryoglobulins could be extracted from the serum of patients with macroglobulinemia, by means of repeated cold fractionations. These globulins contained 1.1 per cent lipids with cholesterol in the free and esterified form, phospholipids, and about 3 per cent polysaccharides. The isolated cryoglobulin proved to be a glyco-lipoprotein. On ultracentrifugation is shown a main component with a sedimentation constant of 17.5 and a small fraction with a sedimentation constant of 18. —M.-H.H.


By means of paper electrophoresis three main fractions of serum lipids were separated in the serum of 180 normal individuals. (1) Fraction A, \( \alpha \)-lipoproteids, containing the lipids migrating with the albumin and \( \alpha_1 \)-globulin fraction. (2) Fraction B, \( \beta \)-lipoproteids, including all the lipids migrating with the \( \alpha_2 \), \( \beta \)- and \( \gamma \)-globulins. (3) Fraction C, containing the lipids which can be demonstrated between the starting point and the end of the \( \gamma \)-globulin fraction. The mean values of these fractions were calculated. Significant differences according to age and sex could be demonstrated. The differences in the lipoprotein, lipid, and protein fractions caused by aging result in physical and chemical changes in the blood. The authors interpret these changes as a sign of physiologic aging. —M.-H.H.


It is shown that normal \( \gamma \)-globulins are glucoproteins. Their carbohydrate group has the same complexity as that of the known \( \alpha \)-glucoproteins. Evidence is presented that the myeloma proteins are also glucoproteins. The carbohydrate group of the protein of \( \gamma \)-myeloma and that of \( \gamma \)-globulin are very similar but not always identical. The investigations were carried out by means of electrophoresis in polyvinylchloride medium.—M.-H.H.


There are to be seen in normal plasma rapid protein fractions that migrate, on electrophoresis, faster than albumin and are detectable by paper electrophoresis. These rapid fractions show a triple colorability for bromophenol, sudan black and Schiff’s reagent, but especially for lipoprotein stains. The rapid proteins may be divided into two components: (a) a \( p \)-component with migration velocity a little greater than that of albumin and apparently fairly homogenous; (b) an \( \beta \)-component and a \( \beta_2 \)-component markedly heterogenous. This latter fraction is likely to correspond to a series of derivates from certain plasma proteins (albumin and globulins) migrating in the electrophoretic field with speeds that vary and prove, for some of them, to be greater than that of albumin.—J.D.


The present studies are an outgrowth of the general problem of developing an “insect Ringer solution” bearing a relation to the composition of insect body fluids. To assist in the formulation of such a solution, it was decided to obtain more detailed information on the composition of the silkworm hemolymph with respect to free amino acids and sugars.
The results of these analyses emphasize the complexity of insect hemolymph. Large proportions of the nitrogen, phosphorus, and carbohydrate of silkworm plasma occur in compounds not yet identified. It is clear that the conventional methods of human blood analysis are inadequate for this material.—O.P.J.

LEUKOCYTES

LACTIC DEHYDROGENASE ACTIVITY OF SERUM IN MICE WITH TRANSPLANTABLE LEUKEMIA

The authors find a progressive increase in the serum lactic dehydrogenase (SLD) in mice with various strains of transplantable leukemia, with highest values just before death. In normal mice, the SLD measures 1100 to 1200 units per ml. per minute; in mice with 4 types of transplantable leukemia the values rose from normal to values of 20,000 to 40,000 units per ml. per minute before death. Similar differences were found in the lactic dehydrogenase content of various tissues—nodes, liver, spleen—when leukemic mice were compared with normal mice. The mechanism of these changes is unknown. The authors previously reported an elevation in SLD in acute and chronic leukemias in human beings (Proc. Soc. Exper. Biol. & Med. 90: 210, 1955).—S.E.

STUDIES ON VARIOUS FACTORS INFLUENCING LEUKOCYTE ALKALINE PHOSPHATASE ACTIVITY.

As previously shown, the alkaline phosphatase activity of polymorphonuclear leukocytes is not high, but in chronic myelocytic leukemia these cells contain none of this enzyme, whereas in myeloid metaphasia and pyogenic infections their alkaline phosphatase activity is very high. In the present report, the authors report biochemical determinations of alkaline phosphatase in separated leukocytes suspended in saline, and the effects of various substances on the phosphatase activity. It was found that antifolic acid compounds increased the leukocyte alkaline phosphatase activity of the leukocytes (i.e., these compounds activated the enzyme). This effect was abolished by folinic acid. TEM also activated the enzyme, but folinic acid did not abolish this effect. Other drugs—pteroylglutamic acid, vitamin B12, nitrogen mustard, CB 1348, urethane, 6 mercaptopurine—had no effect on the alkaline phosphatase activity. Corticotropin increased the activity; cortisone did not. The mode of activation could not be determined.—S.E.


Experimental studies in dogs and rabbits indicate that Chlorpromazine (Largactil, Megafen) in therapeutic doses has an inhibitory effect on the bacterial phagocytosis of circulating leukocytes. The effect is reversible, partly directed towards the leukocytes themselves, partly towards the properties of the blood serum which facilitate phagocytosis. The lowering of the resistance against bacterial infections caused by chlorpromazine is based on the inhibition of the circulating cellular factors as well as on the decrease of non-specific substances of the blood serum (bactericide, complement, etc.).—M.-H.H.


Fourteen patients with various diseases received varying dosages of a bacterial lipopolysaccharide (Pyrexal “Wander”) by intravenous injections. The mobility of their granulocytes was determined in slide preparations. Five hours following the application of the lipopolysaccharide the mobility of the cells was significantly increased. This increase was independent of the rise in temperature of the patient.—M.-H.H.

Although it has long been known that the polymorphonuclear leucocyte is able to exhibit chemotaxis, there is very little information about the mechanism of the directional response and the factors that influence it. It has been reported that calcium, serum and complement are necessary, and that citrate, azide and fluoride abolish chemotactic response without impairing the motility of the cell. In the present study, some of these factors have been investigated. Human polymorphs from a drop of blood obtained by finger-prick were made to adhere to a cover-slip and were then washed three times with physiologic saline in order to remove the serum. The cells were incorporated in a slide-cover-slip preparation which was incubated at 37 C and their movement relative to a test object (a small clump of Staph. albus) was recorded photographically. These experiments show that chemotaxis by polymorphs can occur in the absence of complement, serum or glucose, and in solutions relatively free from ionized calcium or magnesium. Polymorphs apparently have an intrinsic energy store because they are able to survive and remain motile for considerable periods in solutions devoid of any known source of energy. Lengthy survival in solutions containing fluoride and azide is not dependent upon a supply of oxygen. The suggestion that chemotaxis can be inhibited without impairing the motility of the cell has not been supported.—O.P.J.

LYMPHOCYTES


For many years the monophyletic school of hematology has offered evidence to indicate that lymphocytes may serve as precursors of erythroid and myeloid elements. Since 1939, various authors have directed their attention to the filtration of lymphocytes from the circulation and their sequestration in the bone marrow for hematopoietic purposes. The present experiments have been devised to determine the fate of lymphocyte suspensions obtained from lymph nodes and transfused into rabbits whose marrows have been depleted by saponin injections. The total number of lymphocytes to be transfused slowly into the right femoral artery of one animal ranged from 400 to 3,000 millions. The lymphocyte transfusion produced a striking accumulation of lymphocytes in the marrow parenchyma and to a lesser extent in the liver and spleen. During the first 12 hours after transfusion, numerous lymphocytes appeared diffusely scattered over a wide area of the depleted marrow parenchyma. After 24 hours, they showed a tendency to be densely aggregated around arterioles, so that the picture closely resembled that of an embryonic primordium of the lymphatic apparatus. The lymphocyte aggregations degenerated, and did not give rise to genuine lymphatic apparatus nor was there a direct transformation of these lymphocytes into the cells of myeloid or erythroid series. Evidence indicated that the lymphocytes accumulated in the bone marrow were derived from the transfused lymphocytes.—O.P.J.


Meyerhof in 1940 observed that a lymphocytosis could be induced in guinea-pigs by injections of a calf lymph-node extract. He also found that an active principle, insoluble in acetone but soluble in alcohol, extracted from mesenteric lymph-nodes of calves would cause a 200 per cent increase in the blood lymphocytes of guinea-pigs. The present article reports experiments in which guinea-pigs were injected subcutaneously and rabbits intravenously with extracts of human or bovine lymph-nodes. The authors failed to confirm that lymph-nodes contain an active principle which causes blood lymphocytosis.—O.P.J.
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EOSINOPHILIA


It has been suggested that eosinophils may play a part in the detoxification of histamine and that histamine itself has a direct stimulating action upon bone marrow. ACTH is also reported to increase the absolute numbers of eosinophils of the bone marrow in patients undergoing such therapy. Accordingly, experiments were devised to test these points. Equine blood was collected from the jugular vein and bilateral bone marrow biopsies were performed upon the coxal tubera. Salah needles were inserted into the marrow of both coxal tubera, marrow was withdrawn to determine the preinjection status, and then the test fluid was injected in the left tuber and an equal volume of normal saline was injected into the right tuber. Intradermal injections were made into the skin of the lateral aspect of the shaved neck of a pony. After injection of histamine acid phosphate into hematopoietic bone marrow in a dose sufficient to produce a peripheral eosinopenia, a local eosinophilia develops within one hour and lasts about 4 hours. A local concentration of eosinophils also develops after the intradermal injection of histamine. Intramedullary and intradermal injections of ACTH or cortisone fail to do this.-O.P.J.


A solitary form of eosinophilic granuloma localized in the skull is described in a man of 30, an age at which the occurrence of this condition is rare. Hemogram of the blood and the sternal marrow revealed eosinophilia. The histologic finding in this case indicated certain signs of transition to Hand-Schüller-Christian disease; clinical signs of this disease were, however, not present. Cytologically, the smear of the excised granulomatous tissue was characterized by the presence of reticulum cells.—M.N.


In the past decade a new clinical entity has been described in infants and young children characterized by the presence of striking eosinophilia in the peripheral blood and eosinophilic granulomatosis in the liver. Clinical findings are limited to slight hepatomegaly and a minimal lymphadenopathy with the patients remarkably free of symptoms. Beaver and associates have postulated that the disease is due to invasion of the liver with nematode larvae and has identified toxocara canis, the nematode of dogs and cats as the offending agent. The present paper describes two carefully studied cases in which the larva of toxocara canis was found in the liver biopsy material in both patients. The authors discuss the pathogenesis of the disease in young children who ingest soil contaminated with embryonated eggs. The larvae hatch in the human host, migrating to the liver and incite the formation of the numerous allergic, eosinophilic granulomata. At present liver biopsy is necessary to establish the diagnosis of this interesting malady. The benign, self-limited nature of the disease is demonstrated in the two patients presented. The hematologist will encounter this condition in young patients seen with asymptomatic striking eosinophilia.—N.J.S.


A 30 year old patient developed, with a dysenteric initial picture, inflammation of the parotid and sublingual glands followed by intense leukocytosis (68,000 WBC) with extreme eosinophilia (94%). In stools only ankylostome eggs (2,900 per Gm). The histopathology of the salivary glands revealed only a chronic parvicellular infiltrate. High level of globulins...
(6.6 Gm. per 100 ml.) with total proteins of 10.3 Gm. It was not possible to describe the entire picture: muscle biopsy normal, amyloidosis tests negative, liver biopsy without abnormalities, abnormal proteins in urine negative. In the follow-up there was observed a reduction of the leucocyte level to 16,000 but still with 73% eosinophils and a month later an increase to the original levels. After a series of oral organic arsenic therapy (Stovarsol) a short-lasting reduction of leucocytes and eosinophils occurred but after 13 days there was again a rise of the counts. The patient remained in apparently good health, working, but with swelling of parotid and sublingual glands and serum dysproteinemia for the last 10 months period of observation.—M.A.J.

IRON


The isotope used was Fe59. It is obtained as ferric chloride in 0.3/N HCl and may be (a) combined with γ-globulin in a buffered solution or (b) added to 0.1% sodium citrate in isotonic saline and allowed to stand for 15 minutes. There was prepared 13 ml. of a solution having a total activity of approximately 13 μC. Ten ml. of this were injected intravenously: the measurements were of plasma clearance, surface activity over the precordium, spleen, liver and sacrum and the percentage of the injected dose utilized for hemoglobin synthesis.

A total of 70 patients were investigated. Three main patterns were found.

1. A normal plasma clearance, a normal or only slightly reduced maximal percentage utilization and normal surface counts. This was found in leukemia, uremia and malignant lymphoma with only slight anemia.

2. A rapid plasma clearance and high percentage utilization of Fe59 for hemoglobin synthesis, with no diagnostic alteration of marrow pattern in the surface counts. This was seen in iron-deficiency anemias, post-hemorrhagic anemias, polycythemia and some ‘refractory anemias’.

3. A slow plasma clearance and low percentage utilization. There was usually a flat marrow curve with gradually rising liver uptake. These results were commonly observed in patients with aplastic anemia, in some ‘refractory anemias’, in some leukemias with low hemoglobin and in some cases of myelofibrosis.

Other patterns were found where there was hemolysis or extramedullary erythropoiesis.

These techniques are simple and can be done in a routine hospital laboratory provided a physicist is available for the installation, calibration and subsequent maintenance of the apparatus. They are of value in the investigations of the more complex cases.—R.G.H.


In the first paper, the iron utilization in erythroblasts and erythrocytes of normal rats was studied after intraperitoneal administration of Fe59. Three hours after the administration, the radioactivity in the nucleated cells reaches maximal values. Three to six hours is considered to be the mean time of the iron utilization. In mature erythrocytes, the maximal values are reached at about the 24th hour. Immature erythrocytes exhibit an intermediate behavior.

In the second paper, the iron utilization, as investigated in thyroidectomized rats, was found to be slower and smaller than in the previously indicated conditions.

The third paper took into consideration the same experiment in rats after intoxication with lead. A higher iron utilization was observed under such conditions, thus indicating a possible delay or block of maturation. In mature erythrocytes the values are below those of untreated animals.—P.d.N.
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