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THEODORE H. SPAET, M.D., Editor

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ANTICOAGULANT THERAPY


Because of dissatisfaction with control of anticoagulant therapy by means of the simple one-stage prothrombin method, the authors developed a modified “prothrombin and proconvertin” test based on the reagent of Owren and Aas. In the modified method, globulin and fibrinogen are supplied in excess by buffered beef plasma which has been adsorbed with barium sulfate. Test plasmas are diluted to 10% concentration. The method has the advantage of greater sensitivity in the range of high prothrombin levels; and the prothrombin time is not susceptible to variation resulting from storage changes. When patients on anticoagulant therapy were controlled by the Ware and Stragnell prothrombin method, bleeding was not significantly greater than in patients not receiving anticoagulants; the reduction of thromboembolism was similar to that reported by other groups.

The recommended procedure for anticoagulation is as follows: patients are simultaneously started on heparin and a prothrombin-reducing agent (preferably Coumadin). Heparin is continued until the prothrombin is within therapeutic range (10–30%). The Ware and Stragnell prothrombin is not affected by heparin in therapeutic concentrations.

A disadvantage of the method not noted in the paper is that the test is not accurate at prothrombin levels below 10%.—T. H. S.

A HEPARIN PREPARATION WITH PROLONGED ACTION. E. Dollerup, H. Heiggaard and C. Holten. From Medical Department I, the University of Aarhus, Copenhagen, Denmark. Lancet 1:897–898, 1957.

A heparin preparation with prolonged action has been prepared for intramuscular injection by adding 1.25% carboxymethyl cellulose to heparin solution containing 100 mg./ml. In six normal volunteers the effect of a single dose of 2 ml. was considerable after 2 hours.

The initials of abstracters who are not listed in the above masthead refer to those abstracters listed in the masthead of the December 1958 issue of Blood, p. 1206.
maximal after 4 hours, and the clotting time was still prolonged eight hours after injection. This preparation has been used in initial anticoagulant treatment to bridge the gap between the first administration of anticoagulants of the coumarin group and the time of their full effect: usually six 8 hourly injections were given. This seemed to be satisfactory as regards control of the clotting time and was without local or general toxic effects.

—R. H. C.


Five examples of dicumarol hypersensitivity are recorded in which the one-stage plasma prothrombin time was longer than its recalcification time; in a sixth, the times were equal. The effects appear to indicate that brain extract contains inhibitors, since on dilution of the thromboplastin extract with saline paradoxical effects were reversed.—T. H. B.


p-Toluensulfonyl-1-arginine methyl ester (TAME) is hydrolyzed by thrombin, and the amount of titratable acid released in a given period of time is proportional to the thrombin concentration. This reaction has been made the basis of a new prothrombin assay. In the test, plasma prothrombin is converted to thrombin by calcium and tissue thromboplastin, and the thrombin determined by its effect on TAME. When this method is used, the test is not specific for prothrombin, since deficiency of labile factor may produce spuriously low prothrombin values. However, it is considerably less sensitive to changes in stable accelerator than is the one-stage prothrombin time. The TAME assay is not significantly affected by in vivo heparin. In patients being treated with dicumarol the prothrombin response by the TAME method lagged behind that determined in the usual way, and this lag was evident both in rates of fall and recovery. Closer correspondence was found with the 2-stage than with the Quick prothrombin. The recovery lag was also seen in the response of hypoprothrombinemic dogs to vitamin K.

In patients with liver disease, there was good correlation between TAME and 2-stage prothrombins. In patients with thromboembolic disorders normal prothrombin levels were found; none was increased. The technic also seems to be suitable for serum prothrombin determination.

The authors offer as two main advantages of the TAME method: (1) in the presence of adequate labile factor the test is specific for prothrombin; (2) by use of a chemical standard much biologic variation can be eliminated.—T. H. S.


Coagulation studies were performed on patients being treated for various periods of time with phenindione. It was found that the 1-stage prothrombin was detectably prolonged within 12 hours and reached therapeutic levels by 36 hours. Depression of the 2-stage prothrombin was less striking during the first 8 days, but thereafter there was closer agreement. The proconvertin response varied in relation to the 1-stage prothrombin response among the group. In some patients the proconvertin fell proportionally or more than the 1-stage prothrombin. These patients tended to require a larger daily maintenance dose than those in whom the fall in proconvertin was relatively slight. (The authors have not subjected these data to statistical analysis.)

Additional data suggest that the “thromboplastin complex” was also involved following long-term therapy with the drug. After 30 days of treatment most patients developed prolongation of the whole blood clotting time not proportional to prothrombin depres-
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sion, and half of the long-term group showed diminished ability to improve prothrombin consumption in PTC-deficient blood. There was likewise a progressive defect in serum thromboplastin generation activity. A test is described based on the ability of blood to plug a needle inserted into a vein. Patients on long-term therapy tended to be less efficient needle-pluggers.

It is concluded that the differential rates of change in the clotting factors affected by this group of drugs may necessitate a revision in schedules of anticoagulant therapy.—T. H. S.


Tromexan and dicumarol were given to two normal subjects. Within 24 to 48 hours there was a demonstrable reduction in PTC activity in the presence of only moderate hypoprothrombinemia. These findings are at variance with other investigators', including those of this reviewer. Most studies report that PTC is influenced with greater difficulty and after a longer period of time than prothrombin.—T. H. S.


Thromboplastin dilutions on the 1-stage prothrombin time of dicumarol plasma show a biphasic effect indicating that brain extract has an inhibitory as well as an accelerator effect on blood clotting. It is therefore important that a balance between the two must be present in thromboplastin if the 1-stage prothrombin method is to provide an adequate method of control. If an excess of the inhibitor component relative to the accelerator component is present, inadequate therapy for the control of thrombosis will arise; if insufficient inhibitor relative to accelerator is present, shorter and more optimal prothrombin times will occur which may lead to overdosage and hemorrhagic complications. In the authors' experience use of a 4% human brain extract achieves the best results.—T. H. B.


Three hundred and three samples of blood from patients receiving phenylindanedione therapy were packed and posted to the laboratory from areas within a radius of 30 miles. They were received at times varying between 24 hours and 4 days, and “prothrombin time” estimations were done on duplicate samples before and after mailing. Samples up to 24 hours old gave satisfactory results, but if they had been withdrawn for 2 or more days they were of no value. The anticoagulants used were a 3.8% solution of sodium citrate, and balanced oxalate. Better results were obtained with the citrate, and the solid form is more convenient for use by general practitioners. The addition of 0.1% chloramphenicol to the anticoagulant greatly lessens the risk of hemolysis from bacterial contamination, a complication that may be found even in 24-hour samples, and which does not affect the accuracy of the estimations.—R. H. G.

BASOPHILS AND MAST CELLS

CLINICAL STUDIES ON THE RELATIONSHIP BETWEEN THYROID FUNCTION AND LEVEL OF CIRCULATING BASOPHIL LEUKOCYTES. Satoshi Inagaki. From the Dept. of Internal Medicine, School of Medicine. University of Niigata, Niigata.

Using the author's direct method, basophils in the circulating blood were counted in various thyroid diseases. In nearly all cases of thyrotoxicosis, the absolute basophil count
was conspicuously decreased; in myxedema, increased beyond the normal range; in nephrosis, increased markedly; while in struma simplex, it was within the normal range. The number of basophils was in close correlation to the thyroid function and it was normalized with suitable treatments in each case.—K. M.


The lack of a sufficiently reliable and selective method for the identification of mast cells in the tissues of various animals caused the author to devise a method which appears to overcome these disadvantages. The new dye combination is composed of acridine red, basic fuchsin and neutral red. Mast cells of different species frequently show shade differences.—O. P. J.


New and interesting material for study of the mast cell was encountered in the course of experiments dealing with rats fed on a diet low in calcium. The experiments were designed originally to observe growth and repair of bone, including the process of calcification of cartilage and bone matrix. A diet low in calcium causes mast cells to accumulate on the surface of, within, or under the endosteum in larger number than are ever seen under normal conditions anywhere in the body. There is not a corresponding increase in the population of mast cells in mesentery, perivascular connective tissue of muscle, or synovial membrane. Treatment of the animals with large doses of vitamin D restores the normal processes and the mast cells show a gradual thinning of their granules and reversion to a spindle-shaped form. Large doses of parathyroid hormone produce osteitis fibrosa, but do not diminish the number of mast cells or their granules.—O. P. J.

BLOOD GROUPS


When patients have repeated transfusions and develop antibodies as a result, their clinical condition rarely justifies venesection for the purpose of producing large amounts of test sera. A patient with cirrhosis who had had repeated transfusions had the antibody E not only in the serum, but also in her ascitic fluid. Many liters of this valuable fluid were obtained. With the patient’s consent, biweekly injections of EE blood were given intravenously to boost the titer of her serum and of her fluid.—R. H. G.


A comparison of the value of the CDE notation with that of the Rh notation. To quote: "Most of the facts which help to discriminate between the two theories arise from highly specialized genetical investigations; they are, on the whole, more readily and completely explained by Fisher’s theory than by Wiener’s. Either theory accounts about equally well for the greater part of the observed facts, including nearly all those encountered in clinical investigation. To the minds of most people, however, Fisher’s notation appears much more convenient than that of Wiener, and is to be recommended for this reason even if the validity of the genetical theory associated with it be disputed."—R. H. G.
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Detailed studies were done of the blood of dizygotic human twins, and these showed that each was living on red cells, only some of whose ancestors were directly inherited, the rest having been acquired as grafts in utero from the opposite twin. The presence of female "drumstick" nodules on the nuclei of some of the polymorphs of the male twins showed that ancestral white cells must also have been successfully grafted.

The male twin had 86% A1 and 14% O red cells. The female had 99% O cells and 1% A cells. The A1 cells were MSMS, cDE/cde, Fy* Fy*, Jk* Jk*. The O cells were MSMS, cDE cde, Fy* Fy*, Jk* Jk*. In their other groups they did not differ. Secretion tests on saliva showed that the A1 series belonged genetically to the male twin and the O series to the female.—R. H. G.


A 29-year-old woman attended for antenatal blood grouping. When her blood was tested with anti-A serum, moderate sized agglutinates were seen in a sea of free cells. Her blood cells were found to be of two distinct groups. This was also found to be the case in a twin brother. Her parents, husband and her three children were also studied, but showed no abnormality.

The female twin had 49% Group O and 51% Group A; the male had 39% Group O and 61% A. The O cells were Ms Ns, cDE/cde, the A1 cells Ns Ns, cDE/cDE. Each twin had, however, only a single Lewis group, the female having Le (a − b +) and the male Le (a + b −). The secretor status corresponded to this. Nuclear sexing of neutrophils showed foreign leukocytes to be present in the blood of the male twin and probably present in the female.—R. H. G.


Employing the agglutination inhibition technic of Wiener, the mean frequency of secretors in a series of 336 Bengalee Hindu males was found to be 73.21%.—J. B. C.


The blood group antigen Mi* is rare, but inherited as a dominant character. Anti-Mi* was made by a mother in response to immunization by her Mi (a +) fetus. The blood group antigen Vw is also inherited as a dominant character. Anti-Vw was made by a mother in response to immunization by her fetus. These members of a Dutch family who were Vw + were also Mi (a +) and it was assumed that the antigen Vw was identical with Mi*.

It is now shown that antigens Mi* and Vw, though related, are not the same. About half Mi (a +) people are Vw + and about half are Vw −. No Mi (a −) Vw + person has been found in several thousand tests on white people.
From tests on families it has become clear that the gene or genes responsible for both phenotypes Mi (a+) Vw+ and Mi (a+) Vw− are linked to the MNSs locus. The linkage is of the extremely close type found between the CDE genes and between the MNSs genes.—R. H. G.


A great number of the Negroes brought to South American shores during colonial times came from West Africa. They mixed in large proportion with Indians and Caucasians, mainly Spaniards and Portuguese. Indian admixture was assumed in a previous study in Venezuela as an explanation of 11 Diego positive cases found in 150 random Negroes. The present study is of Di′ antigen among 119 inhabitants of three villages in the State of Yaracuy, Venezuela, of 107 Negroes of the Gold Coast, and of 322 Venezuelan Indians. The distribution of ABO and Rh(D) was different in Venezuelan Negroes and Gold Coast Negroes, and the indication was of admixture with another race carrying a high incidence of group O. This characteristic is found in Venezuelan Indians.

The Di′ antigen was not found in African Negroes, but occurred in Venezuelan Negroes, and this could be related to the admixture with Caribs in Curiepe and with Caribs and Arawacs in Yaracuy.—R. H. G.

BLOOD GROUPS AND DISEASE


A number of centers in 7 towns collaborated in an analysis of blood groups in pernicious anemia patients and controls. There were 1,225 cases of pernicious anemia in the analysis, and the percentages were A, 44.9%; O, 43.6%; B, 8.2% and AB, 3.3%. For this analysis 111 cases in Copenhagen were added. Pernicious anemia is significantly commoner in persons of Group A than in those of Group O, and perhaps than in persons of Group B. The greater incidence in Group A appeared in both sexes.—R. H. G.

A NOTE ON ABO BLOOD DISTRIBUTION IN CARCINOMA OF THE OESOPHAGUS AND CARDIA. B. P. Billington. From the Department of Medicine, University of Sydney. Australasian Ann. Med. 6:56–57, 1957.

In 119 cases of squamous carcinoma of the esophagus the ABO blood group distribution has not shown significant difference from that of a control population. The ABO blood group distribution in 86 cases of carcinoma of the cardia of the stomach appears to show a significant difference from that of a control population, the incidence of Group A being 19.7% above the expected value.—G. C. de G.


Patients with carcinoma of the stomach are more likely to belong to group A and those with duodenal ulcer to group O. Patients with gastric ulcer come somewhere in between, and it has been suggested that group A is associated with a tendency for the mucosa of the body of the stomach to atrophy, with consequent hypochlorhydria producing a lessened liability to duodenal ulcer and an increased liability to carcinoma.

In 192 patients with gastric ulcer, and 119 with carcinoma of the stomach, group A predominated when the lesion was in the pyloric antrum, and group O when it was in the body of the stomach. The association appears to be between blood group and the site of the lesion rather than its nature. Most carcinomas are in the antrum and most gastric ulcers in the body of the stomach.—R. H. G.
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The ABO, MNS and Rh blood groups have been determined on 470 patients suffering from active pulmonary tuberculosis. The distribution is similar to that found in the random Australian population except that there are fewer group AB subjects among the patients. This finding is probably not significant.—G. C. de G.

**THE ABO BLOOD GROUPS IN RELATION TO PREMATURITY AND STILLBIRTH.** S. A. Plotkin, Cleveland City Hospital, Cleveland, Ohio. J. Pediat. 52:42–48, 1958.

The author points out that a variety of disease states have been associated with varying degrees of certainty with blood groups O and A. Thus several possible mechanisms exist which would tend to decrease the frequency and reproductiveness of the genes responsible for blood types A and O. This study looks to the premature and stillbirth as a possible balancing factor depressing the frequency of the gene B.

Prematurity and stillbirth are the major causes of death in early life. The blood types of 100 prematures, 1033 full-term infants, and 25 stillborn infants were studied. There was a statistically significant higher incidence of prematures with blood group B. The small series of stillbirths showed the same trend.

More extensive data are needed to confirm this provocative finding. If the relationship between blood group B and prematurity and stillbirth is substantiated it might explain, in part, the low incidence of gene B in the western world.—N. J. S.


The distribution of ABO blood groups among 341 patients with tumors of salivary tissue was determined. The frequency of group A was significantly higher than in 5898 consecutive donors registered at the regional blood transfusion center.—R. H. G.

**BLOOD VASCULAR PROBLEMS**


In previous studies these investigators have found that cortisone reverses the increased vascular fragility of adrenalectomy, but that the somatotrophic hormone (STH) antagonizes cortisone in this situation. Moreover, STH can reduce vascular resistance in the intact animal.

In the present study rats and dogs were subjected to adrenalectomy followed by hypophysectomy or these procedures in the reverse order. In rats following hypophysectomy there was a transient fall in capillary resistance, but subsequently restoration to normal occurred. When subsequent adrenalectomy was performed there was a secondary fall and then an erratic restoration. Following adrenalectomy there was a persistent increase in vascular fragility, but subsequent hypophysectomy resulted in increased vascular resistance. Similar results were obtained in dogs except that hypophysectomy caused a temporary rise in capillary resistance rather than a fall. The authors conclude that adrenalectomy produces increased vascular fragility only in the presence of STH.—T. H. S.

The authors are impressed with reports of antihemorrhagic activity following the use of citrus pulp bioflavinoids (CVP) in conditions characterized by increased vascular fragility. Clinical studies were performed on a geriatric population of patients with increased capillary fragility many of whom had associated hypertension or diabetes. When CVP was administered for one month 27 out of 30 of these patients showed restoration of vascular resistance to normal or near-normal levels, as shown by negative pressure tests. Symptomatic improvement was also claimed for an additional group of patients with "little strokes," rheumatoid arthritis, retinopathy, and epistaxes.

Unfortunately the data are difficult to interpret because of failure to obtain a control series, and because of insufficient studies as to the etiology of the initial vascular defect. —T. H. S.


A case of hemorrhagic disease in a 37-year-old woman is presented. The most significant patterns were as follows: cutaneous hemorrhages, with the characteristics of the Rendu-Osler's disease; normality of all coagulation and hemostatic tests, except the presence of a hypersensitivity to heparin in vitro; histologic lesions, which could be referred to peri- and endovasculitis. The hemorrhagic tendency was considered as caused by a capillary and platelet defect as well. Similar alterations were also found in the children of the patient.—P. d. N.


Three conditions have to be differentiated. These are: (1) von Willebrand's disease, in which there is a capillary defect with a prolonged bleeding time and, frequently, a positive tourniquet test. (2) Glanzmann's disease, where there is a functional platelet defect with increased bleeding time, positive tourniquet test, defective clot retraction, defective prothrombin consumption and defective thromboplastin generation using the patient's platelets. (3) A condition about which no name has been agreed, but of which there have been at least nine cases recorded. There is a capillary defect with increased bleeding time, positive tourniquet test and purpura. Antihemophilic globulin deficiency is present with defective prothrombin consumption and defective thromboplastin generation. There may be a prolonged coagulation time, easy bruising and hemarthrosis.

A description is given of the occurrence of this last condition in a brother and two sisters.—R. H. G.


Three patients with anaphylactoid purpura had clinical and electrocardiographic evidence of myocardial damage. In the first there was retrosternal discomfort, Stokes-Adams attacks, a period of atrial fibrillation and widespread ST-T changes which reverted to normal after five weeks. The second developed atrial fibrillation and ECG changes that suggested diffuse temporary subepicardial damage. The third had anorexia and substernal pain, with transient T wave changes and a wandering pacemaker. It is suggested that the cardiac manifestations were due to direct involvement of the heart by the purpuric process and that this may happen often. Electrocardiograms should be obtained at an early stage in every severe case and in all elderly patients with anaphylactoid purpura.—R. H. G.
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A clinical and biological study was carried out on 51 patients affected with Schönlein-Henoch syndrome. This is marked by the 4 following symptoms:

(a) a purpuric eruption with characteristic form related to a pericapillary infiltrate and not accompanied by any hemostatic disorder;
(b) mild articular manifestations;
(c) abdominal manifestations that may be clinically latent or only revealed by systematic radiologic examination of the small intestine;
(d) a glomerulo-nephritis, not infrequently seen when a systematic count of the urine elements was carried out.

The authors compare Schönlein-Henoch syndrome to hemato-immunologic disorders, this hypothesis being based on the results of their experimental researches.

A careful analysis of the clinical and etiologic data has led to the discrimination of three varieties within the frame of the syndrome:

(a) allergic inflammatory purpura associated with various nonhemorrhagic elements (urticaria, eczema, edema) and manifested by alimentary, or respiratory, or other factors as revealed by the patient’s history or by the skin tests;
(b) Idiopathic acute inflammatory purpura in children, marked by an exclusively petechial eruption, monomorphous and obviously influenced by orthostatism. No allergic factor could be demonstrated and the histaminopexic potency of the serum was found normal. Infection was claimed to be responsible, particularly from the rhino-pharynx, but this suggestion was not confirmed by the authors;
(c) Chronic inflammatory purpura, little different from the preceding variety, yet characterized by its chronic course in successive phases, by possible severity of the nephropathy and by a constant and at times notable rise of the serum γ-globulin. An allergic factor was rarely found. The authors suggest the existence of an analogy between these three varieties of Schönlein-Henoch syndrome with the three varieties of leukopenic or thrombopenic syndromes related to the presence of antibodies: leukopenia or thrombopenia from allergic antibodies, acute leukopenia or thrombopenia from auto-antibodies, chronic leukopenia or thrombopenia from antibodies. This suggestion is susceptible of inciting further researches on the basis of the present data.—J. D.

Grants in Aid

The Leukemia Guild of Missouri & Illinois announce that they will have approximately $100,000 available for grants on July 1, 1959, to be allocated for investigative work in blood dyscrasias.

Application forms are available upon request for filing on or before March 15, 1959. Applicants should include a description of the research problem to be undertaken, the institution in which research is to be carried out, personnel and equipment required to meet the needs of the problem, and amount of time and money needed for fruition. Requests for grants under $15,000 per year will be given preference.

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