EXCERPTA

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Physiology and Pathology of Blood Coagulation
A Review of the Literature of 1956 (First Series)

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The influence of antihistaminic drugs on blood coagulation has been investigated and an inhibitory effect was found. An exact differentiation of the mechanism of this effect was, however, impossible; only the influence on the 3rd phase, i.e. the thrombin — fibrinogen reaction, could be ascertained, as well as the inhibition of heparin — antithrombin, and of serum antithrombin. The preparation „Rodimin“, in particular, produced this reaction. No influence on blood coagulation was found when therapeutic doses of the drugs were administered.


The author concludes that in the normal woman after parturition one cannot as a rule speak of hyper- or hypercoagulability. In most cases of toxemia hypercoagulability is found. Severe or sometimes fatal hemorrhages occurring during pregnancy or delivery in cases of toxemia is caused by several factors. In these cases hypercoagulability is followed by a hemorrhagic diathesis.


Basic metabolism and blood coagulation time (Fonic) were determined in 216 patients with normal, in 71 with increased, and in 11 with decreased thyroid function. No correlation could be found regarding blood coagulation time.


The author presents a survey of the various hemorrhagic disorders and their causes occurring in the newborn. The author mentions that blood transfusion still is the therapy of choice. If for some reason transfusion is impossible, the author, based on his results obtained in 16 children, recommends the intravenous injection of ACC 76 (Behringwerke), a preparation containing factor V, VII, eventually combined with vitamin K1.


The authors studied the alterations in the level of coagulation factors leading to hemorrhagic manifestations in patients with severe liver diseases. Patients with mucous, cutaneous, and subcutaneous hemorrhages almost always show a characteristic pattern of coagulation factors: Severe decrease in accelerator globulin and extreme disturbance of thromboplastin formation are accompanied by normal or even increased activity of antithrombin III/IV. Controls without hemorrhages, on the other hand, showed decreased thromboplastin formation and decreased antithrombin activity. The pathogenesis of capillary damage as observed in severe liver diseases, is also thought to be influenced by the equilibrium of coagulation factors.


Cases in the literature as well as personal observations of the authors indicate that the risk of serious hemorrhage after prostatectomy is less to be feared than is occurrence of thromboembolic complications. By means of classical laboratory tests and thrombelastographic studies
it was found that prostatic patients show a marked hypercoagulability as compared with controls. The prophylaxis of complications starting before the operation is discussed and its main points stressed.


Untersuchungen über enterale Antibiose bei der Ratte. IX. Veränderungen der Blutgerinnungs-

The effect of long-term antibiotic therapy on coagulation factors has been studied by administration of high oral doses of tetracycline derivatives to rats. Coagulation time increased after the fourth week of treatment. Following discontinueation of the drug normalization of values occurred within 7 weeks. Dicumarol tolerance was not influenced by tetracycline, neither was the response to 50 mg/kg of vitamin K impaired. Unsuccessful experiments to prevent the decrease of coagulation factors due to tetracycline by vitamin K led to the conclusion that one does not deal with a vitamin K deficiency caused by altered intestinal flora, but that a disorder of specific protein synthesis is responsible for the decrease of coagulation factors.


The influence of the addition of increasing amounts of urea to normal plasma, as demonstrated by the thrombelastogram, has been studied. With increasing concentrations an increase of reaction time and a decrease of thrombus elasticity was noted. Prothrombin time remained unaltered. The diagrams obtained are compared to those of heparinized plasma. The clinical implications of the results are discussed.


A patient with systemic lupus erythematosus is described in whom thrombocytopenic purpura was associated with hypoprothrombinemia and a circulating anticoagulant. It was concluded that the anticoagulant inhibits prothrombin conversion. It is suggested that this action may be a direct one on prothrombin itself, thereby accounting for the apparent prothrombin deficiency.


Hemolyzed erythrocytes accelerate blood coagulation in vitro. They contain a factor with thromboplastin activity (similar to platelet factor 3), a heparin inhibitor (similar to platelet factor 4), and an inhibitor of thromboplastin formation. Furthermore they probably have influence on platelets thus exerting another indirect effect on coagulation.


The studies of the particularities of blood coagulation in the newborn reveal that there exists a labile equilibrium between coagulation factors and inhibitory factors favoring the latter group. The various reasons for pathologic conditions are discussed and tabulated. Stress - induced disorders are mentioned and the possibility of a "vicious circle" of coagulation disorder and bleeding is pointed out. Among various deficiencies the combined prothrombin - factor VII deficiency is considered most important. Therapeutic possibilities, vitamin K in particular, are discussed and transumbilical infusion is mentioned with the description of an especially designed needle. The necessity of early diagnosis and treatment of hemorrhagic disorder in the newborn is stressed.

Bleeding caused by coagulation disorder is a rare but severe obstetrical complication. It occurs most frequently after premature detachment of the placenta, in severe eclampsia, in missed abortion or missed labour, criminal abortion, amniotic embolism, and very exceptionally following normal delivery. Usually the coagulation disorder is caused by fibrinogenemia or by a circulating anticoagulant. Today's concept of the coagulation mechanism is briefly discussed and some of the author's own observations are mentioned and a discussion of pathogenesis, diagnosis and therapy of these conditions is added.

Gerinnungsphysiologische Studien am Menstrualblut. Ebert, R., Nold, B., Univ.-Frauenklinik, Freiburg/Br., Germany, Schweiz. med. Wschr. 86: 999 (1956).

The determination of coagulation factors in menstrual blood yielded the following results: Absence of fibrinogen. Decrease of factor II, V, and VII. Normal or slightly increased thromboplastin activity. Normal or slightly decreased calcium values. Marked fibrinolytic activity. Markedly reduced platelet number.

Indagini sul quadro enocoagulativo de M. di Cooley. Limoli, S., Fumagola, D., Univ. degli Studi, Bari, Italy, Pediatría 64: 54 (1956).

Thrombelastographic studies were carried out in 20 cases of Cooley's anaemia. Results: Bleeding-, clotting-, and retraction time normal, normal platelet count, frequent moderate hypoprothrombinemia of about 80%, factor VII levels normal, recalcification time increased in 2 cases. Thrombelastographic patterns normal, with 2 exceptions where reaction time was prolonged. The authors think that these findings can be explained by the frequent liver disorders present in this disease. In two very severe cases a latent hemorrhagic diathesis was observed consisting of markedly reduced platelet number, increased bleeding and clotting time, and of hypoprothrombinemia.


Decreased or increased activity of coagulation factors are equally important in disturbed coagulation, as shown by hemorrhagic or thrombotic syndromes. Routine determination methods for coagulation factors are indicated. For the evaluation of the results obtained, the author developed a graphic coagulogramm. This stellar diagram includes the levels of 12 coagulation factors. Thus this coagulogramm takes a characteristic shape for each hemorrhagic syndrome. Discussing these various types the possibilities of this new method are evaluated.


Ingestion of 70 g of butter induces a significant decrease of coagulation time in healthy individuals, and also an increase of factor VII, slight increase of prothrombin and decrease of serum antithrombin activity. The reason for accelerated coagulation time is thought to be marked increase of thromboplastin activity. The significance of fat-poor diet in prophylaxis and therapy of thrombosis is pointed out.


Plasma proconvertin was found to be elevated in pregnancy. It falls sharply toward normal in early puerperium in most cases. Plasma prothrombin was less strikingly altered, but in some cases it was elevated. Proaccelerin was unaffected. No case of thromboembolism was found. It is proposed that these changes, together with elevated fibrinogen, retard blood flow in the legs, and increased platelet adhesiveness, provide a dangerous hypercoagulate state that can readily produce intravascular clotting by minute amounts of thromboplastic elements liberated into the circulation from the gravid uterus or elsewhere.

The activity of clotting factors has been determined in 7 patients with agammaglobulinemia. 4 of the patients had the congenital-hereditary form and 3 had the acquired form of the disease. An elevated platelet count was found in 5 of the 7 patients. No abnormalities in plasma clotting factors were found. Data presented are consistent with the following conclusions: (a) none of the plasma coagulation factors is a gamma globulin, (b) agammaglobulinemia is probably the result of an isolated deficiency in protein synthesis, (c) the deficiency of gamma globulin synthesis in these patients does not involve the liver but rather depends on an anomaly of protein metabolism existing elsewhere in the reticuloendothelial system.


Prednisone (Meticorten, Schering Corp.) was used in doses of 0.8 to 1.6 mg/kg body weight to control the bleeding manifestations of idiopathic and secondary thrombocytopenia, vascular pseudohemophilia, and anaphylactoid purpura. The drug was found to be of special value in the management of vascular pseudohemophilia and acute anaphylactoid purpura. Multiple complications suggested the necessity of careful supervision of the patient during treatment with the drug.


The author presents a detailed study of 100 cases of postpartum hemorrhage. The use of anticoagulant therapy during and after labor is often lifesaving. The case of hemorrhage following such therapy reported here is unusual and should not contraindicate the use of anticoagulants. The possibility of fibrinogenemia should be suspected in any case of continuing profuse uterine hemorrhage without obvious cause. The mechanism of death in most cases of fibrinogenemia is right heart failure and pulmonary edema consequent upon attempted rapid massive transfusion therapy. The earlier administration of adequate amounts of fibrinogen and more cautious use of massive transfusion may well aid the prognosis in fibrinogenemia. The availability of large doses of wide-spectrum antibiotics, massive transfusion therapy, intravenous Pitocin infusion as an oxytocic medicament, maintenance of fluid and electrolyte balance and hemostatic factors, varied anesthesia for poor-risk patients, and early resort to life-saving surgery represent the sine qua non for successful management of postpartum hemorrhage.


Since the ethanol-ammoniacal amperometric method for quantitative measurement of -SH groups in proteins is susceptible to valid criticism, measurements were repeated on certain clotting proteins using the Tris buffer system. This procedure also resulted in the inability to detect -SH groups in the proteins.


Despiration of 3 cases of hemorrhagic diathesis in patients who had taken aspirin regularly for several years. Rumpel-Leede's test was positive and bleeding time markedly increased. After discontinuation of aspirin these tests returned to normal. The author thinks that aspirin, which increases capillary fragility, obviously is responsible for the hemorrhagic diathesis in these cases.

A modification of the heparin tolerance test as described by Silverman, whereby coagulation time is measured after addition of heparin, was used for the studies described. Average coagulation time in the normal was 9.15 mins. Hospitalized patients with various diseases, patients after operation, and in particular cases with thrombosis showed significantly shorter coagulation times. Discarnarized patients with therapeutic prothrombin levels had an average coagulation time of 16.5 mins.


Rabbits maintained for 2 months at 4°C, developed increased platelet and erythrocyte counts, hematocrit and plasma protein concentration, beta-globulins and fibrinogen in whole blood, and plasma clotting times. Decreases occurred in serum albumin concentration and in prothrombin time. It is suggested that retardation of clotting in spite of decreased prothrombin time might be due to an increase in resistance of platelets to or some chemical alteration of thromboplastin.


Repeated administration of synthetic serotonin (5-hydroxytryptamine) intravenously or intramuscularly failed to shorten the bleeding time or to correct the poor retraction of the clot in patients with thrombocytopenia. It fleetingly reduced the prolonged bleeding time in patients with vascular pseudohemophilia. The drug failed to improve the bleeding tendency in thrombocytopenic states. Hemorrhage continued in one case of vascular pseudohemophilia, although the bleeding time was corrected to almost normal values by administration of the drug.


An attempt has been made to analyze recent developments in coagulation using genetic categories. From the standpoint of biochemical genetics, reliable data are scant but a small beginning has been made with fibrinogen and antithrombic factor. The lack of progress along genetic lines in other areas may be attributed to: 1. the rarity of the newly discovered hemophiloid diseases, 2. concentration of most workers on identifying these diseases, 3. intense interest in the biochemical properties of the new factors and their role, and 4. apparent failure to recognize the importance of genetic studies. This last opinion is implied by the failure to develop assay procedures sufficiently reliable for family studies. Specifically, one is impressed by the exhaustive studies on probands and almost complete neglect of relatives. The author thinks that significant genetic advances will be made quickly when the workers in the field will appreciate the possibilities.

b) Fibrinogen (Factor I), Fibrin, Fibrinolysis


The subsequent clinical history is reported of a case of congenital a fibrinogenemia previously reported in 1946. No fibrinogen could be detected in the patient's plasma. Thrombin generation in the patient occurred more rapidly than normal and in excess of the normal amount. The amount of thrombin formed could be reduced to normal limits by the addition of fibrinogen. More than twice the average of thrombin was formed from the patient's plasma by the action
of brain extract and calcium. Experiments with added fibrinogen showed that this was due to
the absence of the normal mechanism of adsorption of thrombin on to the fibrin clot. Normal
amounts of AHG were present. Experiments with fibrinogen-free systems showed that the
thromboelastic principle of the platelets is consumed during the formation of blood thrombo-
plastin. Very large amounts of 5-hydroxytryptamine were present in the patient's platelets.

Contributo allo studio delle afibrinogenemie. Afibrinogenemia acquisita complicata da un

The authors report a case of acquired afibrinogenemia complicated by the presence of a
probably heparin-like anticoagulant. The pathogenesis of this disorder is discussed.

Congenital Afibrinogenemia. Hule, V., Preis, A., Int. Abclg., Kinderspital, Brno, Czechoslovakia,

Description of a case of congenital afibrinogenemia in a 13-months-old girl. This case is
reported as the 23rd in world literature.

Remarques concernant la préparation du fibrinogène. Casal, P., Grafland, R., Mathieu, M.,

Description of the method for preparation of fibrinogen for therapeutic use. Results
obtained will be published elsewhere.

Relationship between passive Hemagglutination of Tanned Red Cells Coated with Fraction I
and Fibrinolysis in Cirrhosis of the Liver. Daussot, J., Bergerot-Blondel, Y., Paraf, A., Centre

In the course of fibrinolysis of the clot, which is an especially rapid process in liver cirrho-
sis, this clot liberates a substance capable to react with tanned erythrocytes coated with a
plasminic substance found in fraction I. It is probable that this phenomenon is not limited
to liver cirrhosis, but can also be found in other syndromes associated with fibrinolysis. It
is believed that this is an exacerbation of a normal physiological process.

La réaction d'hémagglutination passive des hématies tannées et recouvertes d'extrait plasmatique
ou de fibrinogène et ses rapports avec la fibrinolyse du caillot. Daussot, J., Bergerot, Y., Brécy,
H., Collin, M., Centre Nat. de Transfusion Sanguine, Paris, France, Rev. Fr. Th. Etudes clin.
biol. 1: 652 (1956).

Recherches sur l'activité fibrinolytique spontanée du plasma dans le cirrhose du foie. Beaumont,

The lysis of clots has been studied in 180 controls and in 19 patients. Accelerated fibrino-
lysis was demonstrated in 13 cases of cirrhosis. In severe cases total defibrination of the cir-
culating blood may occur, as in one of the 13 patients. Fibrinolysis more than any alteration
of liver cells, seems to be responsible for hypofibrinemia and hypoaccelerinemia found in
severe cases. Prothrombin and convertin levels may be further depressed by this mechanism
in the final stage of the disease. This phenomenon is thought to result from the disappearance
of an inhibitor normally produced by the liver, allowing plasma enzymes to act.

L'action hémostatique du fibrinogène humain à fortes doses. Casal, P., Graffland, R., Izarn, P.,
15: 337 (1956).

Fibrinogen in the form of Cohn's fraction I was used for therapeutic experiments. The
preparation was not purified, contained about 60% of fibrinogen, and was poor in active
plasmin and antihemophilic globulin. A series of 14 cases of hemorrhages was treated with
intravenous injections of 5 to 10 g of fibrinogen. Hemorrhage stopped in 11 cases, in 3 the
results were negative or doubtful. Of the successful cases one suffered from acute afibrino-
ogenemia, 9 from thrombocytopenia and one from an unknown disorder. The mechanism of
action of fibrinogen in cases of thrombocytopenia is unknown. It seems possible that there
exists a physiological compensation of platelet deficiency by an excess of fibrinogen.

The cases of 4 patients with metastatic cancer and hemorrhagic diathesis associated with severe hypofibrinogenemia are reported. In all cases hypofibrinogenemia was accompanied by hypoprothrombinemia, factor V - and VIII - deficiency and a variable degree of thrombocytopoiesis. The decrease in clotting factors was due to an increased inactivation in the blood stream and not to inadequate synthesis. The data indicate that both intravascular coagulation and proteolysis are responsible. All tumors were adeno-carcinomas and originated either from the prostate, stomach, pancreas, or gall-bladder.


A case of a fibrinogenemia associated with massive postpartum hemorrhage after a lower-segment caesarean section is described. It was treated by intravenous infusion of fluids and of plasma, blood transfusions, and intravenous injection of fibrinogen.


Hypofibrinogenemic and a fibrinogenemic conditions are described and their clinical significance is pointed out. A rapid method for the preparation of human fibrinogen solutions for clinical emergencies is described. This preparation also contains efficient amounts of antihemophilic globulin.


Description of a rough test for fibrinogen determination which yields results after 10 mins. (Precipitation of fibrinogen with twice molar potassium phosphate buffer pH 6.6).


3 cases of a fibrinogenemia in obstetrics patients are described. In case 1 the patient died, and necropsy showed wide-spread hemorrhages but no clear evidence of fibrin emboli. Cases 2 and 3 were associated with severe accidental hemorrhages; both were treated with pure fibrinogen by different methods, the merits of which are discussed. In case 3 the effect of administering fibrinogen was assessed by serial estimations of plasma fibrinogen. The intra-uterine blood clot contained 63 g of fibrinogen; and this high figure suggests that the bulk of the fibrin may be deposited in the uterus rather than in the vascular tree.


Serum fibrin levels were determined in 60 cases of bronchial carcinoma and infectious pulmonary infiltrations. Of the carcinoma cases 75% showed decreased values, of the infectious infiltrations none. It is concluded that only decreased values can be evaluated for differential diagnosis.


After a short survey of today's concept of blood coagulation, hemorrhages caused by hypofibrinogenemia occurring in obstetrics are discussed. The various possible explanations of these hemorrhagic disorders are evaluated and therapeutic directions are given.

Dilution of blood by a mixture of physiological saline solution and human serum considerably accelerates the fibrinolysis of clots. This very simple method reveals latent fibrinolytic activity, particularly in liver cirrhosis, thrombocytopenic purpuras, and pancytopenias.


Potential fibrinolytic activity of plasma has been determined in 178 cases of thromboembolic diseases, and the influence of marcumar therapy has been studied. The profibrinolysis time of thrombotic cases differed from that of normals. High activity often paralleled fast healing of thrombosis, whereas chronic recidivating cases often showed decreased fibrinolytic activity. Cardiac infarction and lung embolism during the course of the disease always showed decreased fibrinolytic activity. Anticoagulant therapy had no influence on profibrinolysis time.


The authors describe a new method for the paper-electrophoretic fractionation of blood plasma which permits a quantitative determination of fibrinogen. The method is based on the facilitation and regulation of the migration of the fraction on filter paper in the electric field. This is obtained by a suitable preliminary preparation of paper strips. The procedure is simple and gives precise, reproducible results.


The presence of a fibrinogenolytic enzyme and a cytosfibrinokinase has been demonstrated in extracts of human myometrium, placenta, decidua, and endometrium. It is suggested that the presence of these enzymes may be partially or wholly responsible for the lack of fibrinogen which occurs in the blood stream of obstetrical patients under certain conditions, and in menstrual blood.


Quantitative methods for testing fibrinolytic agents in vivo are described. Clots were produced with 111 labeled fibrinogen. Dissolution of a clot resulted in decrease of radioactivity. Pulmonary, peripheral and coronary emboli were produced by injecting radioactive clots produced and ground, in vitro. Using these methods it was found that maximal tolerated doses of trypsin had no significant fibrinolytic effect.


A quantitative method based on the disappearance of 111 labeled fibrin has been used to study the in vivo effect of fibrinolytic agents. Various preparations of human and bovine plasmin were found to lyse clots effectively. Plasmin preparations given intravenously produced hypotension and leukopenia followed by leukocytosis. Doses above 50 Loomis units/kg caused decrease in fibrinogen and clotting index.
Postpartum Hemorrhage Due to a Depletion of Fibrinogen from the Circulating Blood Stream. Klein, M., Biskind, J. I., Silverberg, A., Mount Sinai Hosp., Cleveland, Ohio, USA, Amer. J. Obst. and Gynec. 71: 51 (1956).

Hypofibrinogenemia as a cause of postpartum hemorrhage is a definite entity. It should be suspected in cases of premature separation of the placenta, dead fetus, and shock associated with hemorrhage. Diagnosis should be made as soon as possible and human fibrinogen and whole blood instituted promptly. Where there is excessive lytic substance in the blood more investigation is needed. Toluidine blue may be used to neutralize the fibrinolytic substance.


A method for preparation and isolation of plasmin from purified human plasminogen after activation with streptokinase is presented. The product is water-soluble, stable in the frozen state and produced no toxic manifestations in the dog after intravenous infusion of 1 mg/kg.


The fibrinolytic activity of human prostatic fluid and semen may be quantitatively determined by measuring the liberation of soluble 131I-containing substances from a substrate consisting of 131I-tagged fibrin. The variations in fibrinolytic activity under the conditions described are wide and preclude the possibility of establishing a "normal" value from present data. However, the mean values suggest that the prostate contributes about 50% of the volume of the whole ejaculate of semen in the cases studied.


A new procedure is presented for the determination of fibrinogen in human or rat plasma. The fibrinogen is converted to fibrin by the addition of a solution of commercial thrombin in physiologic saline and alcohol. The fibrin is estimated by drying and weighing it or alternatively by digesting and nesslerizing it directly. The procedure requires 0.1 ml of normal plasma.


Based on the development of new technics, studies have been conducted on the activation of highly purified human plasminogen, the precursor of the naturally occurring proteolytic enzyme of plasma (fibrinlysin). Three types of activation have been investigated: a) spontaneous, b) urokinase, and c) streptokinase. The results obtained and the methods used are described.


During recent years it has been determined that a coagulation defect may infrequently develop in late pregnancy and in the intrapartum and immediate postpartum period. Because of its low incidence in comparison to the number of deliveries, the syndrome of hypofibrinogenemia is sometimes disregarded until the patient is in the terminal stage of hemorrhagic shock. The syndrome, if undetected and untreated, may constitute the difference between whether the patient survives or dies from uncontrolled uterine hemorrhage.

c) Prothrombin (Factor II), Thrombin


In the control of long-term anticoagulant therapy it makes little difference whether the samples of blood used for the estimation of the one-stage prothrombin time are fresh or 24 hours old. Possible therapeutic implications are discussed.

The different view points on the origin of aseptic necroses of the bone are discussed. The decrease of the prothrombin time, as reported by Chiari and Frank in Morbus Perthes, could not be confirmed.


A case of sprue is described which presented with extensive purpura and gastrointestinal bleeding of such severity a medical emergency. This was found to be due to marked hypoprothrombinemia secondary to vitamin K deficiency. The importance of recognizing and properly treating this clinical problem is well documented by this case study. The mechanisms for the development of vitamin K deficiency in sprue are discussed. The association of purpura with chronic diarrhea should suggest immediate prothrombin studies. Sprue must be considered in the subsequent diagnostic work-up of the patient.


According to the authors prothrombin can be activated in 3 different ways during coagulation: 1. Prothrombin + Ca, platelets and ΔC globulin = autoprothrombin. 2. Prothrombin + thrombin = autoprothrombin II. 3. Prothrombin + activator = bioprothrombin. Autoprothrombin seems to be identical with factor VII. Autoprothrombin II is similar to platelet cofactor I (Christmas factor?), which it can replace. Bioprothrombin is thrombin formed during coagulation, differing from thrombin which forms out of prothrombin in the presence of sodium citrate.


The average plasma prothrombin value of 115 matured dairy cows was 23.2 seconds, and for 90 dairy calves 24.82 seconds. Age, breed, ration, and sex did not alter the prothrombin time values of calves. The plasma prothrombin time of new born calves, prior to nursing, could not be determined since a clot did not form in the plasma-thromboplastin-mixture after the addition of calcium chloride. This finding corresponds with that of human infants during the first week of life. The average hematocrit value was 35.08%.


Arotecin (Associated Concentrates, Inc., 57, 32nd Avenue, Woodside, N.Y.) 30 mg per ml ground to an even suspension with a dialyzed sodium citrate eluate of the barium sulfate adsorbent of fresh exsulated normal plasma, is capable of selectively and almost completely removing prothrombin activity. Proconvertin activity and the ability of the treated eluate to shorten the partial thromboplastin time of hemophilia B plasma are reduced to a much lesser degree. Attempts to elute the prothrombin from arotecin have been unsuccessful to date.


Several derivatives of prothrombin have been prepared. Biothrombin may be obtained by activating prothrombin in several ways with activators obtained from tissues. During the transformation of prothrombin to biothrombin there is very little reduction in molecular weight. If there are any degradation products during the interaction, the quantity must be small. Biothrombin can be transformed to citrate thrombin by dissolving it in 25% sodium citrate solution. Prothrombin can be transformed in the same manner, however, an intermediate forms
which is called citrate autoprothrombin. The latter is an accelerator of prothrombin activation. Prothrombin can be converted to autoprothrombin in solutions containing Ac-globulin, calcium ions, and purified platelet factor 3. Autoprothrombin has accelerator properties under certain conditions of prothrombin activation and is a degradation product of prothrombin. It can be transformed to citrate thrombin like bioprothrombin and prothrombin. Methods are described for obtaining concentrates of citrate thrombin, autoprothrombin and bioprothrombin.


A patient with sprue and spontaneous hemorrhagic diathesis is presented, and the literature on the subject reviewed, with brief mention of therapy.

d) Thromboplastin (Factor III)


Amniotic fluid was added as source of thromboplastin in various coagulation tests. Hypoprothrombinemic blood yielded identical results tested with brain thromboplastin or amniotic fluid. The author stresses the fact that amniotic fluid therefore represents an easily available, inexpensive, and stable substance capable of replacing brain thromboplastin.


Some modifications of the thromboplastin generation test as described by Biggs et al. are proposed: the use of BaSO₄ instead of Al(OH)₃ gel for prothrombin adsorption; dilution of serum with a buffer at pH 7.4, photometrical standardization of platelet suspension. It is demonstrated that platelets, factor V, AHG and serum remain stable for at least 7 days when frozen. Therefore it is possible to prepare and freeze a stock of these reagents. A 30 mg/l emulsion of oil-free phosphatides (Asolcan) may be used instead of platelets. Platelet factor 1 or factor V of plasma have to be present as sources of factor V activity in the thromboplastin generation test. In contrast a normal thromboplastin generation takes place in the absence of factor VII. This factor does not seem to be involved in the earlier stages of thromboplastin formation. Decreased thromboplastin activity in patients undergoing dicumarol therapy is not caused by low factor VII level but by decreased Christmas factor activity.


Evidence is presented which suggests that an intermediate product of thromboplastin (Product I) is formed in a preliminary reaction between calcium, AHG and serum and reacts with the platelet thromboplastic factor. The coagulant formed by the interaction of Product I and platelets appears to be associated with the platelet granules and can be sedimented by high-speed centrifugation. This coagulant is composed of a thermo-stable component derived from platelets and a thermo-labile component that may be identical with Product I. Since it is inactivated by decalcification it appears that calcium forms an essential part of this coagulant. Product I-treated platelets correct the clotting defect of platelet-deficient normal, hemophitic, Christmas disease and factor VII-deficient plasma. The clotting time of aged, oxalated, factor V-deficient plasma is not completely corrected by Product I-treated platelets, and it is suggested that factor V reacts with the coagulant formed in the Product I-platelet reaction.


The observation of decreased superficial bleeding during surgery following anesthesia with a hyaluronidase-containing anesthetic lead to the investigation of the hemorrhagic effect of hyaluronidase. The coagulation promoting effect of hyaluronidase could be confirmed in animal experi-
ments and with a slightly bleeding time determination method in the human. It was found that, as hyaluronidase increases tissue permeability, it liberates tissue thromboplastin, and thus the hemostatic effect is explained.


The authors have demonstrated that ample amounts of thrombin can be generated from both platelet-containing and platelet-free plasma of a patient with paroxysmal nocturnal hemoglobinuria. It is believed that this indicates that platelet substances are present free in the plasma of this patient.


Platelets, saline suspensions of whole brain thromboplastin, and cephalin and lecithin extracts of brain were tested in the thromboplastin generation at accelerated clotting time tests and their activities compared. It was shown that in the presence of AHG the lecithin and cephalin fractions of brain were capable of forming an active a thromboplastin as platelets under the same condition. The lecithin and cephalin fractions and platelets require AHG for their activity. Saline suspensions of whole brain do not. The lecithin and cephalin fractions of brain are capable of fully correcting the prothrombin utilization defect of thrombocytopenic blood. These results are discussed in relation to other studies and shown to explain the apparent lessened activity of lipid-extracted brain tissue compared with the saline suspensions of whole brain.


Thromboplastic activity as measured by normalization of coagulation of hemophilic plasma has been demonstrated, in human seminal fluid, cervical mucus, and ovarian follicular fluid.


Rabbit and human brains, when dehydrated with acetone, yield a product with high, constant and practically equal thromboplastic activity. Human brain extract differs from rabbit brain in that it has greater inhibitory effect at high concentration and is more resistant to heat.


Intravenous administration of protamine markedly increases the amount of slowly infused thromboplastin required for defibrinorrination of dogs. Protamine given during infusion of thromboplastin to a dog already partially depleted of fibrinogen, arrests further decrease in plasma fibrinogen level. Intravenous protamine protects dogs from the lethal effect of subsequent rapid injection of thromboplastin. Mode of action of protamine and possible clinical utilization of its antithromboplastic properties are discussed.

e) Calcium (Factor IV)

f) Factor V (and VI)


Evidence is presented that asolectin is under certain circumstances capable of specifically binding and removing the proaccelerin of normal plasma. Such asolectin adsorbed reconstructed plasma was comparable in its behaviour as a substrate plasma for proaccelerin
activity assay to the naturally occurring parahemophilia plasma used as a substrate in the same assay system. Evidence of the specificity of the assolectin adsorbed plasma substrate response for procoelein activity of the test samples is presented.


Factor V consumption has been studied in normal blood maintained at 37°C for 1 hour after collection. By the end of one hour factor V has been completely utilized. Factor V consumption has been shown to be defective in blood of hemophilic patients, Christmas disease or thrombocytopenia, and in patients receiving phenylindanedione or heparin. The experiments support the concept that factor V is an essential component of blood thromboplastin. They suggest that factor V must enter the reactions involved in thromboplastin formation at a stage later than AGH, Christmas factor, and platelets.

**g) Factor VII**


A simplified method for removing proconvertin from plasma by filtration through powdered wood charcoal has been outlined. The degree of freedom from proconvertin of prothrombin prepared from carbon-filtered plasma is demonstrated. Some applications of the test are illustrated.

The Role of Convertin in Experimental In Vivo Thrombosis. Wessler, S., Sallon, J. D., Gilbert, M., Boston, Mass., USA, J. clin. Invest. 35: 743 (1956).

The experiments carried out indicate that convertin is not essential for the formation of intravascular clots by the method employed and that there are present in the barium sulfate eluate of heavily dicumarolized canine serum one or more potent and as yet unidentified moiety effective in inducing intravascular coagulation.

**h) Factor VIII (Antihemophilic Factor)**


The study of 4 cases observed by the authors and of 6 cases from the literature made possible the definition of a syndrome characterized by a clotting defect, caused by deficiency of antihemophilic factor A, associated with a vascular disorder causing consistently prolonged bleeding time and varying capillary fragility. This syndrome comprises a constitutional hemorrhagic tendency affecting both sexes. No such tendency is found in parents but occasionally hemophilia in the siblings. In one of the cases the parents were consanguinous, which suggests a non sex-linked recessive transmission. Whereas transfusion temporarily corrects the clotting defect, as it does in hemophilia, cortisone does not shorten the bleeding time as it usually does in thrombopathias.


A new test is described for the quantitative estimation of thromboplastinogen. It is based on the principle of the prothrombin consumption test modified by the addition of an extract of hemolyzed erythrocytes. Plasma from a severe hemophiliac is used as the assay medium. In severe hemophilia only a trace of thromboplastinogen is present in the blood. A fairly close relationship between the level of thromboplastinogen, the clotting time and the severity of the bleeding state exists. The laboratory and clinical findings in 50 hemophiliacs are summarized. Evidence is presented that the degree of the hemophilic defect is quantitatively transmitted, and that the intrinsic severity of the disease is the same in all affected members of a family.

The assay of AHG in plasma based on the thromboplastin generation test, is described. The AHG concentration of test plasma is compared to that of a standard normal human plasma. The normal concentration in plasma was found to vary from 50 to 220%, the concentration in hemophiliacs from 2 to 28%. The rate of loss of activity in citrated normal plasma samples stored at 4°C has been studied. There was considerable loss during the first 24 hours, thereafter the rate of loss followed an exponential pattern.


AHG consumption has been studied in normal blood maintained at 37°C for one hour after collection. By the end of one hour the AHG was completely utilized. AHG consumption is defective completely in Christmas disease and heparin therapy, and to a lesser degree in phenylindanedione therapy. In platelet deficiency consumption of AHG is normal. A possible interpretation of these results is discussed in relation to the order of the interactions involved in blood thromboplastin formation.


The authors demonstrate that it is possible to prepare antihemophilic factor in various ways. These preparations are rather poor in protein content and in vitro markedly decrease the prolonged clotting time of blood of patients investigated. Some of these preparations were also very active in vivo. With the experiments described, the question as to whether AHF is a protein is not yet solved.

i) Factor IX, (Christmas Factor, PTC)


Description of a case of congenital Factor IX deficiency in a 6-year-old boy with hemophilic symptoms.


Deficiencies of PTC are not necessarily congenital in origin. Serum levels of PTC were depressed following the administration of two 4-hydroxy-coumarin compounds to 24 patients. PTC activity was also reduced in a patient who developed a deficiency of vitamin K subsequent to an inability to absorb fats (cystic fibrosis of the pancreas). In both groups of patients, PTC activity rapidly increased towards normal following the administration of vitamin K analogues.

j) Other Factors (Factor X, Prower Defect, PTA, Hageman's Trait etc.)


Two patients were presented with defective coagulation but no hemorrhagic symptoms. The laboratory findings were markedly prolonged coagulation time, prolonged recalcification time, and poor prothrombin consumption. This abnormality is identical with the newly discovered familial syndrome named Hageman's trait by Ratnoff. The differentiation from hemophilia is discussed in detail. This anomaly is caused by deficiency of a 5th plasma thromboplastin precursor present in normal plasma and serum. The factor cannot be adsorbed on BaSO₄, is not dialyzable, and resists heating to 56°C for 30 mins.; exposure to 65°C for 15 mins. results in appreciable inactivation. Electrophoretic separation revealed that the factor is
present in the area between beta and gamma globulins of normal serum. The activity of this factor was found in precipitates obtained from normal plasma and serum with 0 to 25%, 25 to 33%, and 33 to 50% saturated ammonium sulfate solution with a maximum in the 25 to 33% fraction.


A mild hemorrhagic disease occurring in a young woman is described, and evidence is presented that it is due to a blood coagulation defect of a type not previously described. This has been named the „Prower defect” and is probably congenital. The principal features of the defect are prolongation of the one-stage „prothrombin time” and impaired plasma thromboplastin generation. Although the majority of the findings are similar to those of factor VII deficiency the differentiating features of the „Prower defect” are that thromboplastin generation is abnormal and that plasma or serum from patients receiving Dintevan partially corrects the defect in vitro.


It was found that the accelerator factor in defibrinated plasma after BaSO₄ adsorption enhanced the interaction between platelets and factor (s) in serum or a serum eluate, yielding a thrombokinase able to convert prothrombin directly to thrombin in the presence of calcium. The accelerator factor, apparently, did not influence the rate of prothrombin conversion. Addition of thrombin to the accelerator fraction showed no definite effect regarding thrombokinase formation. The fundamental phase of coagulation seems to involve the generation of thrombokinase.

1) Combined Deficiencies


A detailed study is presented of a 32-year-old women with a congenital deficiency of prothrombin and factor VII. The defect found is similar to that of dicumarol toxicity and involves thromboplastin generation as well as the prothrombin complex. This deficiency has caused recurrent severe hemorrhages, the nature of which distinguishes this disorder clinically from other hemorrhagic diatheses. Response to vitamin K and its derivatives was poor. Monthly treatment with fresh plasma transfusions was effective in controlling bleeding over a 4-year period. The delayed and prolonged in vivo response of prothrombin and factor VII to fresh plasma observed in this case is unique. Its mechanism is as yet unexplained.


A case of transient hypoprothrombinemia and hypoproteostinemia associated with bleeding and occurring during the 18th and 19th weeks of a twin pregnancy is described. The coagulation defect responded to intravenous Kt therapy but not to water soluble vit K. Death of one fetus and complete infarction of its placenta occurred during the 18th week. It is suggested that these events or their cause, may have adversely influenced liver cell function and precipitated the severe deficiencies of prothrombin and proconvertin.


Description of the case of a new-born who from the first days of life showed symptoms of hemorrhagic diathesis, probably of familiar nature. The cause of the diathesis could be ascribed to a simultaneous lack of proconvertin and proaccelerin.

In a single woman, aged 36, a life-long history of bleeding symptoms, a long bleeding time, abnormal capillary fragility and impaired thrombin generation were associated with normal platelet count. Evidence was obtained that the blood was partially deficient in antihemophilic globulin and in Christmas factor, and that the platelets were defective in adhesiveness and liberation of serotonin. The investigation of multiple partial clotting defects is discussed. The thromboplastin generation test is probably the most suitable of present technics but it may be necessary to dilute the reaction components more than usual to demonstrate partial deficiencies.


A case of parahemophilia in a 31-year-old man is reported. The past history revealed an abnormal tendency to bleeding dating back to the first years of life. At the age of 29 ankylosis developed following hemorrhage into the left knee joint. Investigations showed a slightly prolonged whole-blood coagulation time and a markedly prolonged Quick “prothrombin time”. The factor V concentration of the patient’s plasma was 8 to 10%, Factor VII and prothrombin were normal. In addition, the results of the thromboplastin generation test indicated a deficiency of AHG; Christmas factor was normal, no circulating anticoagulant could be demonstrated. Examination of the patient’s family revealed factor V deficiency in one of the sisters. AHG concentration was however normal and this sister had no symptoms of bleeding tendency. The investigations suggest that factor V is necessary for the formation of thromboplastin.


A 13-year-old girl, the offspring of a consanguineous marriage, with a severe hemorrhagic diathesis is described. The bleeding disorder is characterized by a prolonged bleeding time and a decrease in antihemophilic factor in plasma. 19 similar cases (13 females and 6 males) have been collected from the literature. This syndrome is interpreted as a variant of vascular pseudohemophilia, and the term “pseudohemophilia B” is suggested. Genetically it may be transmitted by autosomal genes behaving either as Mendelian dominants or as recessives. The differential diagnosis of pseudohemophilia B from vascular pseudohemophilia A, from von Willebrand’s disease and from sex-linked hemophilia A and hemophilia B is outlined.

m) General Aspects of Hemophilia


The hemophilia syndrome is characterized as follows: reduced plasma thromboplastin formation due to (1) deficiency of platelet factor III, (2) deficiency of one of the plasma thromboplastin factors (AHG, PTC, PTA, PTF-D), and (3) the presence of a circulating anticoagulant that inhibits the activity of plasma thromboplastin. The latest test methods are described with reference to personal cases. A new observation is reported: Hemophilia B, consisting of PTC deficiency and PTC inhibitor. It is emphasized that in these patients coagulation time may be normal inspite of insufficient hemostasis.


To summarize the therapy of hemophilia, not only during a severe bleeding episode, but between times, as well as in the presence of a high concentration of anticoagulant, a panel of experts was asked the following question: What are your recommendations in a severe case of hemophilia — (a) during a bleeding episode? (b) for therapy between bleeding episodes? (c) in the presence of an anticoagulant mechanism that has developed with repeated transfusions? Chief reliance is placed on transfusions of fresh blood or plasma given in sufficient
amounts to prevent further bleeding and to keep the prothrombin consumption fairly close to normal levels. To those hemophiliacs who develop a high concentration of antithromboplastin, little of value is offered.


The thrombin generation test of plasma from hemophilic patients has been studied. This test has been found useful in the differential diagnosis between classical hemophilia and Christmas disease.


This paper deals with transfusion therapy of true hemophilia, but certain of the principles outlined appear to apply likewise to at least some of the hemophilia-like states. Sources of antihemophilic factor are normal plasma or plasma fractions. Normal plasma from different subjects varies widely in AHF content. In stored blood or frozen plasma approximately half of the initial initial AHF content is lost in 2 weeks. Lyophilized plasma has about one-half the potency of fresh plasma. AHF in reconstituted fraction 1 is about 1/3rd of the mean normal value. Fresh plasma from selected donors appears to be the best source of AHF currently available. The authors discuss the minimum levels of AHF required for hemostasis. It may be as low as 5%, although some data suggest that it may be 10—20%. The rate of loss of transfused AHF is the 3rd problem discussed. It appears to be rapid, the half-life appears to be about 4 hours.


The authors report the observations on a boy with complete deficiency of alpha-prothromboplastin and his second cousin with complete deficiency of beta-prothromboplastin. A likely explanation for 2 closely related males suffering from unrelated and potentially inheritable diseases is the recent occurrence of 2 mutations; one for the more frequent alpha-prothromboplastin deficiency (hemophilia A) and the other for the less frequent beta-prothromboplastin deficiency (Christmas disease, hemophilia B).


### n) Platelets


3 cases of thrombocytopenic purpura following closely on chickenpox are reported. This condition follows many different types of infection on rare occasions and is thought that the most likely cause is an allergic response to the infecting organism. The condition is self-limiting and the prognosis usually excellent. One of the patient had also a large hemangioma and the combination of this growth with thrombocytopenic purpura has been reported previously.


The various methods for the concentration of platelets to be used for transfusions are discussed. A modification of the method by Minor and Burnett is described. Dextran fractions with molecular weights between 170,000 and 255,000 are most suitable. Experiences with platelet transfusions are reported. They proved valuable in cases of acute hemorrhage and in the preparation and treatment of patients with thrombocytopenia of various types who require operations. The survival of the transfused platelets depends mostly on the cause of thrombocytopenia.

The acetylcholinesterase (AChE) activity of individual megakaryocytes from various mammals has been investigated with the microdrover technic. Megakaryocytes of cat, rat, guinea-pig, and man exhibited AChE activity similar to that found in the platelets of the same species. Earlier findings concerning the pattern of repartition of AChE in the erythrocyte-erythropoietic and platelet-megakaryocytic systems are discussed. On the basis of available data the hypothesis is advanced of a common origin of the erythropoietic and megakaryocytic systems.


An intermediate product of thromboplastin (Product I) is formed when calcium and AHG are incubated with normal serum. The addition of Product I to a saline suspension of platelets causes them to become sticky and adhere to one another and to the glass surface. Individual platelets form pseudopodia, swell and release their granules. These platelet changes are conveniently referred to as viscous metamorphosis. Evidence is presented which suggests that viscous metamorphosis is not caused by individual factors in the Product I incubation mixture, or by thrombin or fibrin, but it is dependent on the development of Product I activity. The properties of Product I are contrasted with the reported properties of an abnormal platelet agglutinin.


The author carried out experimental studies on the effect of insulin on agglutination of blood platelets. Results obtained in normal and in diabetic subjects are discussed.


Prompt, spontaneous and limited coagulation may occur in the vicinity of accumulated platelets even in the presence of anticoagulant substances. Using the electronic microscope, this coagulation is found to be characterized by the union of plasmatic bodies which form fibres and bundles strongest at the point where they are nearest to the platelets.


Platelet function has been tested in 200 patients. The report includes results obtained in normals and in patients suffering from various diseases such as hemopathies, malignant growth, diabetes, bronchial asthma, and thrombopholic disorders.


The thromboplastic function of platelets was studied by means of the thromboplastin generation test in 6 patients with thrombocytopenia of varied etiology. In a qualitative platelet defect was demonstrated. Incubation of normal platelets in the sera of the 6 patients showed that in 5 a serum factor was present which appreciably reduced the thromboplastic function of normal platelets. This factor was heat resistant to 56° C. for 30 mins. There was temporary
improvement of platelet thromboplastic function following cortisone. A definite relationship was noted between platelet thromboplastic function and the incidence of hemorrhagic manifestations.


20 samples of stored blood with added ACD stabilizator (modification by Zenker and Groll) were found to contain a sufficient amount of functional intact thrombocytes after 2 weeks. For reasons of volume, however, plasma containing concentrated platelets are preferred to whole blood in cases of thrombocytopenia.


The author describes a family with idiopathic thrombocytopenic purpura, where both purpura and thrombocytopenia occurred in 2 generations. A boy, his 2 sisters, and the father were affected. In the cases described there was no apparent morphological abnormality of the thrombocytes, but no attempt was made to demonstrate increased fragility or a shortened survival time.


After injection of one high dose of 5-hydroxytryptamine into rats, marked increase of platelets and definite decrease of eosinophiles occurred.


The author presents a review of most recent findings concerning platelets stressing the problems of viscous metamorphosis, and of platelets and hemostasis. The importance of thrombocytes for thrombin generation, the vasoconstrictor activity of platelets, their role in thrombosis, their relation to clot retraction, and their influence on blood coagulation as a whole is discussed based on the literature concerning these problems and based on the author’s own findings.


The main points emerging from this study are: (1) the unexpected extent of platelet preservation as assessed by direct platelet counts; (2) the changes in the morphologic appearance of platelets with ageing and the early appearance of numerous fragments in bottles in which there was a rapid initial fall of platelets; (3) the increased amount of initial platelet breakdown in the blood from the bottles where there was a significant loss of platelets in the collection; (4) the correlation between the loss of alumina-plasma thromboplastin activity, fall in one-stage prothrombin index and the amount of platelet breakdown.


The author gives a summarizing report on to-days knowledge in the field of thrombopathia, stressing the ever increasing importance of this problem. Hereditary, sporadic-constitutional, and symptomatic thrombopathias can be grouped into 5 categories: a) thrombopathia of the Aaland islands, b) thrombopathia caused by global or sub-global lack of platelet functions, c) thrombopathia caused by defect of single platelet functions, d) mixed thrombopathias, e) additional thrombopathias.


A case of thrombotic thrombocytopenic purpura is described. The staining reactions of the "thrombi" are compared with those of platelets and of naturally occurring fibrin. The results indicate a strong similarity of the "thrombi" to fibrin rather than to platelets. The following
conclusions are reached: (1) Some factor determines the site of the "thrombi" in the precapillary arterioles. (2) The "thrombi" are composed largely of compact fibrin. (3) Altered permeability of the vessels at these sites explains the occasional presence of fibrin within the wall.

Le traitement des hémorragies thrombocytopeniques par l'injection de fibrinogène humain à fortes doses. Catal, P., Graffan, R., Izarn, F., Mathieu, M., Palau, G., Fischer, J., Montpellier, France, Presse méd. 64: 670 (1956) and Saut, F., Montpellier, France, Presse méd. 64: 670 (1956) and Saut, F., Montpellier, France, Presse méd. 64: 670 (1956) and Saut, F., Montpellier, France, Presse méd. 64: 670 (1956).

In 4 thrombocytopenic patients 10 hemorrhages have been treated with intravenous injections of 3 to 10 g of fibrinogen. As a source of fibrinogen Cohn's fraction I has been used, non purified, containing about 60% of fibrinogen, very little active plasmin, and antithrombic globulin. Hemorrhagic manifestations were discontinued in 9 of the 10 cases. In one case the reaction was negative or at least doubtful. The authors insist on the value of fibrinogen injections for treatment of thrombocytopenic hemorrhage where classic therapy has little effect. The mechanism of action of fibrinogen remains uncertain. It is, however, probable that in vascular thrombosis platelet insufficiency is compensated by an excess of fibrinogen.


The author discusses the various factors which influence retraction of a blood clot. If these factors are correctly evaluated the determination of clot retraction offers a very sensitive qualitative measurement of platelet activity. The method is very important for differentiation of some thrombocytopenias. A simple method for measuring clot retraction is pointed out.


A reaction has been devised for the detection of platelet antibodies, which does not depend on the clumping of the platelets as the indication of sensitization. The criterion is the presence of mixed agglutination of the platelets and sensitized erythrocytes. This occurs in the presence of anti-globulin serum only if the platelets are also sensitized with antibody. The method has been applied to the detection of human iso- and auto-antibodies to platelets reported to occur in cases of chronic idiopathic thrombocytopenia. Up to now only 3 sera from likely cases have been examined but none has possessed a platelet antibody demonstrable by this method.


Comparative thrombocyte counts with various methods revealed that results obtained with Fonio's method and with phase contrast microscopy are identical. Results with Jürgens' method are 54% and with Thomsen's 144% higher. The author concludes that phase contrast is the most convenient method. Fonio's method, however, remains valuable for cases, where the platelet count cannot be carried out immediately after withdrawal of blood.


Case report of thrombocytopenic purpura caused by Sedormid.


The viscous metamorphosis of blood platelets is a process independent of fibrin formation. It is initiated by thrombin plus a heat stable dialyzable factor from plasma or serum. The substances liberated from destroyed platelets under these conditions retract spontaneously. This explains clot retraction, where fibrin accordingly plays a passive role.


Accelerated microcinematography and phase contrast revealed the genesis of platelets from megakaryocytes. The process is demonstrated and explained with excellent photographs, showing the different stages of thrombocytegenesis.

The author studied the effect of various synthetic antihistaminic preparations on morphology and "in vitro" adhesiveness of blood platelets. After addition of these preparations in low concentrations to platelet-rich rat plasma, the platelets were transformed into spheric elements. One phenothiazine derivative, Miltéphen (Spécia, France), in high concentrations induced platelet agglutination in citrated plasma and in physiologic saline solution. The preparations tested in low concentrations increase platelet adhesiveness "in vitro" and have anticoagulant activity. The mechanism and significance of these phenomena are discussed.


From human and bovine thrombocytes the authors isolated a substance which induces retraction of plasma clots. This platelet factor called "rettractin" was also found in liver, brain and spleen tissue. Identification of this factor, which is probably a lipoid, is being studied.


In the thromboplastin generation test platelet concentrations above the optimal range display anticoagulant activity. Platelet lipid was prepared and it behaved like whole platelets in the generation test. When added in the early stages of thromboplastin generation, the platelet anticoagulant caused retarded thromboplastin formation; when added later in the test, it interfered with the action of formed thromboplastin. The anticoagulant was neutralized by preparations containing a great excess of labile factor. It is concluded that excess platelets interfere with the action of labile factor in both thromboplastin formation and prothrombin conversion. This anticoagulant effect may be partly responsible for the hemorrhagic manifestations of patients with thrombocytopenia.


Report of 4 new cases with special observations on patch testing. The diagnosis of quinidine-induced thrombocytopenias can be established by a number of special techniques which are described. The most convenient screening test is based upon inhibition of clot retraction of the patient's blood in the presence of quinidine.


Two case reports.


Normal platelet thromboplastin which has undergone the cothromboplastin reaction with diluted serum is highly reactive toward hemopholic plasma. Hemopholic platelets do not acquire such activity by reaction with diluted serum.


Case report.


3 Cases.

Subnormal concentration of serotonin was found in the serum of 3 of 6 patients with thrombocytopenia, 2 of 11 patients with pseudohemophilia, and 3 of 9 patients with thrombocytosis. The implication of these findings are discussed.


Human platelets have measurable metabolic functions as demonstrated by oxidase and dehydrogenase activity. Respiratory quotient and data on metabolic substrates and inhibitors indicate some degree of carbohydrate metabolism. Dehydrogenase activity appears to be associated with carbohydrate metabolism, while a large part of oxidase activity may be associated with other metabolic functions. The large change in activity effected by changes in ionic strength may indicate the presence in platelets of a membrane or some other similar mechanism. Some correlation between these metabolic systems and the role of platelets in coagulation is present. The assay of in vivo viability by changes in the various parameters studied may prove of value in various problems concerned with platelets.


A case of essential thrombocytopenic purpura in a young woman is reported. Although the platelet count was constantly decreased during the period of observation, it was always at its lowest level during menstruation and at its highest level at the time of ovulation. Purpura of the skin occurred post partum and intermittently during 3 menstrual periods. The relationship between purpura, menstruation, and platelet level is discussed.


Extensive hemorrhage from various sites is a rare complication of measles. There are 22 cases of this syndrome which have been documented. 2 cases of severe thrombocytopenia with extensive bleeding complicating rubella are reported; one patient died, the other survived. Cortisone and ACTH may be of value in curing the hemorrhagic disorder and preventing death when extensive bleeding follows measles.


Platelets are a source of glutamic oxaloacetic transaminase in human blood. The enzyme is an intimate constituent of platelets, being found principally in the water soluble fraction of platelets after separation of lipoids by ethyl ether.


Antifibrinolytic activity is higher in patients with thrombocytosis than in patients with quantitative or qualitative platelet defect. In vitro, antifibrinolytic activity is directly proportional to the number of platelets available and, in platelet-rich plasma is enhanced by procedures leading to lysis of platelets. No antifibrinolysin, however, may be obtained from
platelets washed repeatedly. Addition of plasma or serum to washed platelets also fails to release antifibrinolysin. Whether platelets contain, carry or adsorb antifibrinolysin requires further investigation. Elevated fibrinolytic activity may be seen in patients with severe thrombocytopenia.

o) Spontaneous Anticoagulants


Evidence of a spontaneously occurring anticoagulant was found in a 32-year-old female with occult hemorrhages. A highly active inhibitor of both endogenous and exogenous thromboplastin was found. This inhibitor is thermostable and acts without species specificity. The possibility of toxemia of pregnancy or an acute involvement of the collagen system is considered in relation to this coagulation disorder. The clinical aspects of the case are discussed and compared to previously published cases.


In a family with increased bleeding tendency the blood from the father and the daughter showed a heparin-like, heat-labile substance inhibiting thrombin as well as tissue-and plasma-thromboplastin activity. The disease is congenital and is transmitted to male and female members of the family. Protamine sulfate was found to neutralize the effect of this substance.


The authors report a case of immuno-inhibitor-hemophilia A. The inhibitor is found in the gamma globulin fraction of the patient's serum and is characterized as an antibody against antihemophilic globulin. A continuous decrease of this inhibitor was noticed in the patient's plasma during a 5 months' period when the patient was not again sensitized by blood transfusions. Therapeutic possibilities are discussed. Continuous control of inhibitor level is considered useful.


Disturbed blood coagulation in pancreatic disease has been explained by increased trypsin level in blood. After intravenous injection of trypsin an increase of prothrombin, fibrinogen, Ac-globulin and antithrombin has been noted. All factors except antithrombin quickly returned to normal levels. Therefore, antithrombin determination indirectly measures trypsin concentration. The antithrombin test as used by the authors is described in details. The following results were obtained in 51 patients: In acute pancreatitis the antithrombin test remained positive much longer than the increase of diastase value. In pancreatic carcinoma antithrombin is decreased. In hepatic disease antithrombin increases when hepatic insufficiency develops. Antithrombin titer was found to be always normal in cases of upper abdominal disorders not involving the pancreas.


The authors report the case of a 78 year-old man with acquired hemophilia-like coagulation disorder which was found to be identical with „Hemmkörperfahmophilie“ described by Deutsch. The disorder appeared without previous transfusions 5 months after pemphigus. Pemphigus but not the coagulation disorder was ameliorated by the administration of cortisone and ACTH. Coagulation time could be normalized in vitro by addition of stored serum.

A case of L. E. exhibiting an atypical circulating anticoagulant is described. The anticoagulant was found 6 months before the appearance of L. E. cell phenomenon, and it disappeared spontaneously in the course of the disease without improving the latter. The anticoagulants so far observed in L. E. are antithromboplastins but they do not interfere with formation of blood thromboplastin. The same was found in this case. The peculiar feature, however, consisted in a long, instead of a short serum prothrombin time. The results suggest that this antithromboplastin was either associated with true hypoprothrombinemia, or that the anticoagulant also acted as antiprothrombin.

Purification of a proteolytic inhibitor with anticoagulant activity from normal human plasma and urine has been reported previously. It acts on a prothrombin derivative which forms during the conversion of prothrombin to thrombin and its anticoagulant effect depends on the rate of prothrombin conversion regardless of which conversion factor determines the rate. Trypsin can neutralize the anticoagulant effect by binding the inhibitor. The inhibitor can be considered as a buffer in coagulation, tending to maintain fluidity of blood by preventing thrombin formation at slow rates of prothrombin conversion which might occur in-vascularly, but not interfering with thrombin formation as conversion accelerates extravascularly. It may account in part for the lag-phase seen whenever blood clots and for the paradoxical shortening of clotting time when normal or even hemophilic plasma is diluted. Report of a case with excessive proteolytic inhibitor anticoagulant.

The extraction of heparinase from beef and rabbit liver has been studied. A new method of preparation of the enzyme is described. Active preparations were obtained from liver of man, ox, pig, rabbit, guinea-pig, rat, and gopher; kidney of ox, pig, rabbit, guinea pig, and rat; muscle of rabbit and guinea pig. No activity was obtained from dog liver, ox testis and thymus, or human placenta. Difficulties in assaying heparinase in tissue extracts are discussed.

Antibodies against human AHF were produced in the rabbit. These antibodies act as anticoagulants in vitro by inactivating AHF and preventing normal thromboplastin formation. Species specificity and physical properties of the anticoagulant are described. It is postulated that similar anticoagulants occurring in humans are also antibodies produced by AHF immunization.

An unusual circulating anticoagulant was investigated in a patient with refractory AHG deficiency. A number of novel testing techniques were evolved before reaching a final diagnosis and in an effort to determine the mode of action of the inhibitor. The evidence indicates that this antagonist is a basic lipid, rather than proteineaceous in nature, and suggestions are presented regarding its possible identity.

Resistance to transfusion therapy developing in a patient with PTC deficiency was investigated. The patient, originally considered a hemophiliac, had frequently received blood, plasma,
and fraction I prior to the development of resistance. An anticoagulant was demonstrable in the serum and BaSO₄-adsorbed plasma, as determined by their inhibition of thromboplastin generation from entirely normal constituents in the thromboplastin generation test. Inhibition was potentiated by preincubation with normal BaSO₄-adsorbed plasma but not with normal serum. Inhibitory activity was not evident against plasma thromboplastic activity once generated, or against tissue thromboplastin. Ac-globulin and AHF were not affected by incubation with the inhibitor. On withholding transfusions the refractoriness gradually disappeared within 4 months.


Human defibrinated plasma was separated into 11 fractions by a modification of starch electrophoresis. The eluates were tested for coagulant or anticoagulant activity in a two-stage system. Aliquots of each mixture were added to purified fibrinogen to measure the amount of thrombin formed. One anticoagulant fraction was found to be on the beta-2-globulin position and to have properties similar to the lipid antithromboplastin obtainable from blood by methanol extraction. The other anticoagulant found close to the albumin fraction was an antithrombin. The anticoagulant activity of the beta-2-globulin fraction was markedly increased in hemophilia A plasma.

p) Vitamin K


A quantitative comparison between the effectiveness of 100 mg doses of vitamin K̃̃ emulsion administered intramuscularly and then intravenously in 20 human subjects previously rendered hypoprothrombinemic by dicumarol, shows that intramuscularly given doses were unpredictable in their reversal of the elevated prothrombin times. Intravenous administration is the route of choice for injecting vitamin K̃̃ emulsion. When the need for this vitamin is urgent, as in excessive and dangerous drug-induced hypoprothrombinemia, it should always and only be injected intravenously.


Vitamin K̃̃ and Synkavit were found to be more effective and rapid in returning prothrombin and proconvertin values to normal than vitamin K₂, when given orally on an equimolar basis to coelocystoplastomized dogs with bleeding tendency. Intravenously, on the other hand, vitamin K₁, K₂, and K₃ had approximately the same degree of biological activity in correcting proconvertin levels, but the therapeutic effect obtained was less prolonged in the case of vitamin K₁. An intravenous equimolar dose of Synkavit had only a transient elevating effect when compared with the other 3 preparations.


The authors investigated the effect of Synkavit Roche and Konakion Roche on prothrombin values in women in child-bed undergoing marcoumar therapy, and in newborns. The results show that in severe hemorrhages due to overdosage of coumarin drugs vitamin K₁ should be given intravenously, in less dangerous cases oral or intramuscular administration will be sufficient. In the newborn, both water-soluble Synkavit and vitamin K₂ were of equal value in preventing the physiological decrease of prothrombin during the first few days of life. The incidence of hemorrhagic diathesis, on the other hand, with the exception of gastrointestinal hemorrhage, could not significantly be reduced by either vitamin K₁ or K₂. The clinical significance of these findings is discussed.
q) Heparin and Heparin-like Substances


The authors carried out thromboplastographic and coagulation studies of some synthetic heparin-like substances, such as thrombicid, trefuron, beta-heparin, polysulphuric ester of a polyvinylalcohol, a sulfonmucoid derivative, liquid and natural heparin. The results are evaluated in details and discussed.

Die Heparinbehandlung der Hypertonie. Keller, R., Zurich, Switzerland, Medizinische 83 (1956).


Pretreatment with heparin has no influence on the decrease of ascorbic acid of the adrenal cortex following the administration of sodium salicylate, epinephrin, histamin, or influence of cold.


The author, after having examined with chemical and histological methods the action of heparin on the bone marrow, the spleen, and the liver and at the same time the action of total splenic extract on the same organs comes to the conclusion that heparin does not cause alterations of the bone marrow, the spleen, and the liver. On the contrary heparin has an antagonistic effect on splenic extract and can in short time abolish the most serious alterations caused by splenic extract.


Non-hemorrhagic incidents in the course of heparin therapy, such as heparin shock, anaerobic shock, thrombocytopenia, elevated temperature, and hair-shedding are discussed and the cases of the literature reviewed.


The authors have studied the urinary elimination of heparin in patients suffering from diabetes mellitus. The quantity of eliminated heparin was found to be lower than in controls. The authors think that the disturbance of enzymatic balance occurring in diabetes mellitus is responsible for metabolic deviations involving mucopolysaccharides.


The effects of 7 different commercial heparin preparations and of one heparin-like preparation were compared. Comparing identical concentrations of International Units, significant differences were found from one preparation to the other. The preparations tested were: Heparin-Novio, Heparin-Boots, Heparin-Vitrum, Thromboretten, Liqueemin, Thrombophob,
Heparin-Leo, and Thrombocid. The diversity of action is sought to be due to variations in origin, composition and degree of polymerization as well as to the fact that heparin preparations are standardized with animal blood without consideration of species specificity of response to heparin.


The authors carried out 1800 determinations of the quantitative relation between added heparin and platelet number in recalcified plasma of 12 volunteers. Increasing amounts of heparin progressively prolong the coagulation time in inverse relation to platelet number. Standard curves have been established which render possible the determination of the expected in vitro heparin tolerance for any platelet level. Some conclusions concerning clinical practice of the heparin tolerance test are discussed.


Heparin, some heparinoids, germanin, protamine, and a neodyme salt in vitro inhibit in different degrees hemolysis caused by antibodies. The effect of beta-heparin, sodium citrate and potassium oxalate were as insignificant as the effects of dicumarol-like anticoagulants. The experiments show that the antihemolytic activity is caused by an anticomplement effect. The anticoagulants tested had no influence on the amoebocyte adsorption to red cells, on agglutination and on hemolysis by simple lysins, whereas hemolysis by cobra venom was inhibited. The antihemolytic property of the anticoagulants differs very much from that of antibodies. This suggests a different mechanism of inhibition, which, based on the known anti-enzymatic property of anticoagulants, is ascribed to blockade of lysocetinase of cobra venom.

Part II: The effect of Anticoagulants on Hemolysis Caused by Antibodies in vivo.

Heparin, treburon, liquoid, germanin, sulfonmucosin in vivo prevent hemolysis caused by antierythrocyte serum. The mechanism of this action probably consists in blocking of the complement. Heparin has shown remarkable antihemolytic activity in a case of acquired hemolytic anemia.


Excess protamine in part explains the syndrome of shock and a bleeding tendency that occurs in dogs whose blood has been perfused through an artificial heart-lung machine. A simple method is described which provides an estimate of the minimal amount of protamine needed to neutralize the heparin in the animal at any given time.


The author describes the administration of concentrated aqueous heparin subcutaneously for the initial 1 or 2 weeks in a group of 19 coronary atherosclerotic patients with impending myocardial infarction. The results in this series were good. Many other actions of heparin are reviewed which indicate its superiority over other anticoagulants in the therapy of myocardial infarction. In 15 patients with acute myocardial infarction continuous anticoagu-
lation has been maintained for the first 3 weeks with concentrated aqueous heparin administered every 12 or 24 hours. This method is simple and economically feasible, and requires few laboratory tests for control. Reasons are presented indicating that arguments against the routine use of anticoagulants in all cases of myocardial infarction do not apply to heparin.


Therapeutic doses of heparin have been shown to result in a failure of utilization of antihemophilic globulin and factor V, believed to be essential components of blood thromboplastin formation. The consequent inability to convert prothrombin to thrombin has been demonstrated. The experimental results described are not the consequence of heparin acting on the indicator system. This evidence of complete interference with prothrombin conversion and utilization of blood thromboplastin components may possibly indicate that this represents the main action of heparin rather than does the interference with the thrombin-fibrinogen reaction.


The wide variations in sensitivity of different plasma specimen to the addition in vitro of a standard amount of heparin and protamine have been confirmed. There is a positive correlation between sensitivity to heparin and sensitivity to protamine. This is the reverse of what one would expect if unaltered plasma had a naturally occurring balance between protamine-like and heparinoid substances.


r) Other Anticoagulants


After a report of the studies by Verhagen & Wieke on hemorrhagic cutaneous necroses occurring under dicumarol treatment, the author describes 4 new cases of this complication considered to be caused by the effect of dicumarol on capillaries. The treatment, which is purely palliative is mentioned, and regarding surgical interference, caution is recommended.


47 cases of mesenteric thrombosis and embolism treated at the Maria Hospital are described. The diagnosis was verified during operation in 14 cases, at autopsy in 28. In 5 cases the diagnosis was established based on the clinical features only, it was, therefore, uncertain in these cases. In the group of the 42 verified cases, 3 patients survived. In these cases resection of the intestine was performed, one patient was also given anticoagulants. In the unverified group of 5, 3 patients who were given anticoagulants survived. If the extent of lesions permits, the method of choice in the treatment of mesenteric thrombosis is resection of the injured intestine. It is believed that after operation anticoagulants should be given in order to prevent development of new emboli or extension of thrombosis and intestinal gangrene. Where resection cannot be performed the condition is sometimes relieved by anticoagulant therapy alone.

Based on 12 autopsies the author concludes that anticoagulant therapy can lead to mortal incidences. In 5 cases fatal bleeding occurred inspite of comparatively low anticoagulant dosage. Two hypersensitivity reactions were observed, one with acute bronchial asthma, the other with anaphylactic shock. 5 patients died of massive pulmonary embolism with insufficient dosage of anticoagulants.


The author presents a concise review of clinic and therapy of venous thromboembolism. Accurate estimation of factors involved makes efficient prophylaxis possible. Anticoagulants are the therapy of choice and only in cases of contraindications is conservative treatment allowed, including immobilization for 3 weeks.


342 cases of acute myocardial infarction were investigated. 122 were treated with anticoagulants (Dicumarol, Tromexan, or Marcoumar), 220 without. In the first group 5 (2 fatal) thromboembolic complications, in the second 38 (14 fatal). Letality: 9 cases in the first and 72 in the second group. Complications in the treated group: 6 cases of slight hematuria. Based on these results the authors treat all cases of fresh myocardial infarction with anticoagulants disregarding severity of the case or prognosis, provided that no contraindications are present.


The possibility of harmful effect of dicumarol on the foetus is still widely discussed. In view of the practical importance of this problem dicumarol was administered to 10 pregnant women in whom for various reasons interruption of pregnancy had become necessary. After removal of the foetus organs were examined both micro- and macroscopically. Although the results were not entirely conclusive, histologically manifest lesions of the organs were never found. Experiments in animals showed that higher doses of dicumarol produced marked liver damage in the foetus. The drug is excreted in the milk. Since mother and child may differ in their sensitivity to the drug both should be kept under constant observation. The elimination of the drug constitutes an additional load on the liver of the newborn. The use of dicumarol can actually be dispensed with as a) it is not particularly effective in cases of severe thrombosis, and b) heparin is more effective and causes less damage.


Based on the hypothesis put forward during previous studies, that vascular lesions caused by dicumarol-like substances are due to a hyaluronidase-like effect of the anticoagulant, the authors tested the action of vitamin E in rabbits poisoned with marcoumar. From the results obtained it is concluded that in these animals alpha-tocopherol increases survival time, limits the anticoagulant effect, blocks or reduces the hyaluronidase-like action of marcoumar on the mesenchymal intracellular and infratubular substance, and exerts a hepatoprotective action.


Phenylpropyl-hydroxycoumarin has been tried in 104 patients, mostly cases of coronary thrombosis and phlebothrombosis. It is considered a most potent anticoagulant. The
initial dose is about 24 mg, maintenance dose varies between 0.75 and 6 mg. Frequent prothrombin estimations are necessary for control. The drug seems to be particularly free from toxic effects and in this series the only adverse reactions were microscopic hematuria in 4 cases and frank hematuria in one case. Vitamin K is a rapid and effective antidote. (Trade name: Marcoumar).


Anticoagulant therapy with ethyl-bisoumacetate greatly reduced the incidence of thromboembolic complications and the mortality rate in a series of 102 cases of cardiac infarction. Prolonged treatment with intramuscular heparin was without notable effect in 62 cases. In view of the large number of deaths occurring early after an episode of cardiac infarction, large doses of heparin should be given for at least 24 hours together with oral anticoagulants.


12 cases of obstruction of the axillary vein treated with anticoagulants are described and discussed in relation to 19 previously reported cases. The cases fall into 2 distinct groups: with pain and without. The first probably consists of cases with primary thrombophlebitis and in these cases anticoagulants produce rapid relief of pain and reduce the residual swelling. The second group are not greatly benefited by anticoagulants, and are probably cases of extravascular obstruction. Anticoagulant therapy with combined heparin and antiprothrombin agents should be given early to achieve the best results, and, to prevent recurrence, should be continued until the patients return to full activity.


A report is given on experiences with prophylactic treatment of thrombosis based on a yearly series of 5000 surgical patients. The systematic administration of anticoagulants is based on the favorable influence of Thrombocid. Accurate indication, time of onset of prophylaxis after operations, and initial dose of coumarin (Marcoumar) are most important factors in avoiding hemorrhagic complications. Contra-indications are discussed. Coagulation tests allowing accurate diagnosis of incipient thrombosis do not yet exist. The selection of patients, therefore, lies with the physician in charge according to already known criteria.


Long-term treatment with anticoagulants is now increasingly used in the management of infarctions and should seriously be considered in many cases of angina pectoris. At the present it is advisable to reserve this treatment for severe cases in which the hitherto current methods do not afford relief, and for cases in which the patient's symptoms and manner of living give occasion to anticipate infarction and complications. The author considers a high primary thromboembolism index and a high blood cholesterol level a further indication for anticoagulant treatment.


103 patients were treated postoperatively (urologic operations) with Sintron as prophylaxis or therapy of thromboembolism. The author concludes that this preparation is very similar to tromexan. However, the easy management of the drug, the very small daily dose and its excellent compatibility represent significant advantages for clinical use.


After preliminary study of the effect of intravenous heparin injections on the biological phenomenon of the spot, and confirmation of the hyaluronidase-like effect of marcoumar, the author studied rabbits under marcoumar plus intravenous heparin (10 mg/kg). It was noted in all cases that while marcoumar increases the rate of intracutaneous diffusion of fluids,
heparin reduces it in normal animals, and brings the area of spot to former extension in rabbits with marcuparn intoxication. It is therefore concluded that, regarding this particular problem, heparin has an antagonistic effect to marcuparn, blocking its hyaluronidase-like action, and possibly preventing its toxic effects on the capillaries.


The action of neodyme sulpho-isonicotinate on various coagulation factors has been studied in human and rabbit blood. Neodyme interferes with proconvertin, eliminating all endogenous thromboplastin formation, and to a lesser degree with prothrombin. All other coagulation factors, including the complement, are uninfluenced by neodyme. Human blood is more sensitive to its action than rabbit blood. The effect of this neodyme salt has been compared to that of heparin and dicumarines. In spite of some similarities a fundamental difference exists.


Anticoagulant therapy involves hemorrhages in 10 to 20% of the treated cases. The bleeding is mostly caused by increased bleeding tendency of the patient or by difficulties concerning dosage of the drug. The severity of these incidences can markedly be reduced or even abolished by prophylactic or therapeutic measures. Prophylaxis consists in exclusion of patients from therapy with increased bleeding tendency. Therapeutically hemorrhages may be influenced by reduced dose of anticoagulant, or by administration of less dangerous dicumarines instead of heparin, or by simultaneous administration of capillary-active P-factors, or even by administration of antidotes.


Dicumarol was found to inhibit DPNH oxidase activity of heart muscle preparation. The inhibition depended both on the time of preincubation of the enzyme complex with dicumarol and on the final concentration of dicumarol. Diaphorase, cytochrome c reductase, and cytochrome c oxidase activity were not inhibited by dicumarol. The inhibition was not reversed by calcium phosphate gel or vitamin Ks. Cytochrome c protected the enzyme completely against inactivation when added prior to dicumarol, and reversed the inhibition to a large extent when added after preincubation with dicumarol.


67 patients surviving myocardial infarction were treated with dicumarol for an average of 1.5 years. 5 patients died under treatment, 2 from myocardial infarction. No serious hemorrhagic complications were noted. Prothrombin determinations were carried out according to Owen's technic.

*Un nouveau anticoagulant de synthèse: la warfarine. Retina, A., Presse méd. 64: 433 (1956).*

Warfarin (3-[α-phenyl]-β-3-acetylethyl]-4-hydroxycoumarin) has been used during the last 2 years successfully by various American authors. This paper summarizes their results. Warfarin may be administered intravenously as well as orally with the same results. One single dose appears to be sufficient for 3 to 6 days, therefore constantly stable hypoprothrombinemia is easily obtained. It should not be lower than 10%. Small doses of vitamin Ks are effective antidotes.


The author reports results obtained with a new coumarin derivative of the "short action" type, its average of 24 hours, normalization of Quick values after discontinuation of the drug occurs after 36 hours. Clinical results were satisfactory. Sintrom is in particular suitable for therapy of postoperative and postpartum thromboembolism because of its short-acting properties. Danger for the sudding is considered highly improbable.


The mode of action of anticoagulants in acute coronary occlusion is reviewed. It is suggested that a direct action on the occluding process in the coronaries takes place besides the protective effect against thromboembolism. Anticoagulants should be introduced as soon as the diagnosis has been ascertained. Heparin is used until dicumarol has produced therapeutic "prothrombin" levels. Daily control of prothrombin levels is absolutely necessary. In 166 cases of acute coronary occlusion treated with heparin and dicumarol, + episodes of slight hemorrhage occurred (−3%). In 4 cases thromboembolic complications appeared.


Available data suggest that heparin is preferable to its substitutes in acute episodes, whereas the coumarin and indandione derivatives are not only more convenient in chronic use but seem to gain efficiency with time. Perhaps heparin rather than its substitutes should be used in acute myocardial infarction, but this must be established by further study. Meanwhile, it would seem reasonable to distinguish sharply between heparin and other preparations in both experimental and clinical studies on the evaluation of anticoagulants.


A course of PID therapy was given 100 times to 89 patients. Initial doses 200—600 mg. Average maintenance dose 135 mg. The elderly and patients with congestive heart failure required smaller initial and maintenance doses of the drug. Hemorrhagic complications were rare, not dangerous and easily controlled by small doses of Kt. Larger doses of PID were required than those often recommended in the literature.


Sintrom is compared with other hypoprothrombinemic agents in the same human subjects. Comparing dosages which result in the same peak prothrombin time, both speed of onset and duration of effect are found to be a function of the rate of biotransformation. Rapid biotransformation results in fast onset and short duration of action and vice versa. Sintrom is
intermediate between the slow, long-acting compounds (Dicumarol, Warfarin, Coumophyrin) and the fast, short-acting Tronexan. Only 16 to 32 mg dose of Sistrom rapidly results in a desirable hypoproteinemia which is maintained by a single daily dose of 2 to 10 mg.


Rest and elevation of the part in the patient with thrombophlebitis are still the most important factors in the treatment of this condition. The relief of vascospasm by heat and sympathetic ganglion block are valuable aids in the therapy. Antibiotics are recommended when fever is present. Anticoagulants are an important addition to therapy and will in most instances limit the clotting process and prevent embolism. Ligation of veins should be done only when anticoagulants are contraindicated. Constrictive stockings are important in controlling edema in the postphlebitic period and must be worn as long as perceptible swelling persists. Continuous long-term anticoagulant therapy is a safe procedure and will mostly prevent the recurrence of thrombophlebitis and embolism.


The test described is made on whole capillary blood. The total clotting time for capillary blood is 15 to 18 seconds (deviation 2.5 secs.). The level during therapy is maintained at twice the normal (36 to 40 secs.). The results indicate that this blood prothrombin test is a practical bedside, office, or hospital procedure. It has eliminated the need for hospitalization of patients under anticoagulant therapy, and has made therapy available at home, in the office, and in communities where trained technical personnel or special equipment are unavailable.


Autopsy records of 151 patients dying of acute myocardial infarction, in a large private hospital, were reviewed. Half of the patients received anticoagulant therapy. Hemorrhage was not a significant cause of death in dicumarol-treated patients. Embolic complications, often undiagnosed clinically, were of common occurrence. Adequate anticoagulant therapy effectively reduced, not only the total number of emboli, but also the number of serious or fatal emboli. In this role anticoagulants serve a useful purpose in the treatment of myocardial infarction.


Evidence is set forth to show the value of continuous long-term anticoagulant therapy by comparison with a control group of patients who have also had multiple coronary occlusions or single infarcts, followed by severe angina pectoris or episodes of coronary failure. Statistical life-estimate determinations are included. Bleeding complications are encountered less frequently with improved methods of management and are considered a justifiable risk in view of the serious consequences of the natural progress of the disease. After a program of long-term anticoagulant treatment has been instituted, cessation of therapy may be hazardous.


The effect of dicumarol on various coagulation factors was studied in 9 patients receiving the drug. The observations indicate that dicumarol does not induce a true hypoproteinemia. The production of an altered or abnormal prothrombin by dicumarol is suggested as an explanation for the prolonged Quick prothrombin time.


Coagulation studies were performed on 21 patients receiving dicumarol. From the ratio of the heparin clotting time (HCT) to the one-stage prothrombin time (PT), an index of over-all coagulability was obtained. Studies on patients with acute myocardial infarction revealed hypercoagulability fluctuating with hypocoagulability, superimposed upon the dicumarol effects. Hemorrhagic manifestations seemed more closely related to over-all coagulability than to the prothrombin time alone. The significance of over-all coagulability in the control of anticoagulant therapy is discussed, particularly in relation to myocardial infarction. These studies suggested that the PT alone maybe inadequate as the basis of a therapeutic range and in the control of dicumarol therapy.


It is generally considered that the administration of dicumarol is followed by a decrease in prothrombin concentration, and it has been suggested that another plasma factor may also decrease. The authors have found that there are 2 derivatives of prothrombin called autoprothrombin and autoprothrombin II. In this paper data are presented which show that the concentration of autoprothrombin II can be reduced practically to zero with dicumarol without observing a bleeding tendency. The decrease in concentration coincides with a decrease in prothrombin concentration but is more rapid.


Vit. K1 given intravenously in massive doses to dicumarol-treated rats and chicks did not influence the concentration of dicumarol in whole liver, the subcellular fractions of liver, or whole blood, while the usual dicumarol-induced hypoprothrombinemia was prevented. The tissue distribution of dicumarol in the chick is similar to that in the rat.


The development of significant clotting time prolongation is measurably slower than the development of an adequate effect on Quick's test at the beginning of dicumarol therapy. The same clotting time levels may be maintained in various patients with markedly different prothrombin times. No close correlation was found between clotting time and Quick test results. No thromboembolic complication or hemorrhagic accident occurred when the clotting time was within therapeutic range (40 patients).


Agranulocytosis is an infrequent but serious complication of anticoagulant therapy with phenindione. Despite the availability of steroid therapy, agranulocytosis may be fatal unless promptly recognized and treated. A diffuse scarlatinaform eruption was also present in the case described.


Thromboembolic complications frequently occur following myocardial infarction. Following the general acceptance of anticoagulant therapy there have been some patients who have
recommended that this therapy be withheld from "mild cases" unless they develop thromboembolic complications. The authors believe that this is not justified unless there are contraindications for anticoagulants, provided that proper facilities are available. Summaries of experience with 14 so-called "good risk" cases of myocardial infarction who developed a total of 18 certain and 4 probable thromboembolic complications are presented. Complications are discussed in detail.


The current indications for the use of anticoagulants in cerebrovascular disease include:
- Intermittent insufficiency of the basilar artery system. Intermittent insufficiency of the internal carotid system. Thrombosis within the basilar artery system. Recurrent cerebral emboli associated with a likely cardiac source, and possibly, recurrent cerebral thrombi.


An interrupted schedule of administering maintenance doses of warfarin sodium every 3rd or 4th day appears not to be satisfactory. Administration of the drug guided by the day's prothrombin determination would seem to be the best method, and, if a pattern is established the prothrombin determinations can safely be reduced in frequency. Individual dosage requirements vary widely, but for the majority, after an initial dose of 75 mg., daily or every-other-day doses of 12.5 mg. will be satisfactory.

s) Thrombosis


In 7 patients with severe septic thrombosis and thromboembolism the author obtained highly satisfactory antibiotic effect as well as favorable influence on the thromboembolic process by oral administration of daily 1–2 g of terramycin for about 10 days. No effect of terramycin on the various coagulation factors could be established, the author nevertheless assumes some kind of anticoagulant activity of terramycin.


The author reports a case of spontaneous venous thrombosis in the leg in a man of 52. Further studies of this patient and his 2 brothers revealed increased activity of prothrombin, factor VII and factor V. Thrombelastographic diagrams yielded normal results. Diagnostically and therapeutic view points are discussed.


Behandlung von Thrombophlebitiden der oberflächlichen Beinvenen mit Batazolidin, Hartert, I., Univ.-Frauenklinik, Heidelberg, Germany, Medizinische 460 (1956).


The author thinks that varicose veins are more easily removed and with longer lasting success by means of obliterating injections than by operation. Treatment of deep venous thrombosis by administration of Butazolidin is considered more efficient than anticoagulant therapy.


Three case reports.


Case report.


The possible value of biopsy in the diagnosis of thrombotic microangiopathy is discussed. Biopsy should be considered as soon as the diagnosis is suspected, so that time may be gained for investigation of the disease and of possible lines of treatment. Combined rib, muscle, and skin biopsy may prove to be the method of choice. 3 cases are described in which the diagnostical histological changes of thrombotic microangiopathy were found in surgical specimens before the clinical syndrome developed.


In a group of 301 cases of acute or subacute venous thrombosis, 44 occurred in patients with cancer and only 5 of these were before operation. During this period 792 patients with carcinoma of pancreas, stomach, or bronchus were seen. Idiopathic venous thrombosis occurred in 23 patients who had been followed for 6 months to 5 years without developing evidence
of carcinoma. Contrary to the impression suggested in the literature the authors' experience would indicate that there is no significant association between idiopathic venous thrombosis and hidden cancer.


In 15 cases of unsuspected malignant disease thrombophilias was the principal symptom leading the patient to seek medical aid. Greater suspicion of cancer in cases of apparently spontaneous thrombophilias among patients more than 40 years old may stimulate earlier indirect investigation and diagnosis which may lead to more successful treatment in these cases. The mechanism of increased tendency toward thrombosis in this syndrome is unknown. The thrombosis, characteristically, is relatively refractory to anticoagulant therapy.


Thrombelastographic (TEG) studies of disorders of the pre- and the first coagulation phase lead to the following results: Disorders of the prephase (hemophilia) show increased reaction time and thrombus formation time. A differentiation of hemophilia A, B, and C is not possible with this method. Disturbance of the first phase, i.e. decreased factor V or VII are not seizable with TEG. Combined coagulation disorders in new-borns are not revealed by TEG. And neither are decreases of prothrombin, factor VII and X produced by anticoagulants. Bleeding tendency in hemorrhagic diathesis is also not detectable by TEG. The authors come to the conclusion that quantitative determination of single factors, as well as differentiation of hemophilias by thromboplastin generation tests are methods much superior to TEG for studying problems of pre-and first phase.


Thrombelastographic determinations were made in cases of AHG-, PTC- and PTA-deficiencies, in thrombocytopenias and in normal plasmas after the addition of heparin and heparin-like substances. The components of the thrombelastogram (TEG) were correlated with respect to reaction time (s), the point of clot formation (K), and the maximal amplitude (ma). Hemophilic syndromes showed prolonged r and k, thrombocytopenias prolonged k and decreased ma. The behaviour of heparinized blood was characterized by a hemophilia-like prolongation of r and k and a thrombocytopenia-like decrease of ma, with variations depending on the compound used. The correlation between r, k, and ma are suggested to be used for evaluation of TEG.


The author studied the effect of intravenous administration of sodium-o-naphthylamine-4-sulfonate on thrombelastographic results in 62 normal individuals. 174 tests showed that one single dose of 20 ccm of "Intra-Tuffon" results in a decrease of the reaction time 4 -- 8 hours after the injection. The rate of thrombus formation also is increased by the drug. No thrombotic incidence occurred during this study. The effect of cumarin drugs could not be normalized by Intra-Tuffon. Based on the results obtained the author comes to the conclusion that Intra-Tuffon is a valuable hemostatic principle.