

and applied radiation in the diagnosis of brain tumors. This is a remarkable volume and will undoubtedly serve as an important reference work in the field of cancer for many years to come. It is highly recommended.—*William Dameshek*

ABSTRACTS

JOSEPH F. ROSS, M.D., *Editor*

ABSTRACTERS

Helen W. Belding, M.D., <i>Winston-Salem, N.C.</i>	Conrad Maier, M.D., <i>Zurich, Switzerland</i>
Robert B. Chodos, M.D., <i>Boston, Mass.</i>	César F. Merino, M.D., <i>Lima, Peru</i>
Roger C. Crafts, Ph.D., <i>Cincinnati</i>	Miloš Netoušek, M.D., <i>Praha, Czechoslovakia</i>
C. R. Das Gupta, M.D., <i>Calcutta, India</i>	Charles E. Rath, M.D., <i>Washington</i>
Solomon Estren, M.D., <i>New York</i>	Jean P. Soulier, M.D., <i>Paris, France</i>
Ronald H. Girdwood, Ph.D., <i>Edinburgh, Scotland</i>	Ramón M. Suárez, M.D., <i>San Juan, Puerto Rico</i>
Oliver P. Jones, Ph.D., <i>Buffalo</i>	Timothy R. Talbot, Jr., M.D., <i>Philadelphia</i>
	Philip F. Wagley, M.D., <i>Baltimore</i>
Ian Welch, <i>Johannesburg, South Africa</i>	

LEUKOCYTES

THE ASSESSMENT OF STRESS IN HUMAN SUBJECTS BY MEANS OF QUANTITATIVE AND QUALITATIVE CHANGES OF BLOOD LYMPHOCYTES. *J. A. Frank and T. F. Dougherty*. From the Department of Anatomy, University of Utah College of Medicine, Salt Lake City, Utah. *J. Lab. & Clin. Med.* 42: 538-549, 1953.

Observations were made on the lymphocytes of untreated normal subjects, normal subjects given ACTH, and normal subjects given epinephrine, and correlated with blood levels of 17-hydroxycorticosteroids. In addition, the lymphocytic changes accompanying advanced cirrhosis, infectious mononucleosis, tuberculosis, and other disease entities were studied.

Previous investigations had indicated that in mice (see abstract above) the "stress" lymphocytes are identical to Type II lymphocytes described by Downey, et al. in human beings. These appear in infectious mononucleosis as well as a wide variety of other disease entities.

A portion of the authors' own summary follows.

"Lymphocytes were classified as normal and Type II lymphocytes (stress lymphocytes). The ratio of Type II/normal lymphocytes was designated as the lymphocytic index, assuming that an increased index (more stress lymphocytes, fewer normal lymphocytes, or a combination of both) reflected greater stress.

"Type II lymphocytes are not specific for infectious mononucleosis but occur in blood of normal subjects and various types of diseases.

"Type II lymphocytes appear to be less susceptible to the lytic effects of adrenocortical hormones than normal lymphocytes. It is suggested that Type II lymphocytes are produced by a nonadrenocortically mediated response to stress.

"The numerical response of lymphocytes reflects and anticipates changing blood levels of 17-hydroxycorticosteroids and varies inversely with the amount of adrenocortical hormone in the blood.

"The numbers and types of circulating lymphocytes reflect the degree of balance existing between adrenocortically mediated and nonadrenocortically mediated responses to stress stimuli.

"The accurate correlation of the lymphocytic index with the clinical evaluation of patients with tuberculosis suggests further trial of this sensitive measurement in this and other disease entities."—*T. R. T.*

DISCUSSION ON THE CHEMOTHERAPY OF THE RETICULOSES. *J. W. Wilkinson, A. Haddow and J. D. N. Nabarro.* From the Dept. of Haematology, Manchester Royal Infirmary, The Royal Cancer Hospital, and University College Hospital, London, England. *Proc. Roy. Soc. Med.*, London 46: 685-700, 1953.

Dr. Wilkinson's main conclusions are that intravenous tri-(2-chloroethyl)-amine hydrochloride is very effective and can be easily controlled in the treatment of chronic leukemias and most reticuloses; myleran is of great value for chronic myeloid leukemia, while urethane is also effective in some chronic leukemias. Aminopterin, ACTH, and cortisone are of some value in acute leukemias, but not in other reticuloses and chronic leukemias. Triethylene melamine is dangerous and toxic, readily producing thrombocytopenia, aplastic anemia, and neutropenia.

Professor Haddow also had had little success with triethylene melamine and doubts whether any of the agents mentioned above will have a permanent place in the treatment of the reticuloses. Other more specific and more powerful agents are expected.

Dr. Nabarro thinks that oral triethylene melamine is an effective palliative agent for patients with Hodgkin's disease and that it is indicated in cases showing marked constitutional disturbance or wide dissemination of the disease. He, too, warns against the dangers of its use.—*R. H. G.*

FOLIC ACID EXCRETION STUDIES IN THE INVESTIGATION OF MALIGNANT DISEASE. *R. H. Girdwood.* From the Department of Medicine, University of Edinburgh, Scotland *Brit. M. J.* 2: 741-745, 1953.

A test dose of 5 mg. of pteroylglutamic acid was injected subcutaneously into one hundred forty-eight patients, and the urinary excretion measured. In forty-three patients without evidence of malignant disease or prolonged infection, the excretion was less than 1.5 mg. in only one, and he had hypertensive failure with edema. Many of these patients had nonmegaloblastic anemia. In fifty-three patients suspected of having malignant disease (including the reticuloses) the urinary output was less than 1.5 mg. in twenty-three instances and all these patients had generalized or advanced malignant disease. Occasionally in chronic infection of long duration a positive test (excretion of less than 1.5 mg.) was obtained and a diminished output also occurred in many cases of megaloblastic anemia. It was, however, possible to have malignant disease even of an advanced character with a normal folic acid output, and the results of the test did not seem to be a guide to prognosis.—*R. H. G.*

IRON METABOLISM

INTRAVENOUS IRON IN RHEUMATOID ARTHRITIS: POSSIBLE PROGNOSTIC FACTORS. *M. R. Jeffrey.* From the Rheumatism Research Unit, Bath, England. *Brit. M. J.* 2: 912-913, 1953.

In fifty cases of rheumatoid arthritis, the hemoglobin returned to normal with intravenous iron therapy regularly where there was an ESR of less than 30 mm. per hour, microcytosis, gross hypochromasia, and raised total iron-binding capacity of the serum. However, it frequently returned to normal when these criteria were not present, so that intravenous iron therapy is always worth trying in the anemia of rheumatoid arthritis.—*R. H. G.*

ETHYLENEDIAMINETETRAACETIC ACID IN THE MOBILIZATION AND REMOVAL OF IRON IN A CASE OF HEMOCHROMATOSIS. *H. Wishinsky, T. Weinberg, E. M. Prevost, B. Burgin, and M. J. Miller.* From the Department of Laboratories, Divisions of Biochemistry and

Pathology, and the Department of Medicine, Sinai Hospital, Baltimore, Md. *J. Lab. & Clin. Med.* 42: 550-554, 1953.

Ethylenediaminetetraacetic acid, EDTA, is a chelating agent with strong affinity for calcium and many other divalent metallic ions. In this study the disodium calcium salt of EDTA was used, on the basis of previous work by Foreman et al. showing that the excretion of radioactive iron from rats could be accelerated by the administration of this material.

A patient with an alcoholic history, evidence of cirrhosis of the liver, diabetes, and liver biopsy showing excessive iron deposits, in addition to the characteristic findings of Laennec's cirrhosis, was studied. EDTA was given intravenously in saline, after a five day control period, for four days. The charts indicate 2.0 Gm. per day. At any rate, there was a three-fold increase of urinary iron during administration of the drug. The total iron excreted in four days was 10.2 mg. In 100 ml. of whole blood there would have been about 50 mg.

Prothrombin activity was measured daily by an unstated method, and fell from 75 to 80 per cent to about 30 per cent as judged by the graph presented.—*T. R. T.*

THE ABSORPTION OF IRON. RADIOIRON STUDIES IN IDIOPATHIC HEMOCHROMATOSIS, MALNUTRITIONAL CYTOSIDEROSIS, AND TRANSFUSIONAL HEMOSIDEROSIS. *T. H. Bothwell, H. van W. van Doorn-Wittkamp, M. L. Du Preez, and T. Alper.* From the Department of Medicine, University of Witwatersrand, South Africa. *J. Lab. & Clin. Med.* 41: 836-848, 1953.

This report is concerned with a study, by means of orally administered radioiron, of iron absorption in five cases of idiopathic hemochromatosis, five case of malnutritional cytosiderosis, three cases of transfusional hemosiderosis and eight control subjects.

From 7 to 20 μ C. of Fe^{59} were given with about 20 mg. of carrier iron, with 40 mg. of ascorbic acid. An effort was made to collect all stools for one week, in order to measure the amount of Fe^{59} not absorbed. In vivo studies were made of radioactivity over the liver, skin, heart, and muscles, beginning seven days after the administration of the iron. Blood samples were taken frequently during the first few days and at intervals thereafter for several weeks or months, and the amount of Fe^{59} in the blood measured by appropriate means.

Increased iron absorption was found in idiopathic hemochromatosis. A portion of the absorbed iron was utilized for hemoglobin formation and the remainder was deposited in the liver and other organs.

The absorption of iron seemed low in four cases of malnutritional cytosiderosis. In the remaining one a significant blood uptake and an abnormal deposition in the liver were found.

Iron absorption was not absent in transfusional hemosiderosis, but hemoglobin utilization was usually very low.

The authors point out the wide variation in the level of radioiron in the control subjects and state that there is suggestive evidence that all the absorbed iron was not necessarily being immediately utilized for hemoglobin formation. Inspection of their data provides the suggestion that the control subjects may have absorbed less iron.

This is an interesting report, involving a great deal of careful work and indicates that our concepts of iron absorption from the gut are probably based on insufficient knowledge.—*T. R. T.*

BLOOD COAGULATION

MEASUREMENT OF THROMBOPLASTIC FACTORS AND PROFACORS IN PLASMA. I. DEFICITS IN THROMBOPLASTIN. STUDY OF REAGENTS. MEASUREMENTS OF ANTIHEMOPHILIC AND OF PLATELET ACTIVITIES. *J. P. Soulier and M. J. Larrieu.* From the Centre National de Transfusion Sanguine, Paris, France. *J. Lab. & Clin. Med.* 41: 849-864, 1953.

This extremely interesting report is difficult to read but contains very valuable information.

The authors define thromboplastic factors from a "functional conception" for purposes of clarity in their paper as follows: "those factors are thromboplastic which are indispen-

able and sufficient to form thrombin in the presence of an optimum quantity of calcium and a constant excess of all other known factors of coagulation, namely, prothrombin, proconvertin (factor VII, cothromboplastin, S.P.C.A.) and proaccelerin (factor V, AC-globulin, labile factor). In these conditions the speed of coagulation of the system will depend only upon the thromboplastic factors, or profactors (platelet factor, antihemophilic factor)."

They further state that "The reagent for any method claiming a precise and specific measurement of thromboplastic activity should satisfy the following requirements: (a) Be totally devoid of the factor being measured, thus strictly incoagulable after recalcification at 37°C., even in a glass tube, but coagulate rapidly with traces of thromboplastin. (b) Contain an excess of all the other known factors of coagulation, so that variations in these factors in the plasma being tested be negligible compared with the quantities contained in the reagent. (c) Not be an artificial medium composed of coagulation factors which have been 'isolated', since the chemistry of proteins does not at present permit true purification. The products always contain impurities, and the fractionation often partially activates or denatures the factors."

This study is concerned with two procedures for the evaluation of thromboplastin and profactors. One concerns the measure of antihemophilic activity using human hemophilic plasma together with platelet factor; the other permits the estimation of platelet activity using horse plasma as reagent.

Oxalated horse blood is centrifuged several times in the cold to remove platelets and thromboplastin. The resulting horse plasma (HP) is incoagulable upon recalcification and was shown to contain high proportions of the necessary coagulation factors except antihemophilic factor (AHF). Human hemophilic plasma reagent (HR) was prepared in a similar manner, and is also strictly incoagulable. It contains all of the factors of coagulation except AHF. Platelet reagent (PF) is prepared from a suspension of human platelets heated to 64 C. for 30 minutes to AHF and thermolabile thromboplastic lipoprotein, leaving a thermostable platelet factor.

Fourteen cases of hemophilia were studied in order to measure the amount of AHF activity.

The difference between patient and control times is directly related to the patient's lack of AHF, and if AHF is absent or very low, the patient and saline times coincide. The deficit in AHF is seen even when the coagulation time of venous blood is normal and when the prothrombin consumption is only moderately disturbed.

Measurement of deficits in platelet activity can also be made.

A discussion of present terminology is given.—*T. R. T.*

IMMUNOHEMATOLOGY

IMMUNOLOGIC MECHANISMS OF LEUKOCYTE ABNORMALITIES. *S. C. Finch, J. F. Ross, and F. G. Ebaugh, Jr.* From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals and the Department of Medicine, Boston University School of Medicine, Boston, Mass. *J. Lab. & Clin. Med.* 42: 555-569, 1953.

It has been demonstrated that immunologic mechanisms are responsible for certain erythrocytic disorders such as hemolytic anemia, and platelet disorders such as thrombocytopenic purpura. It is thought probable that similar mechanisms may be responsible for diseases involving the leukocytes, although there are few data to corroborate this. It is pointed out that in 1907 and 1908 evidence was presented that in certain human leukocytic diseases a plasma factor could be demonstrated which was capable of producing phagocytosis, clumping, and lysis of leukocytes. More recently, the L. E. cell has been described and its production shown to be due to abnormal plasma gamma globulin. Also, in certain cases of agranulocytosis and drug-induced leukopenia a plasma factor thought to be leukocyte antibody has been reported.

The present report concerns observations on the action of an experimentally produced leukocyte antiserum on human leukocytes. The antiserum was prepared from suspensions of human granulocytes and lymphocytes (obtained from leukemic patients) injected into rabbits.

Following the incubation of human leukocytes with this antiserum three features were

observed in the stained smears: (1) clumping of granulocytes, (2) phagocytosis of granulocytes, and (3) vacuolization of neutrophilic granulocytes and monocytes. The second feature was often indistinguishable from L. E. cells.

Agglutination studies by either the sedimentation or tube agglutination technics indicated that the antigranulocytic serum produced marked agglutination of human granulocytes but not lymphocytes. The antilymphocytic serum had very limited capacity to promote agglutination of either. Leukophagocytic activity was not reduced by heating the serum to 56 C. for 30 minutes. The reaction did not occur below 10 C. or above 40 C. but occurred at room temperature and over all pH ranges from 7 to 8 at 37 C. It was observed if the anticoagulant was heparin or sodium citrate but not with balanced oxalate.

It appears that these mechanisms may be operating in human disease states as a result of autoimmune antibodies against leukocytes, in a manner similar to those recognized as operating against erythrocytes and platelets.

A complete and carefully prepared discussion and bibliography is given.—*T. R. T.*

STUDIES ON PLATELETS. XI. ANTIGENICITY OF PLATELETS AND EVIDENCE OF PLATELET GROUPS AND TYPES IN MAN *M. Stefanini, G. I. Plitman, W. Dameshek, J. B. Chatterjea, and I. B. Mednicoff.* From the Blood Research Laboratory, New England Center Hospital and the Joseph H. Pratt Diagnostic Clinic, Boston, Mass. *J. Lab. & Clin. Med.* 42: 723-738, 1953.

The heteroantigenicity of platelets was established by Marino in 1905. More recent observations suggest the iso- and autoantigenicity of blood platelets; for example, the work of Harrington, et al. on the plasma factor in idiopathic thrombocytopenic purpura, and the fact that patients with "amegakaryocytic" purpura show progressively less benefit from platelet transfusions. Evidence for the existence of several platelet groups and types in man is presented in this article. The reviewer is impressed with the careful thought and scholarly care with which this work was done. The details of this article are such that justice cannot be given it in any summary and the authors' own summary is therefore given.

"Strong evidence for the antigenicity of platelets is afforded by the development of specific agglutinins against heterologous platelets in animals, and of iso- and (occasionally) autoagglutinins in patients (especially with "amegakaryocytic" or secondary thrombocytopenic purpura) receiving multiple platelet transfusions. Development of platelet agglutinins is not prevented by the administration of ACTH or cortisone, and occurs more promptly when "viable," well-preserved platelets are given. The detection of platelet iso- and autoagglutinins in patients with idiopathic thrombocytopenic purpura (particularly of the "chronic variety") is also suggestive of different antigenic structure of platelets.

"By direct cross-testing techniques it has been possible to determine the existence of two naturally occurring platelet agglutinins in human beings. Four groups probably exist as determined on the basis of the antigens found in platelets: I, II, III (I plus II) and IV (O: no antigen). Their incidence has been determined in 285 individuals. Agglutinin absorption tests and in vivo immunization tests have confirmed the presence of such groups. They are unrelated, but immunologically have the same significance as the ABO antigenic system of the red blood cell, since they are detected by the use of naturally occurring agglutinins.

"By the use of "immune" plasmas (plasma from patients who had received repeated platelet transfusions) it has been possible to distinguish 6 serologically different platelet types. The incidence of the various types has also been determined. By agglutinin absorption techniques and in vivo immunization studies, only 3 serologic types have been confirmed (1, 3 and 6). Since they are detected with "immune" plasma, platelet types correspond to the Rh-Hr system of the red blood cell. No antigens comparable to the M-N system of the red blood cell have been thus far detected in the platelets. Notwithstanding these results, some doubt must remain as to the existence of platelet types since, in in vivo experiments, patients with platelet agglutinins quickly dispose of injected type-compatible platelets, while their plasma causes thrombocytopenia when injected in type-compatible normal recipients. The relationship of group- and type-antigens remains uncertain.

"Occasional patients receiving multiple transfusions develop agglutinins against their

own platelets (autoagglutinins) as well as isoagglutinins and then become thrombocytopenic. It is possible that some such mechanism, with the development of platelet auto-sensitization, may result in idiopathic thrombocytopenic purpura.

"In some cases of idiopathic thrombocytopenic purpura, a platelet autoagglutinin may be detected. In 5 of 9 cases the agglutinin disappeared following successful splenectomy, although the platelet isoagglutinin, also present, persisted after the operation. This finding may indicate that autoimmune thrombocytopenia is improved by splenectomy, even if isoagglutinin production continues, and suggests an additional possible mechanism to explain the favorable effect of splenectomy in many cases of the disease."—*T. R. T.*

STUDIES ON ANTIBODIES ELUTED FROM THE RED CELLS IN AUTOIMMUNE HEMOLYTIC ANEMIA. *Z. D. Komninos and M. C. Rosenthal.* From the Ziskind Laboratories (Hematology Section) of the Joseph H. Pratt and the New England Center Hospital, and the Dept. of Medicine, Tufts College Medical School, Boston, Mass. *J. Lab. & Clin. Med.* 41: 887-894, 1953.

This study is concerned with the *in vitro* behavior of antibody from sixteen cases of acquired hemolytic anemia of the autoimmune type. Red cell stroma was prepared from cells taken from defibrinated blood, and eluted by the methods of Kidd and Landsteiner and by hypertonic saline. Somewhat more potent eluates were obtained using Kidd's method. The eluates were then tested for activity by five separate methods: saline agglutination, albumin agglutination, Indirect Coombs test, trypsinized red cell test, and a combined trypsin-Coombs method.

Antibody was eluted and demonstrated in thirteen of the sixteen cases. The indirect Coombs and the combined Coombs-trypsin methods were more sensitive than the trypsin test. The antibody in the eluates could not be absorbed by and did not react against cells of rabbits, guinea pigs, sheep, or monkeys. Boiling destroyed the receptor, for these eluted antibodies, in human cells.—*T. R. T.*

COLD AGGLUTINATION OF SHEEP ERYTHROCYTES AS A FACTOR IN FALSE-POSITIVE HETEROPHILE AGGLUTINATION TESTS. *C. J. D. Zarafonitis, H. L. Oster, and V. F. Colville.* From the Departments of Internal Medicine, University of Michigan Medical School and Temple University School of Medicine. Philadelphia, Pa. *J. Lab. & Clin. Med.* 41: 906-912, 1953.

The authors' own summary is given:

"(1) Cold agglutinins for sheep erythrocytes may be present in sera from patients with infectious mononucleosis and other disorders. (2) The cold agglutinin titer for a given serum specimen may vary widely in tests with erythrocytes from different sheep. (3) As a corollary, erythrocytes from one sheep may give high cold agglutinin titers with the test sera, while cells from another sheep may agglutinate poorly or not at all in similar tests with the same sera. (4) Since many laboratories record titers of heterophile agglutination tests directly after overnight refrigeration of the test, it seems reasonable to conclude that many so-called "false-positive heterophile agglutination" results are due to the phenomenon of cold agglutination. (5) It is possible to eliminate the cold agglutinin factor by the simple expedient of rewarming the test serum-cell mixtures following overnight refrigeration."—*T. R. T.*

ANTIRABBIT PLATELET AND RED CELL FACTORS IN NORMAL BLOOD. *C. W. Mushett, E. H. Reisner, Jr., L. Werner, R. Nakashima, and J. Collett.* From the Merck Institute of Therapeutic Research, Rahway, N. J. *J. Lab. & Clin. Med.* 42: 713-722, 1953.

During the course of investigating the plasma factor of idiopathic thrombocytopenia (ITP), the authors injected plasma and serum from a patient with ITP as well as from a normal control into rabbits. Both groups of animals exhibited severe thrombocytopenia, hemorrhage, and death. The phenomenon was therefore studied further.

Rabbits were injected intravenously with varying amounts of fresh citrated human or animal plasma, fresh serum, or reconstituted lyophilized pooled human plasma. Erythro-

cyte, total, and differential leukocyte counts and platelet counts were performed before injection and at intervals thereafter.

There was a fall in platelets and red cells following the injection. This was usually apparent at one-half hour and reached a low point from one to three hours after injection. There was no definite change in white cells. If reconstituted plasma was aged, it lost the anti red cell effect more than the antiplatelet effect, although both were reduced. Heating to 56 C. produced no loss of effectiveness.

In vitro agglutination of red cells, as well as hemolysis, was demonstrated with lyophilized plasma.

Fresh dog plasma was precipitated with calcium phosphate gel and the precipitate eluted with 0.2 M. sodium citrate. The eluate produced thrombocytopenia, but no red cell effects in two rabbits, and the residual plasma so treated produced the anti red cell effect but no thrombocytopenia.

ACTH, cortisone, antihistamines, and splenectomy did not prevent any of the above effects in rabbits.

It is of interest that precipitation of plasma with calcium phosphate removes prothrombin, some A-C globulin, and SPCA.

The authors state that "the existence of such naturally occurring antiplatelet substances . . . is noteworthy, if only in providing a tool for the ready production of thrombocytopenia in rabbits. The possibility that the activity of such substances may be enhanced by non-specific immune reactions coexisting independently, bringing about a destruction of platelets that initiates the formation of more specific autoplatelet agglutinins, is submitted, in the absence of specific proof, as a working hypothesis to explain the pathogenesis of idiopathic thrombocytopenic purpura."—*T. R. T.*

THE AVIDITY OF ERYTHROCYTES, SALIVA, AND PLASMA-AGGLUTINOGENS FOR THE CORRESPONDING ISOAGGLUTININ. *S. Lewi.* From le Centre National de Transfusion, Paris, France. *Rev. d'hémat.* 8: 198-203, 1953.

In secretors, the globular mass contains much more agglutinin than plasma. When the amounts are equal, the agglutinin of the red cells is more avid for the agglutinin than the soluble agglutinin of plasma or saliva. The fixation of agglutinin on the red cells is almost immediate, the soluble agglutinin takes 6 to 9 minutes to be fixed. When equal quantities of globular and soluble agglutinin are present, the agglutinin is fixed electively on the red cells. The globular agglutinin liberated by hemolysis behaves like the soluble agglutinin. The presence in the plasma and organs of group substances cannot play a protective role when large quantities of agglutinin are introduced into the body as happens in the transfusion of blood from a dangerous universal donor.—*J. P. S.*