ABSTRACTS

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HEMOSTASIS


Compounds sharing one or more of the pharmacological effects of acetylsalicylate were tested for their ability to inhibit the second wave of platelet aggregation induced by adrenaline and aggregation induced by tendon extract. Most drugs with anti-inflammatory activity, such as acetylsalicylate, meclofenamic acid, indomethacin, etc., also inhibited platelet aggregation reactions. It was concluded that the inflammatory reaction may be related to platelet function.—A. L. B.


Platelet factor 4 (antithrombin principle) was not available in intact platelets but was released by freezing and thawing and by agents which caused platelet aggregation, including ADP, thrombin, adrenaline, 5-HT and collagen. Platelet factor 4 so released was present in the supernatant fraction after removal of platelets by fast centrifugation.—A. L. B.


Platelet abnormalities were found in 17 of 47 patients. Platelet factors 1, 3 and 4, retraction, thrombodynamic activity, platelet count and thromboelastography were studied. Thrombodynamic activity was investigated by evaluating the correction of maximal amplitude in thromboelastograms of platelet-free plasma by platelet suspensions. Patients with chronic and acute
leukemia, lymphogranuloma and myeloma were included in the study.—P. d. N.


Thrombin-like activity was found in normal saliva. Thrombin time and thromboelastography were studied in various coagulation mixtures.—P. d. N.

PROACCELERIN (FACTOR V) LEVELS IN LEUKEMIAS. A. Girolami. From the University, Padova, Italy. Tumori 53:541–550, 1967.

Fifty-four patients with acute and chronic leukemia were studied. Factor V was usually normal or low in acute myeloblastic and chronic myeloid leukemia. In acute lymphoblastic and chronic lymphocytic leukemia, Factor V was frequently normal or high. In ten patients, Factor V was markedly low (less than 40 per cent). In two patients with acute promyelocytic leukemia, Factor V was normal or high.—P. d. N.


Factor X was determined in 128 patients with liver and blood diseases or other diseases. Twenty-four had a Factor X level below 60 per cent.—P. d. N.


In a study of 22 patients with disseminated neuroblastoma, the most frequent changes were: thrombocytopenia, hyperfibrinogenemia, increased fibrinolytic (activator) activity and an occasional decrease in the prothrombin complex. Factor VIII was always normal. One patient had severe fibrinolytic purpura.—P. d. N.


Five cases developed during the post-partum period and thromboelastography was very useful for early diagnosis.—M. K.


Activity of fibrinolysis, as well as arterial blood pressure, were measured in patients during the post-operative period and compared to healthy persons. Activation of fibrinolysis was accompanied by a sharp fall in arterial blood pressure, probably due to release of bradykinin-like substances into the circulation.—M. K.


The partially purified products of plasmin-degraded fibrinogen were able to increase the permeability of skin capillaries after intracutaneous injection. These derivatives enhanced markedly a similar effect of bradykinin. The role of the products of fibrinogen proteolysis in the pathogenesis of local and general disturbances during the process of inflammation was discussed.—M. K.


Increased activity of intracellular proteolytic enzymes in rats were provoked by x-ray irradiation. Both fibrinolytic inhibitors, EACA and PAMBA, inactivated completely the intracellular proteolytic enzymes activated by the irradiation. The inhibitory effect of EACA and PAMBA was not observed in control rats without increase in the activity of intracellular proteolytic processes.—M. K.
IMMUNO-HEMATOLOGY


An attempt has been made to elucidate the factors responsible for the ability of heterologous anti-lymphocyte plasma (ALP) to depress lymphocyte counts when injected into an animal of the same species as that which provided the lymphocytes for immunization. The results suggest that ALP depresses lymphocyte counts by virtue of its content of antibody directed against antigenic moieties which are contained in lymphoid cells and which are distinct from the individual and species specific antigens of the animal. The results also indicate that the ability of ALP to produce a lymphopenia is, to a significant degree, dependent on normal adrenal function in the recipient of the plasma. In addition, the findings confirm previous observations which have indicated that the immunosuppressive potency of ALP could not be correlated with either its content of agglutinating and cytotoxic antibodies directed against lymphocytes or its ability to depress lymphocyte counts.—J. E. U.


An injection of rabbit antiserum to mouse lymphocytes causes temporary lymphopenia and prolonged survival of A-strain skin grafts on CBA mice. Cortisone or amethopterin without further antilymphocyte serum prolongs lymphopenia and immunosuppression. When cortisone or amethopterin precedes administration of antiserum, the immunosuppressant action of the combination is less than that of the antiserum given alone. Whether the serum or the drug is given first does not affect the induction of lymphopenia by the serum. Thus, immunosuppressant action of antilymphocyte serum can be distinguished from its ability to induce lymphopenia. The results suggest that this serum may act as a mitogenic agent redirecting the proliferation of lymphocytes into immunologically incompetent pathways.—J. E. U.


Anti-lymphocyte globulin (ALG) has been used clinically in renal transplantation. Because some ALG preparations induce lymphopenia, it might at first appear that the blood lymphocyte count would prove a useful guide to dosage, but the immunosuppressive effects of ALG are not always accompanied by lymphopenia. Experiments were described in which striking ALG-induced changes in the composition of the circulating small lymphocyte population of mice were not reflected in the absolute blood lymphocyte count. The blood and lymphoid tissues of mice which had been injected with ALG proved to be depleted particularly of long-lived small lymphocytes. The blood later became repopulated predominantly by short-lived small lymphocytes. This change in the composition of the circulating small lymphocyte population, which was observed in intact animals and in mice thymectomized as adults, was not reflected in the absolute blood lymphocyte count. These findings indicated one mechanism by which ALG exerted its prolonged immunosuppressive effects.—J. E. U.


Although it has repeatedly been shown that lymphocytes possess activities normally associated with antibody formation, immunoglobulins or immunoglobulin fragments have never been separated from lymphocytes. In the present communication, the authors report that fractions possessing properties of immunoglobulins and immuno-
globulin fragments could be separated from human small lymphocytes by mercaptoethanol. These fractions possess recognition sites for antigens to which the donors had previously been immunized.—J. E. U.


There is evidence that the immune response may be to some extent under humoral regulation. Antibody itself, notably immunoglobulin C, can apparently operate as a very effective feedback mechanism to limit and even to terminate further antibody synthesis. Humoral factors of thymic origin appear able to stimulate immune responsiveness and increase proliferation of lymphoid cells and synthesis of DNA and protein. The most recently described and least understood of these regulating factors is an immunosuppressive alpha globulin (or alpha globulins) present in normal plasma or serum. Allograft rejection and antibody production can be suppressed in animals injected with this alpha globulin. The mechanism by which a normal plasma protein fraction exerts immunosuppression is still unknown. In the present paper, the authors report that an alpha globulin prepared from normal human plasma by column chromatography prevents homologous lymphocyte transformation and the stimulation of DNA, and also protein synthesis induced by phytohemagglutinin and specific antigens. These observations support the concept of a normal circulating immunosuppressant factor which prevents lymphoid cell proliferation.—J. E. U.


The serum paraprotein (γG) concentration was about 2 Gm./100 ml. The serum contained 125,000 units of antistreptolysin O per ml., i.e., an extremely high titer. This was not due to β-lipoprotein; by special electrophoretic technics the antistreptolysin activity was shown to be associated with the paraprotein. The authors have now observed a total of 7 M-components with this type of antibody specificity.—S. A. K.


The 'new' precipitating antibody was found in the serum of patients with Down's syndrome and several other types of chromosome anomalies. The antibody reacted with an antigen, Pe antigen, which was rare in human sera, differed from known serum proteins and had at least two serological specificities. The antigen was almost entirely restricted to patients with hematological disorders, including various types of leukemia, thalassemia and Fanconi's anemia. It was also found in fetal human and calf serum and may be a fetal protein. The reasons for the presence of the antibody in certain sera and the nature of the antigen are speculative. (It is of interest that another fetal protein, HbF, may persist or reappear in the red cells of patients with similar hematological disorders.)—A. L. B.


During the first 8 days of acute radiation sickness, the level of albumin, α- and β-globulins decreased greatly. The lowest level of globulins was observed 16 days after irradiation. The content of albumin on this day was very high. Afterwards, the proteins recovered gradually. The authors did not find any difference between normal animals and animals thymectomized one month before irradiation.—M. K.

The Influence of Ultraviolet Irradia-

ABSTRACTS
ABSTRACTS


Phagocytosis of Congo Red was used as an indicator of activity of the RES in rabbits. A decrease in phagocytic activity was observed after ultraviolet irradiation. The possible mechanism was discussed.—M. K.

ERYTHROCYTES


Erythropoiesis was studied in chronically uremic patients submitted to repeated hemodialysis and to bilateral nephrectomy. The percentage of marrow normoblasts fell after nephrectomy but after thirty days they returned towards the preoperative level. When red cell mass was corrected by transfusions, the percentage of marrow normoblasts decreased significantly, suggesting persistent response of erythropoiesis to the hemoglobin level. Plasma erythropoietin assays were performed 65 times in 11 anephric patients. In one case, there was a marked elevation of erythropoietin after a bleeding episode; a slightly elevated level was observed in one other case. The authors suggested that although the decrease of marrow normoblasts after bilateral nephrectomy may be due to lack of a factor necessary for erythropoiesis, this or a similar factor may be produced in an extrarenal site and humoral regulation of erythropoiesis persists in anephric man.—A. L. B.


Excretion of Vitamin B12 in the feces of rats after removing the proximal or distal part of the small intestine was estimated with a bacteriological method. Vitamin B12 excretion was greatly increased after extirpation of the distal part of the intestine. The results seemed to indicate that the distal part of the intestine was the site of Vitamin B12 absorption.—M. K.


Eighteen of 64 patients with Crohn’s disease had serum folate levels below 3 μg/ml. The low folate levels occurred most frequently in patients with the most active disease; in this group also there were more patients with hematological signs of folate deficiency but with normal serum B12 levels. In a few patients, the folate deficiency could be partly explained by subnormal absorption due to duodenal or jejunal involvement, but in other patients it may have been due to inadequate dietary intake or excessive utilization by inflammatory cells. In seven patients treated with folic acid, there was marked clinical improvement and in three severely deficient patients there was a definite hematological response. In three patients, folate deficiency remitted spontaneously after surgical treatment of the Crohn’s disease. The authors pointed out that B12 deficiency should be excluded or treated before giving folic acid in order to avoid precipitating neurological damage.—A. L. B.


Folic acid is absorbed in the duodenum and the upper part of the jejunum. Absorption of folic acid goes on due to active transport and passive diffusion through the intestinal wall. Folic acid is also absorbed in the caecum due to passive diffusion only.—M. K.


A total of 141 subjects, 61 to 97, with
hemoglobin levels higher than 70 per cent, and 51 subjects, 20 to 31, taken as controls, were studied. A relatively low reticulocyte count with a "shift to the right" in the Heilmeyer maturation series was found in the aged and related to the bone marrow hypoplasia.—P. d. N.


Red cell volume was measured and radioactive scanning of the splenic area was performed after injection of red cells labeled with $^{14}$CO. When necessary, the splenic outline was delineated with greater precision by scanning after injection of damaged $^{85}$Rb labeled red cells. From the data thus obtained, together with a scan of suitable standards, the splenic red-cell mass was calculated. (This was a preliminary communication and did not include full technical details. Some of the references are still ‘in the press’).—A. L. B.


Red cells were labeled with non-radioactive sodium chromate, incorporating $^{51}$Cr. The survival of the red cells in vivo was followed by subjecting samples to a neutron flux in a reactor. $^{50}$Cr was thus converted to radioactive $^{51}$Cr and its activity was measured, after allowing for decay of short half-life radioactive nuclides. When performed in three patients simultaneously with a conventional $^{51}$Cr technic, very good correlation was obtained. The method had the possible advantages of allowing the simultaneous comparison of the survival of two different red cell populations using the same chemical label, and also allowed the determination of red cell survival without exposing the patient to radiation. The main disadvantages were the lengthy nature of the analyses, the cost and the need for access to a reactor.—A. L. B.


Ultraviolet irradiation of the skin in rabbits for 20 min. daily during 4 weeks brought about an increase in erythrocytes and reticulocyte counts and an increase in hematocrit value. The life span of $^{51}$Cr-tagged red cells was significantly prolonged. —M. K.


The activities of phosphofructokinase, aldolase and G-6-PD and the rate of production of lactic acid were determined in the erythrocytes from a case of Blackfan-Diamond anemia during 4 years of observation. An increase in the rate of lactic acid synthesis with a decrease in activity of aldolase was found during development of anemia. Hematological remission was accompanied by the return of these altered metabolic functions to normal values with a simultaneous increase in the activity of phosphofructokinase. The significance of the described disturbances for recognition of immaturity of a red cell population was discussed.—M. K.


No Cooley-like facies nor skull abnormalities, but slight jaundice and hepatosplenomegaly were noted in a 32 year old man from Naples. Hb F was 92 per cent and Hb Lepore was 8; Hb A1 and Hb A2 were absent (starch and cellogel electrophoresis, chromatography). The father, two brothers and one daughter were heterozygotes for Hb Lepore; the mother, one brother and
ABSTRACTS

1009

the other daughter were carriers of beta-delta-microcythemia.—P. d. N.


Normal subjects (554) and 86 carriers of beta-microcythemia were studied. HbA2 mean values in the two groups were 2.15 and 4.30 per cent, respectively. Alkali-resistant Hb mean values were 1.08 and 1.82 per cent, respectively. These results were not different from those in other Italian provinces.—P. d. N.


Hemolysis and morphological changes of the erythrocytes have developed in patients with prosthetic cardiac devices, such as artificial valves and Teflon patches. In consideration of possible mechanisms of this cell damage, the present study was undertaken to evaluate the effect of shearing stress on human and rabbit erythrocytes in vitro. A special device was constructed employing a closed concentric cylinder viscometer with the bottom of the bob machined to a conical shape. Shearing stresses above a critical level resulted in overt hemolysis of some erythrocytes and damage to others evidenced by diminished survival of Cr51-labeled erythrocytes. In addition, shearing stress induced morphological changes of erythrocytes similar to those observed in patients with prosthetic cardiac valves.—J. E. U.

LEUKOCYTES


The presence of a high proportion of PAS-negative lymphoblasts in the initial pretreatment marrow sample of children with lymphoblastic leukemia was associated with a short length of first remission and survival and also with high initial peripheral blast cell count and short duration of symptoms. Conversely, a high proportion of PAS-positive lymphoblasts was associated with more advantageous features.—A. L. B.


In many children with acute leukemia of various types, HbF was slightly raised but evenly distributed throughout the red cells. Red cell carbonic anhydrase isoenzymes were quantitatively normal. In a child with juvenile myeloid leukemia, very high concentrations of HbF were present in many cells. As the disease progressed, the concentration of HbF and the number of affected red cells rose and the concentration of HbA2 and carbonic anhydrase activity fell, apparently reverting to a fetal pattern. The authors suggested that this type of leukemia may be due to proliferation of a 'rest' of stem cells or to a somatic mutation.—A. L. B.


The plasmas of 255 patients with neoplasms of the blood-forming organs and 44 controls were screened for "virus-like" particles. Plasma samples were banded by cesium chloride density-gradient centrifugation and negatively stained, and representative electron-microscope fields were photographed and particles counted. The number and distribution of particles were evaluated according to diagnosis, clinical status of the patient, white cell count and platelet count. No relation between any of the classes of particles and clinical features was found. A large percentage of both control and disease
groups had about the same numbers of particles. No common clinical characteristics of
patients with extremely high particle counts
were found. “Virus-like” particles seen by
this technic in the plasmas of patients with
leukemia and related disorders were consid-
ered to be unrelated to their disease.—
J. E. U.

NEW ANTIGENS IN HUMAN LEUKAEMIC
CELLS AND ANTIBODY IN THE SERUM OF
LEUKAEMIC PATIENTS. J. F. Dore, R. Mott-
ta, L. Marholese, I. Hrsak, H. Colas de la
Noue, G. Seman, F. de Vassal and G.
Mathé. From Hôpital Paul Brose, Ville-

In 12 of 51 patients with leukemia or
lymphoma, serum antibodies against their
own leukemic cells were detected. The stud-
ies were made before treatment using four
different technics. Intracellular virus-like
particles were found in only five and also
in four other patients with negative immu-
nological tests. There was no strict correla-
tion between the results of the various im-
munological tests. The results suggested that
there may be new antigens on human leu-
kemic cells and that antibodies may develop
against them.—A. L. B.

KINETICS OF LEUKEMIC CELL PROLIFERA-
TION. E. P. Cronkite. From Brookhaven
National Laboratory, Upton, N. Y. Per-
spectives in Leukemia, Grune & Stratton,
Inc., 1968.

A normal, small, lymphocyte-like stem cell
may have a 6 hour generation time, myelo-
blasts and promyelocytes 24 hours. Myelo-
cytes transit to segmented leukocytes in over
48 hours, and the latter have a half-time in
peripheral blood 6.6 ± 1.4 hours. Ehrlich
ascites tumor cells seem to have generation
times of 8-22 hours, and 3H-thymidine stu-
dies in vivo suggest 24 hours for acute hu-
man leukemic blast cells (all of which are
not leukemic stem cells). Their sojourn time
in peripheral blood is of the order of 33
hours. Chronic human leukemic myelocytes
also have a disappearance time in peripheral
blood longer than normal (4 to 12 times).
The main therapeutic objective is still con-
sidered to be, as in animal tumors, to kill
the last leukemic stem cell. (Abstracter’s
comment: Or to enable leukemic cells to
differentiate?)—P. C. R.

PRELIMINARY INVESTIGATIONS OF A SCREEN-
ING-TEST FOR LEUKAEMIA IN COWS. W.
Barnecki. From the High School of Agri-
culture, Wroclaw, Poland. Med. Weteryn.
24:4-6, 1968.

Gelification of blood in the presence of
Mastirapid indicated a rise of leukocytes
above 10,000 per mm³. This method may
be very useful as a simple and rapid screen-
ing-test for the diagnosis of cows’ leukemia.
—M. K.

RETICULUM CELL NEOPLASM, TYPE B, OR
THE “HODGKIN’S-LIKE LESION” OF THE
MOUSE. T. B. Dunn and M. K. Deringer.
From the National Cancer Institute, Be-
thesda, Md. J. Nat. Cancer Inst. 40:771-
821, 1968.

Recent reports on the Type B neoplasm
(the Hodgkin’s-like lesion of the mouse)
have been reviewed, gross and miroscopic
descriptions are given, and personal observa-
tions are reported. Information is furnished
on two recently introduced inbred strains,
the SJL/J and NZB/Bl, in which tumors of
this type are reported. Finally, questions are
asked concerning the significance of this le-
son, suggestions are made for further work,
and its relation to Hodgkin’s disease in man
is discussed. A timely review.—J. E. U.

EXTENDED-FIELD RADIATION THERAPY IN
HODGKIN’S DISEASE: A PROGRESS REPORT.
M. A. Bagshaw, H. S. Kaplan and S. A.
Rosenberg. From the Stanford University
Medical Center, Palo Alto, Calif. Radiol.

Seventy-five previously untreated patients
with Stages I and II Hodgkin’s disease have
been randomly distributed between two
treatment groups, i.e., either local irradia-
tion (4000 rads) to involved nodes only or
irradiation to involved sites (4000 rads) plus
adjacent lymph node regions (3500-4000
rads). At this time, no significant differences
in survival have been observed in the over-
all groups. When the groups were further
subdivided according to generalized sympt-
oms, improved survival was noted in those
patients with Stages IB and IIB disease who
had received extended-field therapy. Pa-
patients with Stage III Hodgkin’s disease were
able to sustain extended-field, high-dose ir-
radiation to all regions of involvement with

ABSTRACTS

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remarkable tolerance. Eleven of 22 patients have survived without evident disease for periods up to five years.—J. E. U.


This report described 7 patients with celiac disease whose illness was complicated by malignant lymphoma. In 5 patients, steatorrhea had been present for over 7 years. There were 5 cases of Hodgkin's disease and 2 of reticulum cell sarcoma. The common mode of presentation was failure of response to treatment for steatorrhea or a recurrence of symptoms in patients who had improved as a result of treatment. Abdominal pain, skin rashes, fever and an abdominal mass occurred frequently. It was hard to make any assessment of how often lymphoma follows celiac disease. It has been suggested that celiac disease may be due in part to a disorder of immunological mechanisms. Abnormal antibodies, disorders of the serum globulins, lymphoreticular insufficiency and response to steroids have been considered to support this idea. An impaired immune response also has occurred in association with cancer. It may be significant that patients with lymphoma and some patients with celiac disease shared this abnormality.—J. E. U.


L-asparaginases of agouti serum and Escherichia coli cause a profound lowering in the level of free asparagine in the blood of treated mice and also in the tissues. During treatment, normal tissues and resistant 6C3HED lymphomas survive unharmed with intracellular asparagine levels which are critically low for sensitive lymphomas. An explanation for this contrast between the two types of lymphoma is provided by the finding that resistant cells have not only a higher asparagine synthetic capacity than sensitive cells but appear able to utilize endogenous asparagine preferentially for protein synthesis. Cell-free extracts of resistant cells contain an asparagine synthetase, but this is not found in preparations from sensitive cells.—J. E. U.


In this paper, the significant information dealing with leukocyte physiology is reviewed with particular emphasis on the granulocyte; 212 references.—J. E. U.


Arneth counts were done on blood granulocytes in 20 healthy individuals and 78 patients (hematological and others) in whom serum concentrations of vitamin B12 and FIGLU excretion had been studied. As expected, hypersegmentation (≥ 6 nuclear segments) was most frequent in B12-deficiency but was also encountered in many other conditions, particularly in infection and malignancy.—S. A. K.


After extracorporeal irradiation of the blood, a calf got 3H-thymidine, and the mitotic labeling index was measured in thoracic duct lymph samples for 24 hours. A control calf was not irradiated. Between 30 and 270 min. all mitoses were labeled in both calves. Mitoses in basophilic cells had distinct labeling peaks at 1–4, 8–9 and 12–16? hours. Mitotic times were estimated at 17 minutes, DNA synthesis at 3½ hours, and generation times at 5.5 hours. This
time was shorter than for other mammalian cells. (Abstracter’s comment: Similar times were reported for erythroblasts in dog and man.)—P. G. R.


A study has been made of the frequency with which two or more cells with an apparently identical stable chromosome aberration are found in preparations of blood cultures from heavily irradiated individuals. Of 133 patients examined following exposure to acute doses of X-rays or to chronic irradiation from retained thorium, 16 were found to have stable aberrations. The conditions were discussed in which such cells may be regarded as originating from a lymphocyte clone present in vivo, and four patients were found with unequivocal evidence of a clone.—J. E. U.

MISCELLANEOUS


Of 4698 patients biopsied with 0.5–0.7 mm needles for eosinophilic granulomas, and salivary gland, renal, thyroid and mammary tumors, 2662 were operated on so that histology could be compared. Aspiration biopsies were smeared and stained like blood smears. Of histologic salivary gland cancers, 84 per cent were diagnosed cytologically, as were 67 per cent of thyroid cancers, 76 per cent of mammary cancers. About 1 per cent of salivary gland tumors were malignant lymphomas.—P. G. R.


Seven smoking men with impairment of central and color vision were treated with 1 mg cyanocobalamin weekly. Six got hydroxocobalamin and their visual acuity improved 5 times after 6 months. Improvement after cyanocobalamin was only by a factor two. Tobacco amblyopia was considered to be caused by cyanide.—P. G. R.