ABSTRACTS OF SPECIAL INTEREST

CLINICAL EXPERIENCES WITH 7-AMINOCAPROIC ACID (EACA) AS AN ANTIFIBRINOLYTIC AGENT.
I. M. Nilsson, S. E. Björkman and L. Andersson.

EACA is a potent inhibitor of plasminogen activation. EACA was given to 57 patients, 16 of whom had hemorrhage due to fibrinolysis. This group included patients with postpartum bleeding, leukemia, cirrhosis of the liver, prostatic disease and postoperative bleeding. The drug controlled the increased fibrinolytic activity, and the clinical response was convincing, in some cases probably lifesaving. In 12 patients without hemorrhage but with increased fibrinolytic activity, this activity disappeared following EACA therapy. The drug appeared of value as an antidote to streptokinase; it stopped abnormal menstrual bleeding and hemorrhage in ulcerative colitis although no fibrinolytic activity was demonstrable in the blood. In these cases the hemorrhage is thought to be due to local fibrinolysis. EACA had no effect in hemophilia A, thrombocytopenia and congenital hypofibrinogenemia, nor did it have antipyretic or antiallergic properties. One Gm. per 10 Kg. body weight every 4-5 hours is considered to be adequate. The drug is equally effective whether given orally or intravenously. Side effects consisted of dizziness, nausea, or diarrhea in 16 of 57 patients.

S. A. K.


An antibody is described in the serum of a patient who had received many transfusions, which reacted in an antiglobulin test with the red cells of 89 per cent of females, but only with 62 per cent of the red cells obtained from males. This difference is very highly significant and indicated that the gene concerned is carried on the X chromosome. This is unlike all the other known blood group antigens and joins the genes for color-blindness, hemophilia, Duchenne’s type of muscular dystrophy, glucose-6-phosphate dehydrogenase deficiency and other, rarer characteristics, which are all borne on the X chromosome. The new antibody has been called anti-Xg*, the phenotypes Xg(a+) and Xg(a−), and the gene responsible Xg*.

I. C.

This is a continuation of work on the incorporation of Fe59 by rat bone marrow megakaryocytes in vivo. Differential counts were made from 1,000 cells with respect to radioiron incorporation of Fe59 by rat bone marrow megakaryocytes and TAME; however, since calcium is not necessary, it does not appear that the serum factor is required for this action and heparin releases the histamine content of rabbit platelets. The authors believe that the serum factor may be the chemical activator of the platelets or indirectly through the generation of thrombin.-R. C.


Freshly prepared defibrinated serum rapidly releases the histamine content of rabbit platelets. Calcium ion is required for this action and heparin and TAME, but not soybean trypsin inhibitor, inhibit this action. The releasing activity of the serum factor slowly declines on aging of the serum. Release of histamine is also promoted by thrombin. This action is also inhibited by heparin and TAME; however, since calcium is not necessary, it does not appear that the serum factor for releasing histamine is preformed thrombin. The authors feel that the serum factor may be blood thromboplastin which acts directly on platelets or indirectly through the generation of thrombin.—R. G.


Phosphatidyl choline from egg yolk, phosphatidyl serine, and ethanolamine from ox brain, were prepared by methods which the authors state separated them from other substances and from each other so that each was prepared free of traces of the other two. Synthetic phosphatidyl ethanolamine and choline were also used in the experiments. The procedure used for determining the effect of coagulation of these compounds was the effect on the clotting time of chicken plasma with and without the addition of sphingosine. Some studies were carried out using the recalcification of human plasma. The results were (1) none of the isolated phospholipids alone had as great an activity as the crude brain phospholipid fractions; (2) phosphatidyl choline (PC) alone was inactive, as was freshly isolated ethanolamine (PE); (3) phosphatidyl serine (PS) in low concentrations promoted coagulation, but never to the extent of the crude preparation, and in high concentrations it acted as an inhibitor; (4) PS and PE together were the most active, the combination being about as active as the crude material; (5) PS and PC were slightly less active; (6) PS and PC were considerably less active; (7) the synthetic PE + PC acted similar to the natural occurring compounds. The authors believe that at least two phospholipids are necessary for the highest thromboplastic activity.—R. G.

ABSTRACTS


The term “Kline plasminogen” has become a household word in fibrinolysis. Since 1953, an acid extraction technic has been used with Cohn’s Fraction III to produce highly purified human plasminogen. The specific activity of this material was higher than that produced by any other method of plasminogen purification except column chromatography. Unfortunately, chromatography is limited to the production of relatively small amounts of plasminogen, and has proved to be less reproducible than the original Kline technic. On the other hand, it has produced a product which is soluble at pH 7.5. The specific activity of the Kline plasminogen was approximately 45-80 Rem-mert-Cohen units/mg. of nitrogen. The present paper describes two simple steps which, together with a simple modification of the original method, produce a product with much higher specific activity (110-173 casein units/mg. of N), and which is homogeneous in the ultracentrifuge and on electrophoretic analysis. This degree of purity is analogous to the best material produced by chromatography at the present time. The procedure can be applied to large quantities of material, requires no special laboratory technics, is reproducible, and can be used to reprocess plasminogen which had deteriorated. In addition, variations between batches of Fraction III can be made uniformly superior by a single repetition of the purification procedure. The two additional steps involved (a) the extraction of plasminogen by 0.1 M lysine at pH 5.5 and (b) the precipitation of plasminogen at pH 2 by the addition of solid sodium chloride to final concentration of 1 M. The method appears to be an excellent revision of the purification...
procedure which has already become standard practice in the industry.—A. J. J.


A method is described, using ion exchange resin-loaded paper for chromatography, for the assay of the synthetic amino acid, EACA, in plasma. Following sample preparation with trichloracetic acid, chromatography was carried out with acetate buffers as developing solvents. Development was said to take less than two hours and EACA could be clearly separated from the natural amino acids. After staining by the ninhydrin-copper method, concentrations were read in a recording densitometer. The mean error of the method was taken to be less than 20 per cent at EACA levels above 10 mg. per 100 ml. The method was found to be extremely flexible, and was also potentially useful with other amino acid systems.—A. J. J.


EACA was absorbed rapidly following its administration orally in man, and was distributed through the extravascular as well as the intravascular compartment (readily penetrating human red blood cells and other tissue cells at varying concentrations). Eighty per cent of a single oral or intravenous dose was recovered in the urine within a 12-hour period. Plasma levels of $10^{-3}$ M EACA, were achieved by the oral or intravenous administration of 1 Gm. of EACA per hour, a concentration well suited to inhibit systemic fibrinolytic states. A priming dose of 4–5 Gm. was generally used prior to the sustaining dose. Effective inhibitory levels in the urinary tract were maintained with relatively small doses of EACA because of the renal concentrating mechanisms. No severe toxic side effects were observed in this study. The ability of EACA to equilibrate with the intracellular compartment presumably accounted for the prolonged excretion rate observed after sustained infusions of EACA.—A. J. J.

FIBRINOLYSIS INDUCTION IN VITRO BY AROMATIC DERIVATIVES. K. N. Von Kaulla. From the University of Colorado School of Medicine, Denver, Colo. Arch. Biochem. 96:4–12, 1962.

As working hypothesis, hydrotrophy was considered the common denominator of several urea derivatives which elicited marked fibrinolytic activity in human plasma. Studies with preformed plasma standard clots, heated and non-heated bovine fibrin plates, and casein, revealed proteolytic activity in the activated plasma following preincubation with these compounds. The fibrinolytic activity appeared to increase as the number of methyl groups on the sulfonated benzene ring increased. The required concentrations of the compounds varied from 8 per cent for urethane to 2 per cent for ethyl-urethane, depending on the type of assay. The mode of action of the synthetic compounds on the fibrinolytic enzyme system was not clear, although fibrinolysis was induced in human plasma by a class of compounds which would not elicit fibrinolysis in bovine plasma. These studies were concerned primarily with the compounds acting on human plasma. The author speculates that they might act by dissociating an enzyme-inhibitor complex endogenous to the action of urea on the soy-bean trypsin inhibitor-trypsin complex. The study is of special interest because of its unique approach to the problems of fibrinolysis.—A. J. J.


Many changes have been studied in the coagulation system after trauma. Among these, thrombosis, aggregation of the formed elements of the blood, and formation of fat emboli are the most prominent. Hypercoagulability and fibrinolysis have also been reported. The authors have made bilateral femoral fractures in nine dogs. These were followed, within 10 minutes, by an increase in fibrinolytic activity which lasted 48 hours. The fractures were also followed by a prompt decrease in fibrinogen, AHG, and factor V. When heparin was given, no decrease occurred in AHG, factor V, fibrinogen, but increased fibrinolysis ensued nevertheless. Thus, it was felt that the decrease in these factors was due to their consumption in the coagulation process. Eight to twelve hours after trauma there was a generalized inhibition of the fibrinolytic system, with a simultaneous and progressive increase in fibrinogen. The origin of the fibrinolytic activity is not known. A decrease in the number of platelets also occurred in the circulating blood after trauma. This was ascribed
to their consumption in the hemostatic process (with AHG, fibrinogen and factor V). The prothrombin consumption was normal, however, indicating that disturbances of platelet function were probably not severe.—A. J. J.


The authors have studied the hemorrhagic syndrome in 170 patients operated for the correction of cardiac defects with the aid of a pump oxygenator. The study indicates that, as a rule, more than one factor is responsible for postoperative bleeding tendencies in these patients although it was of interest that the pre-operative studies on several of these patients showed an increased prothrombin time, low platelet count, considerable antithrombin activity and occasional prolongation of clotting time. During the bypass procedure, the prothrombin time was increased, the fibrinogen concentration decreased, moderate amounts of plasma hemoglobin were found and the platelets were often decreased. These changes and significant shortening of the recalification and thrombin generation times were thought to be the result of an induced hypercoagulability. They concluded, further, that hypercoagulability and intravascular clotting produced an increase in plasminogen activator activity. The maximum plasminogen activator activity occurred at the time of termination of the bypass or shortly thereafter (when it occurred). The quantity released seemed to be related to the duration of the cardiac bypass. EACA was used as an adjuvant in the treatment of bleeding following the bypass procedure. It resulted in a marked decrease in plasminogen activator activity, and, in a few instances, dramatic cessation of the bleeding. The problem is a complex one, however, and complex therapeutic agents will probably be required for its treatment. An additional striking abnormality was the marked antithrombin activity which was found frequently prior to surgery, as well as after surgery. This defect was not influenced by pre-treatment with EACA.—A. J. J.


Coagulation studies were performed in 176 hemophilic patients belonging to 130 families. Hemophilia A was found in 78 per cent of the families. A positive heredity was found in 71 per cent of the families with hemophilia A and in 86 per cent in hemophilia B. Circulating anticoagulants were demonstrated in eight patients. No combined coagulation defects were found except one family with mild hemophilia B and a coincident decrease in AHF level, and one patient with mild hemophilia A who also had a factor V deficiency.—S. A. K.


The thromboplastin generation correction test was utilized for evaluating the carrier state among a group of mothers and sisters of patients with classical hemophilia. With this technic it was possible to demonstrate a deficiency of AHG in 6 of the 14 mothers, and 5 of the 17 sisters. Although other assay methods have been more successful in delineating the carrier state in hemophilia A, the authors recommend this test because of its simplicity.—J. B. S.


This report describes a family in which both males and females manifest a relatively mild form of hemophilia (factor VIII deficiency) with no apparent vascular defects. The males appeared to have a quantitatively greater deficiency than the females. There was evidence of transmission from female to male and male to female, but no evidence of transmission of male to male. The mode of transmission was uncertain. It is suggested that the transmission was sex-linked and of intermediate dominance; but a quantitative variant of classical hemophilia or autosomal transmission could not be ruled out.—R. G.


In four patients with factor IX deficiency from four different families, a decrease in factor VII was also demonstrated. This decrease was not very marked (percentage figures were not given,
just the comparative clotting times with normals) in a test which measures factors VII and X. Factors X and V were found to be normal. They found the thrombotest to be prolonged in the patients and did not find the spontaneous activation observed in normal blood after 24 hours storage at 4 C. if the blood was left undisturbed. Repeated pipetting of the hemophilic B blood did activate it. They postulate that the conversion of inactive to active factor VII is slow in hemophilic B blood and that factor IX has a role in the activation of factor VII.—R. G.


Hysterectomy was done in a patient with proaccelerin deficiency (proaccelerin less than one per cent of normal). Immediately prior to surgery, she received 1,000 ml. of whole blood, followed by 500 ml. of fresh plasma the first postoperative day and 250 ml. of plasma daily for five more days. No abnormal bleeding occurred during or after the operation. The half-life of proaccelerin appeared to be 12–15 hours. The critical hemostatic level of proaccelerin seems to be about 5–1 per cent. Although the patient received several transfusions no evidence for a decrease in response to transfusions was found.

—S. A. K.


The authors found that the thrombotest was not sensitive to factor IX and that—like the prothrombin time—it was prolonged by decreases in prothrombin and factor VII. No mention was made of factor X. The authors also describe a modification of the one-stage prothrombin time which consists in the addition of aged normal serum and is said to make the test specific for prothrombin.—R. G.


This study was made to assess the ease or difficulty with which a satisfactory and practical program of prolonged anticoagulant therapy could be carried out. One hundred and thirty-nine cases were treated with dicumarol for periods varying from 3 to 69 months. Only 57 per cent of these patients had prothrombin times in the therapeutic range for more than 80 per cent of the time. Hemorrhagic complications occurred in 30 per cent, and included major bleeding complications in 10 per cent. Three patients died as a result of hemorrhagic complications. Most of the bleeding occurred when the prothrombin times were in the therapeutic range. Seventeen per cent of the 64 patients in whom anticoagulant therapy was stopped had recurrent vascular or thromboembolic episodes within two months. Surgery was performed in 20 cases during therapy. For major surgery, prothrombin times were brought to normal, but for minor surgery, including dental extractions, anticoagulant therapy was not interrupted. Excessive bleeding did not occur in any case. In view of these findings the authors feel that the indications for prolonged anticoagulant therapy should be carefully appraised before such treatment is undertaken.—R. G.

ERYTHROCYTES


The production of both protoporphyrin and heme was found to be greater in the early reticulocytes than in the later forms. However, whereas heme production decreased towards zero as the cell matured, porphyrin synthesis reached a certain minimum level which presumably was kept up for the total life span of the red cell. It is postulated that the rate of heme synthesis depends on the rate of iron uptake by the cell, since the available porphyrin will be transformed into protoheme only in the presence of iron. The freely diffusible porphyrin synthesized continuously in mature cells but not utilized for heme production may be a source of exogenous porphyrin for use by other tissues.—A. J. E.


Previous studies have shown that there are two distinct hemoglobin components in the adult
Humoral Regulation of Erythropoiesis. VI.


The effect of erythropoietin on rats irradiated with 200 r and 400 r was restudied. Both irradiated controls and irradiated animals receiving erythropoietin developed a delayed but definite reticulocytosis, the delay being dependent both on dose of radiation and dose of erythropoietin. It was proposed that both radiation and erythropoietin will deplete a hypothetical pool of stem cells (by radiation injury and by accelerated differentiation into nucleated red cells). If depopulation of the stem cell pool serves as a stimulus for regeneration, it is possible to explain that irradiation, although suppressive at first, later results in an accelerated rate of red cell production.—A. J. E.

Humoral Regulation of Erythropoiesis. VII.


Rat red cells formed in response to phenylhydrazine-induced anemia, bleeding anemia or erythropoietin were found to have a shorter life span than normal cells. The life span was measured with Fe59 and the total circulating red cell content of Fe59 was followed. Cs51 was used to measure blood volume. It was pointed out that this method would give more accurate life span measurement than the method used by Van Dyke and Berlin, a method which had led these workers to conclude that red cells produced in response to an injection of erythropoietin had a normal life span.—A. J. E.


The size distribution of red blood cells of rats recovering from phenylhydrazine-induced anemia was measured by means of a Coulter counter. Repeated Price Jones curves showed that the first crop of reticulocytes released from the bone marrow were far larger than succeeding crops. This initial macrocytosis was related to the shortened life span of cells formed in response to acute erythropoietic stimuli. (See preceding abstract.)—A. J. E.


Erythropoietin levels in plasma and urine of 16 patients with acute and chronic erythroid hypoplasia were measured. Various bioassay procedures were used. The recipient rats were starved or polythemic, the plasma was administered whole or as an extract and it was injected i.v. or i.p. Urine was dialyzed and concentrated and was given i.p. Different procedures appeared to give comparable results. Definite plasma elevations were found in 14 of the 16 patients examined and definite urine elevations were found in 11 of the 12 patients examined. There was a rough inverse relationship between erythropoietin level and hematocrit in one patient who was tested repeatedly during a spontaneous remission.—A. J. E.

Modern technics were used in a re-examination of the old finding by Altman and Miller that anthranilic acid (a tryptophane metabolite) is excreted in an increased amount in children with congenital aplastic anemia. In two patients with this disease, a number of tryptophane-nicotinic acid metabolites were found in high concentration in the urine after tryptophane loading. The mother of one of these patients was also found to handle tryptophane in an abnormal manner. However, in screening a large number of patients with various hematologic disorders, it became evident that many had elevations in the urinary excretion of one or more of the tryptophane metabolites studied.—A. J. E.


Eight cases of failure of erythropoiesis presenting between 2 to 18 months of age are described. Red cell precursors were often abnormal morphologically and in three patients megaloblastic change was present. Steroid therapy produced a hematologic response in seven cases, but in two the response was poor. This was thought to be due to the development of megaloblastic change which, however, only disappeared slowly on folic acid therapy.—I. C.


Thirty children with congenital hypoplastic anemia are described. Evidence of anemia was usually present by three months of age. The anemia was normochromic and generally normocytic and the bone marrow examination was normal except for erythroid hypoplasia. Pallor was the outstanding sign in all of the patients and mild to moderate hepatosplenomegaly was present at the initial examination in about one-third of the patients. None of the usual hematinics was successful in any of the patients and many required, at least for a time, regularly spaced transfusions. Eighteen patients failed to respond to any form of therapy, but seven of these children developed a spontaneous remission after eight months to 14 years of transfusions. Eight of the 18 patients were splenectomized and two developed remission. Three of the splenectomized children died subsequently of overwhelming infection. Complications were related to the need for repeated transfusions, and included secondary hypersplenism, growth retardation, failure of secondary sexual maturation, hemosiderosis and cirrhosis. Twelve children developed a sustained response to corticosteroids, and are described in the subsequent paper.—J. B. S.


Twenty-two children with congenital hypoplastic anemia who received one or more trials of corticosteroid therapy are described. 12 patients developed a sustained remission, the response being evident in each patient within two weeks. The most significant factor in determining the likelihood of steroid-induced remission appeared to be the duration of disease prior to treatment. All seven patients treated within three months of onset responded to therapy, four of six patients treated 4–12 months after onset responded, and only one of nine patients treated after more than a year of transfusion therapy developed a remission. Initial therapy was usually prednisone, 30 mg. per day; after remission was evident, a low maintenance dosage given three or four days a week was sufficient to maintain the response. After one to five years of treatment, three patients have continued in remission off therapy. Attempts to discontinue therapy in other patients resulted in relapse. The major side effect of steroid therapy has been growth retardation; the use of intermittent therapy appeared to lessen the likelihood of this complication.—J. B. S.


Fourteen cases representing a wide variety of marrow aplasia were treated with fetal liver cells given intravenously. Two patients with chronic pancytopenia had remissions following this therapy. Blood studies, however, did not reveal any chimerism and the authors indicate that spontaneous remission remains a possibility.—I. C.

Erythrocyte Osmotic Fragility in Nigerian Infants and Adults. R. G. Hendrickse and E. J.
ABSTRACTS


Approximately 10 per cent of normal Nigerian infants show an abnormal fast-moving hemoglobin at birth. Osmotic fragility studies carried out on the red cells from these infants showed a reduced fragility. The same fragility pattern was observed when testing normal Nigerian adults whose hemoglobin, however, had a normal electrophoretic mobility. The diagnosis was suggested to be thalassemia, and it was 51mg/trophoretic mobility. The diagnosis in the adults whose hemoglobin, however, had a normal electrophoretic mobility was confirmed by massive proteinuria. Hyperlipemia was not present in either patient. Renal biopsy demonstrated engorgement of glomerular capillaries with evidence of interstitial inflammatory response and spotty tubular atrophy. Because of the resemblance to nephrosis, prednisone was administered, and a diuresis ensued in both patients.—I. C.


Two pre-adolescent boys with sickle cell anemia are described, in whom marked generalized edema occurred. The edema was accompanied by hypoalbuminemia with reversal of the A/G ratio, and by massive proteinuria. Hyperlipemia was not present in either patient. Renal biopsy demonstrated engorgement of glomerular capillaries with sickled erythrocytes. In addition, a moderate degree of glomerular fibrosis was present, as was evidence of interstitial inflammatory response and spotty tubular atrophy. Because of the resemblance to nephrosis, prednisone was administered, and a diuresis ensued in both patients.—J. B. S.


Complement titrations were performed in five patients with acquired hemolytic anemia and cold antibodies. In all cases, total complement and in particular the second component was reduced, suggesting immune hemolysis in vivo.—S. A. K.


The results are compared of exchange transfusion in hemolytic disease of the newborn performed during the first 9 hours of life with an exchange performed between 9 and 24 hours. There were 80 infants in each group and they were equal as regards birth weight, cord hemoglobin concentration, which was greater than 11.5 Gm. per 100 ml., and cord bilirubin levels. Although jaundice was more common in the group treated after 9 hours, the results of the exchange were equally good in both groups. There was a suggestion that the infants treated later tolerated the procedure better.—I. C.


The rate of decline of serum haptoglobin (Hp) levels in the blood of infants following exchange transfusion was used to evaluate the role of continuing hemolysis in the post-transfusion bilirubin rebound. The immediate post exchange Hp level was usually more than 70 per cent of the donor blood level. In infants with and without erythroblastosis, the Hp level decreased in a single exponential fashion. The Hp level generally decreased more rapidly in those infants in whom feto-maternal erythrocyte incompatibility existed. The shorter the Hp half-life, the more likely was the need for a repeat exchange transfusion. Of 15 infants demonstrating a Hp T½ of less than 10 hours, 10 required repeat exchange, while among 21 infants with Hp T½’s of longer than 10 hours, only three required repeat transfusion. The authors conclude that continuing hemolysis is a significant factor in the majority of infants requiring repeat exchange transfusion.—J. B. S.


A case is described of a man of 25 who had an atrial septal defect repaired by the insertion of a Teflon felt patch. Postoperatively he became anemic and jaundiced, the urine being dark. There was reticulocytosis, and the stained blood film showed red cell fragments and many irregular crenated cells. Intravascular hemolysis was indicated by the presence of free hemoglobin and methemalbumin in the serum. The urinary excretion of hemoglobin varied from 2.6 to 6.0 Gm. per day. The direct Coombs’ test was negative. This state of affairs persisted for over five months, repeated transfusions being necessary.
It was suggested that the Teflon felt patch had not become covered with endothelium due to the impact of a regurgitant jet of blood from an incompetent mitral valve and that the erythrocytes were being damaged mechanically by this procedure. A second operation confirmed this hypothesis and the bare Teflon patch was covered with endothelium. Following this procedure, hemolysis ceased and the abnormal findings disappeared.—I. C.

**ERYTHROCYTE LIFE SPAN: COMPARATIVE STUDY WITH DIFFERENT METHODS USED TO DEMONSTRATE HEMOLYSIS.** V. Maspes. From The Universidade de S. Paulo, Brazil. Tese (Doutoramento) Faculdade de Medicina da Universidade de S. Paulo, Brazil, 1961.

Of the methods available for the demonstration of a hemolytic condition, measurement of the mean life span of the erythrocytes is the only reliable one. The determination of the mean life span of the patient’s erythrocytes in his own circulation and that of normal erythrocytes in the patient’s circulation permits the recognition of corpuscular or extracorpuscular factors. Paroxysmal nocturnal hemoglobinuria is a combination of both mechanisms, the abnormality of the red cell being acquired and the environmental agent a normal constituent of blood plasma. Thalassemia major (five cases), exhibits a shortened erythrocyte life span with two hemolytic factors: a corpuscular defect and an environmental one, the enlarged spleen presumably as the latter since it is abolished by splenectomy. Erythrokinetic studies showed a low rate of hemoglobin synthesis as an additional factor contributing to anemia. In hereditary spherocytic hemolytic anemia (eight cases), the very short erythrocyte mean life span is only a corpuscular defect and is accompanied by a high rate of hemoglobin synthesis. In idiopathic pancytopenia (13 cases), there is a shortened erythrocyte life span with reduced synthesis of hemoglobin. Even a moderate shortening of mean survival time of the red cells is accompanied by severe anemia due to bone marrow failure. In some patients, erythrokinetic studies demonstrated a high rate of hemoglobin synthesis, but this high rate was inadequate to compensate for the red cell destruction. In malignant hemopathies there is a shortening of the patient’s erythrocyte life span in his own circulation and also accelerated hemolysis of the red cells from normal subjects transfused to the patients, demonstrating an environmental factor. In sickle-cell anemia, the erythrocyte mean life time is short. In rare cases, with splenomegaly, there is accelerated hemolysis of normal erythrocytes in the patient, indicating occasional environmental participation. This probably results from the splenomegaly, since removal of the spleen is followed by disappearance of this environmental factor. Erythrocytes of sickle-cell anemia patients transfused to normal individuals have a shorter life span than in the patient’s own circulation.—M. J.

**LEUKOCYTES**


Phagocytosis brings about a general intensification of the metabolism of macrophagic cells, as well as the liberation of substances capable of killing the engulfed microorganisms. Whether or not the phagocytic stimulus is followed by a specific anabolic event leading to the production of substances reacting with microorganisms remains unknown. This problem has been studied by assaying the incorporation of some precursors of RNA and of proteins into various subcellular fractions isolated from phagocytosing human circulatory leukocytes. Heat-killed *Staph. albus* were used for phagocytosis. The incorporation of phosphate labeled with 32P into nuclear RNA was markedly stimulated by phagocytosis, but not the incorporation of C14 glycine into nuclear proteins. However, when purified leukocytic nuclei were fractionated, fraction I, with contained 30–40 per cent of the total nuclear proteins and about 7 per cent of the total nuclear RNA, exhibited a marked increase of the incorporation of glycine into proteins and of orotic acid into RNA. It may be that this activation corresponds with the synthesis of “phagocytin,” which is subsequently transferred to the secretory granules and eventually released therefrom.—O. P. J.


Antibiotics (chlorotetracycline, chloramphenicol, benzylpenicillin potassium and sulphafurazole) given topically or orally were associated with a temporary reduction in size of the Barr body in unfixed buccal smears.—I. C.
ABSTRACTS


Emigration of white blood cells through vessels in acute inflammation has been studied extensively by light microscopy, and the basic sequence of events is well known. However, the mechanisms involved and the precise manner in which leukocytes pass through the vessel wall are still not fully understood. The pancreas from five dogs was studied after an acute inflammation had been produced by ligation of pancreatic lobules. Tissue adjacent to ligatures was removed from the side with intact circulation after intervals of 1, 2, 3 and 4 hours. Electron microscope studies revealed that the earliest changes were vacuolation of endothelial cytoplasm and development of numerous cytoplasmic processes projecting into the vessel lumen. Leukocytes appeared to become enmeshed in these processes and were subsequently completely enveloped by endothelial cytoplasm. After emerging from the extraluminal margin of the endothelial cell, a new basement membrane formed which permitted the release of the leukocytes into the extravascular space. Under the experimental conditions employed, endothelium appeared to participate very actively in these reactions and a striking specificity for neutrophils was manifested.—O. P. J.


An early manifestation of the "graft versus host" reaction in chick embryos injected with allogenic adult chicken spleen cells is the splenic enlargement of the host embryo. The authors wished to determine the optimum conditions for the splenomegaly syndrome with regard to the age of the embryo at the time of introduction of donor cells by intravenous (i.v.) injection or implantation and the optimum time of removal of the host spleen. The greatest splenomegaly was obtained by i.v. injection of donor cells into 13-15 day embryos and removal of the spleen 5 days later.—O. P. J.


In addition to methods already used in establishing the presence of a chimera, the authors have found that chromosomal sexing of peripheral blood leukocytes grown in tissue culture provided a decisive method of recognizing cells of male origin in a female recipient and vice versa.—I. C.


While investigating the bizarre cellular changes that occur in lymphatic tissue of lethally irradiated mice given foreign bone marrow cells or spleen cells intravenously, it was observed that an equally remarkable series of cellular alterations took place when the recipients had not been exposed to x-rays. In the present work, groups of mice were given sheep red cells intravenously and then killed at daily intervals to obtain serum for measuring sheep red cell agglutinins. The spleens were fixed for histologic study so that changes in the germinal centers could be compared to the time of production of titratable serum antibody. The histologic evidence favored the idea that the antibody-forming cells of the plasmacytic series in the red pulp were derived from the proliferating cells in the white pulp, and these in turn seemed to be derived from dissociated germinal center cells.—O. P. J.


The reticuloendothelial system (RES) has been generally considered as a major factor in the defense of the host against infection. However, doubt has been raised concerning its clear relationship to natural resistance. Since the Kupffer cell is known to be a site of considerable enzymatic activity, enzymes might be instrumental in non-specific resistance against infection. The biochemical behavior of acid phosphatase in the RES cells of the liver and spleen of two genetically resistant and susceptible mouse stocks were examined during the course of infection with Salmonella...
IMMUNOLOGICAL PROCEDURES FOR THE DEMONSTRATION OF THE L.E. FACTOR AND LEUKOCYTE ANTIBODIES. 


Morphologic technics, as well as serologic procedures using leukocytes as antigens, may be employed for demonstrating the L.E. factor. The authors mention the technics used in their tests for iso-antibodies and auto-antibodies against leukocytes and give a detailed description of the methods for demonstrating the L.E. factor by means of leukocytes and nucleated chicken erythrocytes. Their studies showed that the antiglobulin consumption test with leukocytes and chicken erythrocytes as antigens is a valuable addition to the usual morphologic examination for L.E. factor. Varying results may be accounted for by the fact that in disseminated lupus erythematosus auto-antibodies are formed against various components of the nuclear material and against antigens in the cytoplasm.—H. F.

HISTOCHEMISTRY OF THE CENTRIOLES AND CHROMOSOMES OF THE LEUKEMIC CELLS FROM HUMAN MYELOBLASTIC LEUKEMIA. 


Leukemic myeloblasts obtained from two patients with acute myeloblastic leukemia exhibited exceptionally prominent centrosomes and readily identifiable centrioles. Histochemical studies indicated that centrioles are composed of basic and sulfur-containing proteins associated with pentosenucleic acid, phospholipid and polysaccharide. The centrosome possessed less structural protein and pentosenucleic acid than the centrioles and cytoplasmic matrix.—O. P. J.

A NEW CHROMOSOME ABNORMALITY IN CHRONIC GRANULOCYTIC LEUKAEMIA. 


In addition to the abnormality of the Ph1 chromosome previously noted in chronic granulocytic leukemia, the replacement of one of the other small acrocentric chromosomes by a minute fragment was noted in a patient with this disease. These abnormalities were more easily found in direct marrow preparations than in cultures of the peripheral blood.—I. C.

PARALLEL RESPONSE TO CHEMOTHERAPY IN IDENTICAL TWIN INFANTS WITH CONCORDANT LEUKEMIA. 


A pair of monozygotic female twin infants with acute blastic leukemia is described. The leukemia was first detected in both twins at five and one-half months of age, when each presented with pallor, mild adenopathy and moderate hepatosplenomegaly. An initial remission was obtained using 6-mercaptopurine and a second remission occurred after the addition of prednisone and methotrexate. The responses to chemotherapy were almost identical and the infants died at 14 months of age, less than three days apart.—J. B. S.

ATYPICAL $\beta_2$A—MYELOMA. A CLINICAL STUDY OF TEN PATIENTS WITH FAST SEDIMENTATING ($S_{20} = 8-12$ S) SERUM PARAPROTEINS AND AN IMMUNOCHEMICAL ANALYSIS OF THESE PATHOLOGICAL PROTEIN COMPONENTS. 


In 9 of 10 cases reported a diagnosis of multiple myeloma was made based on multiple osteolytic osseous foci and plasmacytosis of the bone marrow. The sera from these patients contained paraproteins with a sedimentation constant of $S_{20} = 8-12$ S, which immunoelectrophoretically were $\beta_2$A globulins. In the past, similar cases have been classified as "atypical macroglobulinemia." However, the correct designation is "atypical $\beta_2$A-myeloma." Another interesting observation is the demonstration in the $\beta$-globulin region of a protein having antigen identity with albumin. This fraction is tentatively called "$\beta$-albumin."—S. A. K.

MISCELLANEOUS

CYSTEAMINE IN TREATMENT OF DYSPROTEINAEMIA WITH RAYNAUD’S SYNDROME. 

A case of dysproteinemia (increased $x$-2-A-globulin) with Raynaud's syndrome, myelosclerosis and splenomegaly developing after polycythemia vera is described. The patient has been treated for six months with cysteamine (Becaptan) and no new vascular symptoms have developed since the commencement of treatment. The serum protein pattern is returning towards normal and the ESR has fallen from 90 to 28 mm/hr.


In the present work, some experiments are reported which suggest that the coating substance causing a direct antiglobulin consumption test of thrombocytes and leukocytes may be a normal plasma protein attaching itself to the cells under certain conditions. The results reported indicate that leukocytes and thrombocytes may absorb in vitro plasma proteins, which adhere to the cells very strongly, so that even repeated washings do not separate them. The absorbed protein causes a positive direct antiglobulin consumption test, indistinguishable from the test obtained when cells are sensitized in vivo due, presumably, to an immune mechanism. If the results obtained in vitro may be compared with in vivo processes, we may assume that bacterial toxins, breakdown products of drugs, high temperature or any other damage to the cells in the body may change them in such a way as to prepare them to absorb irreversibly normal autoplasma proteins. The finding, therefore, of a positive antiglobulin consumption test indicates only that the cells are coated with globulin, which may either be an antibody or a normal protein absorbed on a damaged cell.

CHLORAMPHENICOL BONE MARROW TOXICITY. P. R. McCurdy. From Georgetown University, School of Medicine, Washington, D. C. J.A.M.A. 176: 588, 1961.

An important paper for all clinicians who use chloramphenicol. The author analyses the individual case reports of 15 patients who developed bone marrow suppression while on chloramphenicol, but recovered completely when the drug was discontinued. It is stressed that the early phase of bone marrow suppression probably is reversible if the drug is discontinued, but if the suppression is not recognized in time, it will develop into an irreversible and usually fatal aplastic anemia. The laboratory test which appears to give the earliest and most consistent warning of chloramphenicol-induced bone marrow suppression is the reticulocyte count.—A. I. E.


Dogs were subjected to acute exsanguination and their blood was tested at various stages of the bleeding for adhesive or aggregated blood elements by passing the blood through a microfilter with pores 20 $\mu$. After loss of 25 to 35 per cent of the blood volume, the leukocytes and platelets became progressively more adhesive, but significant aggregation was not observed. Treating blood with pyrex glass wool removed a significant number of adhesive elements from the blood and allowed it to pass through the filters more easily. Blood stored with ACD as the anticoagulant showed an increase in the adhesiveness of the platelets and leukocytes. When these were removed by glass wool or by differential centrifugation, the flow through the microfilter was maintained at a lower pressure.—R. G.
ABSTRACTS

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