Authors’ Summaries of Articles Accepted November, 1966


A bleeding diathesis in a case of IgA myeloma was found to be associated with at least two abnormalities in the hemostatic mechanism. Both were related to the presence of the abnormal myeloma protein and improved with plasmapheresis and with response to tryptophane mustard therapy. The first abnormality stems from interference with fibrinogen polymerization and is responsible for prolonging the clotting time, acting as an anticoagulant on addition of the patient's serum to normal blood, and giving rise to the gelification phenomenon noted on clotting. This abnormality is partially but not completely corrected by calcium; it has previously been described in other patients with multiple myeloma. The second abnormality results from coating of collagen (as well as other surfaces) by the abnormal protein and causes the prolonged bleeding time and poor in vivo adhesion of platelets. This abnormality has not been previously described and appears to be partially responsible for the patient's bleeding.


United States soldiers with acute relapsed P. falciparum malaria had accelerated intravascular coagulation which was manifested by thrombocytopenia, a prolonged prothrombin time and partial thromboplastin time, a decrease in multiple coagulation factors, and evidence of decreased plasminogen activation with an accumulation of fibrinogen breakdown products in the blood. These changes may be important in the pathophysiology of malaria and cause the hemorrhage and thrombosis found in many organs of patients dying with falciparum malaria.

Siegel, B. V., and Morton, J. I.: Influence of immunologic hyperstimulation on murine viral leukemogenesis. First submitted June 29, 1966; accepted for publication Nov. 4, 1966.

Mice inoculated with Rauscher leukemogenic virus, following a series of weekly injections of complete Freund's adjuvant in combination with virus-unrelated antigens, showed increased survivals and delayed appearances of circulating nucleated erythrocytes characteristic of the leukemia. Virus-neutralizing serum antibody was not observed to be produced as a result of this hyperimmunization. The retardation of leukemogenesis was attributed to a transient diminution of numbers of host target cells available to viral infection as a consequence of their prior commitment along immunologic pathways.

The in vitro synthesis of heme and globin has been studied in bone marrow cell suspensions obtained from five patients with Di Guglielmo syndrome. In all, a defect of heme synthesis was demonstrated, but globin synthesis was greatly reduced in only two of the five; in these two, the clinical course was a rapid one.


A technic for the in vitro labeling of human platelets with DFP32 is presented, critically evaluated, and compared to in vivo methods employing DFP32 and to in vitro methods using Cr51. The initial recovery of platelets labeled in vitro with DFP32 averaged 79 per cent, but the survival curve was characterized by an irreversible initial loss of platelet radioactivity. Experiments in which platelets were simultaneously labeled in vitro with both DFP32 and Cr51 suggest that this is not due to elution of DFP32. The survival curve of platelets labeled in vivo with DFP32 shows an initial transient reduction in platelet radioactivity. It is suggested that both of these aberrations in initial survival are the result of platelet injury by DFP32. Significant "tailing" was observed in the survival curves obtained with DFP32, and possible explanations of this phenomenon are discussed. DFP32-labeled platelets circulating after 5 hours apparently survive normally and disappear from the circulation as a rectilinear function over the next 6-8 days. Although both in vitro and in vivo labeling methods employing DFP32 provide a meaningful approximation of platelet lifespan, the initial and terminal aberrations of the survival curves greatly complicate further interpretation. Dextran had no detectable effect on platelet survival, and epinephrine, Mecholyl, and cutaneous vasodilatation did not alter the platelet count or the specific activity of circulating labeling platelets in human subjects. The problem of initial platelet survival and the question of an extravascular or marginal platelet pool is discussed in the light of these data.


Bone marrows from patients with neutropenia, characterized morphologically by a paucity of mature neutrophils, underwent normal maturation when removed from the body and grown in tissue culture. In addition, certain leukopenic plasmas appeared to stimulate development of normal and bone marrows under similar circumstances. These observations suggest that the granulocytic elements in benign forms of neutropenia are innately capable of normal sequential growth and that sustained peripheral neutropenia may distort the normal feedback mechanism which regulates leukopoiesis.

Two patients have been described who were found to have a megaloblastic anemia due to folate deficiency while receiving treatment for pulmonary tuberculosis with isoniazid and cycloserine. In an additional 120 patients studied with tuberculosis, serum folate concentrations were subnormal in 7 of 12 inadequately nourished and in 5 of 24 well-nourished patients with untreated tuberculosis, in 15 of 29 patients taking isoniazid and cycloserine, but in only 2 of 55 patients receiving other combinations of drugs for tuberculosis. In vitro studies showed that isoniazid had a depressant effect on the growth of L. casei, but only when added in a concentration that greatly exceeded the pharmacologic dose; cycloserine had a similar effect at a concentration that was only threefold greater than that usually found in patients receiving therapeutic doses of this drug.

Serum concentrations of vitamin B12 were normal in both patients described with megaloblastic anemia as well as in all 36 patients with untreated tuberculosis; the concentrations were in the indeterminate range in 14 and subnormal in 3 patients who were receiving drug therapy. The addition to medium in vitro of cycloserine, but not of isoniazid or pyrazinamide, depressed the growth of L. leichmannii.

These results confirm previously reported observations by others which indicate that folate deficiency is a frequent occurrence in patients with untreated tuberculosis. They suggest that abnormal folate determinations in these patients are due principally to inadequate dietary intake. In addition, the significantly greater incidence of abnormal folate determinations that was observed in adequately nourished patients taking cycloserine and the results of the in vitro studies suggest that this drug can be responsible for folate deficiency in some instances. The mechanism for this is unknown.


The glucose metabolism in intact lymphocyte cells was found to be altered in the presence of phytohemagglutinin. The operation of the pentose phosphate pathway and, to some extent, the pentose cycle pathway in lymphocytes was found to be significantly enhanced. This finding is interpreted to reflect an additional need of biosynthetic intermediates and TPNH by the lymphocytes to accommodate mitotic activity induced by phytohemagglutinin.


The in vivo intrasplenic cloning of hemopoietic cells was used as an experimental system for the study of some aspects concerned with the regulation of erythropoiesis. Experiments on the effects of polycythemia on the formation of erythroid clones demonstrated that the “feedback” suppression
of such clones was inhibited if the polycythemic animals were kept under hypoxic conditions. Overloading with oxygen is thus an essential factor in the polycythemia-induced suppression of erythroid clones. Polycythemic animals which were transferred to hypoxic conditions for only 48 hours before the termination of the experiment showed the formation of erythroid clones. Analysis of clone formation following such short exposures to hypoxia suggests that the endogenous erythropoietin which had been functioning in this situation acted not upon the single clone-forming cell, but rather on small cell populations which derived from the clone-forming cells in the absence of erythropoietin. There is, therefore, an early, erythropoietin-independent phase of replication of the clone-forming cells. The application of erythropoietin only during this “early” phase of replication resulted in the formation of erythroid clones, which, following the discontinuation of erythropoietin, disappeared from the spleen. Similar results were obtained when the action of endogenous erythropoietin was terminated by subjecting animals to polycythemic conditions a few days after the injection of bone marrow. It appears that in both these cases the reduction in the number of spleen colonies following discontinuation of erythropoietin activity is due to the total maturation of the erythroid colonies, ending in the evacuation from the spleen of the mature red blood cells. The differentiation of the cloned cells is, thus, causally related to the cessation of the replicating effect of erythropoietin.

Retief, F. P., Gottlieb, C. W., and Herbert, V.: Delivery of Co$^{57}$B$_{12}$ to erythrocytes from $\alpha$ and $\beta$ globulin of normal, B$_{12}$-deficient and chronic myeloid leukemia serum. First submitted Sept. 9, 1966; accepted for publication Nov. 24, 1966.

In a study of Co$^{57}$B$_{12}$ uptake by reticulocyte-rich erythrocytes, transfer from chronic myeloid leukemia (CML) serum was less efficient than from normal serum. Decreased transfer of Co$^{57}$B$_{12}$ was not due to excessive transfer of endogenous B$_{12}$ (which is normally elevated in CML) but was associated with an $\alpha$-globulin B$_{12}$-binder (isolated from “baby” DEAE columns) unable to normally deliver B$_{12}$ to erythrocytes. Delayed plasma clearance of intravenously injected B$_{12}$ in CML may be due to this phenomenon.

B$_{12}$-deficient serum delivered slightly more added Co$^{57}$B$_{12}$ to erythrocytes than did normal serum, possibly due to less interference by endogenous B$_{12}$-$\alpha$- and $\beta$-globulin B$_{12}$ binders from B$_{12}$-deficient serum transferred bound Co$^{57}$B$_{12}$ as efficiently as did normal serum $\alpha$- and $\beta$-binders; the $\beta$-binders delivered more than the $\alpha$-binders. CML $\beta$-binder delivered as well as did $\beta$-binder from pernicious anemia and normal serum. These findings suggest that the $\alpha$-binder of CML serum is physiologically and therefore chemically different from the $\alpha$-binder in normal and pernicious anemia serum.

Reticulocyte-rich, B$_{12}$-deficient erythrocytes from pernicious anemia patients took up Co$^{57}$B$_{12}$ less well than did B$_{12}$-sufficient reticulocyte-rich erythrocytes. This may partially explain delayed plasma clearance of B$_{12}$ in B$_{12}$ deficiency.

Rat liver homogenate uptake of Co$^{57}$B$_{12}$ was much greater when B$_{12}$ was transferred from normal serum than from normal gastric juice or saline. Preliminary investigations showed that both $\alpha$- and $\beta$-binders from normal serum transferred B$_{12}$ to liver homogenate but CML $\alpha$-binder transferred poorly.
Weinstein, R. S., and Bullivant, S.: The application of freeze-cleaving technics to studies on red cell fine structure. First submitted Aug. 16, 1966; accepted for publication Nov. 24, 1966.

A simplified freeze-cleave and replication method of tissue preparation for examination in the electron microscope is applied to studies on red blood cell fine structure. With this technic, the cytoplasm of red blood cells appears to have a uniform pattern of packed granularity, with individual particles approximating the dimensions anticipated for replicas of individual hemoglobin molecules. The cell surface is smooth and partially covered with small particles which may represent antigens, enzymes, or some structural proteins. The possibility that particles seen in cells and on cell membranes may represent an artifact is discussed. Pretreatment of cells prior to freezing influences the plane of cleavage through packed cells so that the plane of cleavage can be preferentially directed either through the cytoplasm or along red cell membranes. The freeze-cleave technic may be of particular value in applications where extensive areas of membrane must be surveyed, such as searching for leukemogenic viruses budding through cell membranes.