Physiology and Pathology of Blood Coagulation
A Review of the Literature of 1950*
(First Part)

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1. General Aspects Europe:


A brief survey of recent advances in the field of coagulation is presented: 1. The active thromboplastin of the blood is due to cooperation between a thrombocyte factor and one of plasmatic nature. 2. Factor V an inactive substance is activated during the coagulation process to form factor VI which accelerates the formation of thrombin. 3. Factor X helps convert prothrombin into thrombin in the presence of factor VI, thromboplastin and calcium. The prothrombin content of the serum is elevated after spontaneous coagulation of the blood and subsides gradually within several days or weeks. Quick’s prothrombin consumption test fails to determine the prothrombin in the serum, due to the deficiency of factor X in the serum. 4. Prothrombin is thought to be a simple specific substance, not a complex of several factors as Quick suggests. It is converted into thrombin under the influence of an activator complex of intricate nature. Besides calcium, factor V and factor X, a thrombocyte factor and antihemophilic globulin are included in this complex. The author also suggests that the thrombocytes may contain the substance that effects the start of the entire coagulation process.


Prothrombin time (Quick’s one-stage method) can be accelerated by adding certain amino acids.


* The following abstracts have been compiled from periodicals available and from reprints sent to us. The institute from which the paper originated was reported whenever its name was mentioned in the original article. In order to complete this list as well as possible we would greatly appreciate receiving reprints from the authors of papers on coagulation problems, as another series of abstracts under the same headings will be published in a later issue. The reprints should be addressed to the editor of these abstracts: Department of Medicine, Rantons-spital, Zurich.

Ko 179, Physiology and Pathology of Blood Coagulation


A short survey of blood coagulation is given with addition of the newly established facts.

U.S.A.:
The reliability of the Lee-White method for determination of coagulation time is discussed.
Studies of the effect of therapeutic and toxic doses of digitalis upon the coagulation time revealed no change from the normal.

Dept. of Med., Tufts College Medical School, Boston, Mass.
This review article presents the author’s theory of blood coagulation plus a classification of hemorrhagic diseases on the basis of their abnormality of blood coagulation process.
Blood coagulation and Hemorrhage following total body X irradiation in rabbit. Rosenthal, R.J.

2. Prothrombin Europe:
A modification of Sternberger’s two-stage method was applied to the measurement of serum prothrombin. Values obtained are lower than those found with the one-stage method, but higher than those obtained with the two-stage method of Soulier.
Observation on prothrombin consumption during clotting of normal blood in glass. De Vries, A.
Only a small part of the available prothrombin is utilized to induce clotting of normal blood. More than 95 % is converted within one hour after the clot has been formed.

Rothschild Hadassah Univ. Hosp., Jerusalem, Israel.
The prothrombin of hemophilic serum was studied with a one- and a two-stage method; the one-stage method was found unreliable. The hypothesis is brought forward that in serum with elevated prothrombin levels the prothrombin conversion accelerator is bound to the prothrombin, being liberated when most of the prothrombin is transformed into thrombin.

A markedly positive consumption test (Quick’s method) was found in the males of a newly discovered bleeder clan in Switzerland, whereas the decrease in

12 R. Roller, Physiology and Pathology of Blood Coagulation
prothrombin time (Quick’s method) was not so distinct in the carrier females. Also in constitutional thrombopathia (Willebrand and Jürgens) a slower rate of prothrombin consumption was stated, number of thrombocytes and coagulation time being normal.
A new method for measuring prothrombin consumption in venous and capillary blood is proposed. It was used in 89 patients with hemorrhagic syndromes. The normal consumption time is above 1 min. for venous blood and above 3 min. for capillary blood. In hemophiliacs the
venous and capillary consumption times are equal and both below 8 sec. In thrombocytopenia, the venous time is between 6 and 18 sec, while the capillary time is often normal.


Observations have been presented on the prothrombin consumption defect present in hemophilia and thrombocytopenia. Whereas in normal subjects less than 40 % of the prothrombin present in the plasma remains in the serum one hour after coagulation of the blood has occurred, in these two conditions anything above 70 % may be present. In many of these cases the apparent amount of prothrombin in the serum is greater than in the plasma. After removal of platelets from normal plasma by high-speed centrifugation, prothrombin consumption ceases. By mixing the plasmas of hemophilia and thrombocytopenia, it can be shown that each of these is capable of correcting the defect in the other. Furthermore, the quantities which must be added in both instances are not the same, and these two facts appear to be in favour of the separate identity of these two substances. The addition to hemophilic plasma of quantities of normal plasma comparable to those which correct the defect in the coagulation time, of the order of 1 %, prove equally adequate with regard to prothrombin consumption. It is likely that the acting substance is the same in both instances and is probably «antihemophilic globulin». In platelet-free plasma, platelets must be added in much larger quantities before the defect is corrected. Depending on the speed and duration of centrifugation, between 10 % and 30 % or more may be needed. In this respect hemophilic platelets are as good as normal platelets.


By means of Quick’s consumption test the author found that in normal women with normal menses during the menstrual period and especially at its beginning there is a slight but significant reduction of prothrombin consumption, as compared with intermenstrual intervals.


The one- and two-stage methods of prothrombin determination are described. Disadvantages of the one-stage method are pointed out. For quick bedside tests micro-methods are advantageous. The value of prothrombin determinations for differential diagnosis of hemorrhagic diatheses are explained.


The authors state that prothrombin determinations by Quick’s or similar one-stage methods do not reveal the level of prothrombin in blood. Quantitative prothrombin determinations, however, are possible if two-stage methods are used.


In order to exclude the influence of the variability of ac-globulin in serum on the 2-stage prothrombin time determination, the author recommends adding prothrombin-free beef serum, which contains a great amount of ac-globulin, to the dilution.


The quantitative connection of the amount of prothrombin and ac-globulin in blood plasma as clotting aids were investigated by Schultze’s modification of Rieben’s two-stage method. In liver diseases the amount of ac-globulin and especially that of prothrombin are lowered particularly at the onset of the liver-parenchyma damage. One finds similar circumstances in experimental liver-damages of dogs. The investigation of liver diseases and the close connection between the amount of prothrombin, as well as ac-globulin, to the amount of albumins in the serum indicates that the formation of the 3 albumin bodies is involved in the function of the liver.


Prothrombin time determinations according to Quick’s method reveal that the lowering of the prothrombin level increases in the following succession of the investigated diseases: thyroid toxicity, epidemic hepatitis, cardiac enlarged liver, cirrhosis of the liver, acute yellow liver atrophy. The prothrombin determination can therefore be used clinically as a worthwhile liver function test in cases of toxic and infectious liver pachenchyma damage and similar conditions.


Prothrombin time can only be determined by a two-stage method, which also makes it possible to determine ac-globulin.


It is shown that P.I.D. is an anticoagulant with a powerful and specific action on the blood prothrombin concentration. Vitamin K has an antagonistic effect on the action of P.I.D.

Furthermore P.I.D. has certain advantages over dicumarol. It has no definite effect on the concentration of factor V.


The author advises small doses of dicumarol in the aged. He feels that it is best to give this drug in small daily doses after initial heavier dosage. For pro-thrombin estimation he recommends emulsified human brain as thromboplastin. For effective therapy a prothrombin clotting time of 30 to 50 seconds should be maintained with this preparation.


The micromethod (/. P. Soulier) for prothrombin determination is discussed. The results obtained by this «slide-method» do not show significant errors compared to the ones obtained in control cases determined by methods of Quick and Fiechter. The one-stage method by Soulier is sufficient for clinical use. But to obtain exact scientific results macromethods are appropriate.


Advantages and disadvantages of one- and two-stage methods are discussed.


The effect of P.A.S. on the prothrombin time was investigated in a number of patients receiving large therapeutic doses over long periods as treatment of pulmonary tuberculosis. A slight prolongation was noted, but this is thought to be without clinical significance in patients receiving a full diet.


Irregular results in measuring prothrombin time are obtained when laboratory glassware and containers in which blood is collected are washed with soapless detergents.


The investigations proved that an increase in prothrombin time in presence of a heterologous thromboplastin cannot be explained by the presence of anti-thromboplastin of the plasma, nor by the formation of a less active plasma, nor by the specific characteristics of the plasma factor non-identical with classical prothrombin.

Azione dell’acido p-aminosalicilico sul tasso prothrombinico e tromboplastinico nella tubercolosi pulmonare. Marra, A. Arch. fisiol. 5, 341 (1950). Istituto Sanatorio Principe di Piemonte, Naples, Italy.


The prothrombin level was controlled before, during and after X-ray and radium treatment. Results: increase in 75%, no change in 21%, and decrease of prothrombin level in 4% of the cases only.

Azione dell’acido p-aminosalicilico sul tasso prothrombinico e tromboplastinico nella tubercolosi pulmonare. Marra, A. Arch. fisiol. 5, 341 (1950). Istituto Sanatorio Principe di Piemonte, Naples, Italy.

The test accurately identifies those conditions which involve a deficiency of thromboplastin (hemophilia, thrombocytopenia).


The conversion of prothrombin to thrombin during normal blood coagulation occurs with increasing velocity and is thought to be an «autocatalytic phenomenon». After experimentally having compared the action and properties of SPCA to serum ac-globulin, the authors believe that SPCA is the autocatalytic factor which accelerates the conversion in the presence of a plasma component. According to the writers, serum ac-globulin consists of plasma ac-globulin and SPCA. They believe that the plasma ac-globulin which is labile and not easily absorbed by BaSO₄ or BaCO₃ (contrary to the stability and easy absorption of SPCA) is the same substance as Quick’s labile factor, necessary for rapid prothrombin conversion.

The authors present a procedure for the prothrombin time of serum (prothrombin consumption time) based on Quick’s method. They have studied the intensity of the influences of the following 4 coagulation factors: 1. unconverted prothrombin; 2. unconverted labile factor; 3. serum accelerator effect; 4. concentration of thrombin on the serum prothrombin time. They conclude that serum prothrombin time is influenced mainly by the concentration of residual prothrombin and the accelerator effect of serum. In hemophilia and thrombocytopenia the formation of thrombin is limited due to inadequate activation of thromboplastin.


The authors investigated the comparative effect of low temperature storage upon plasma prothrombin activity of newborn infants and adults and also the effect of storage on plasma prothrombin activity. Using the Quick method, the results showed a decrease in plasma of prothrombin concentration in adults and newborn infants both before and after vitamin K therapy. Plasma stored for more than one week was found to be ineffective as a source of prothrombin.


The author further dissociated coagulase – globulin from prothrombin by means of adsorption of CaF₂ and by Seiz’ filtrations, thus indicating that coagulase – globulin is not the same as prothrombin.


The author used oxalated plasma, deficient in ac-globulin due to storage, as a source of prothrombin in the 2-stage assay of ac-globulin.


The increase in the Quick prothrombin time is due mainly to a decrease in co-thromboplastic activity. The activity of thromboplastin when exposed to diluted serum or plasma, is increased due to co-thromboplastin. The authors explain variations in results of one-stage prothrombin tests as due probably to varying degrees of exposure of the thromboplastin to blood during its preparation from tissue.


A plasma component called «labile factor» is necessary to convert prothrombin to thrombin. The level of labile factor in serum is discussed. The labile factor is consumed in relation to the amount and velocity of prothrombin conversion. The significance of the observation is discussed.


Normal individuals differ in their mean prothrombin time. There is no significant variation in prothrombin time taken before or after meals, exercise or high-cholesterol diet.

The prothrombin time determination is performed by the following method: 5 mm3 of blood are collected in a dry capillary tube containing calcium oxalate, and immediately pressed on a slide with thromboplastin suspension. Time is stopped after appearance of the first fibrin threads. The significance of different methods for prothrombin estimation and their relative values. 


In cases like suspected liver damage or control of prothrombin concentration under dicumarol therapy, results obtained by the two-stage method are more reliable than those obtained by the one-stage method. To control the effect of heparin therapy the latter is more appropriate.


In a 5-year-old infant with true hypoprothrombinemia the exceptionally rapid disappearance of injected prothrombin from plasma led the authors to believe that possibly there is a normal consumption and regeneration of prothrombin and that, whenever prothrombin synthesis in the liver is interfered with, there may be other body stores which will supply the prothrombin. They found that BaSO₄ removed one of the accessory prothrombin plasma constituents and recommend the disuse of BaSO₄ as a diluent in one-stage prothrombin determinations.


Roller, Physiology and Pathology of Blood Coagulation 185

The increase in the Quick prothrombin time after the use of dicumarol is explained partly, but not entirely, by a decrease in co-thromboplastin activity, which often effects a far larger change than occurs in prothrombin. Due to co-thromboplastin, exposure to highly diluted serum or plasma increases the activity of thromboplastin, especially with respect to dicumarol plasma. Variations in results obtained with the one-stage prothrombin test may be due to varying degrees of exposure of the thromboplastin to blood during its preparation from tissue.


This paper presents new one-stage procedures for the quantitative determination of the plasmatic concentration of prothrombin and labile factor. The development of these procedures has been necessitated by the discovery that other factors besides those considered in the classical theory of the coagulation of blood influence the formation of thrombin. An analysis of the principles, technic and applications of the new methods is given.

Enzyme studies on human blood. VII. Prothrombin as determined with the isolation technic, in patients receiving dicumarol. Shinowara, G. Y., W. B. Smith. Amer. J. clin. Path. 20, 341 (1950). Dept. of Pathology, Ohio State Univ., Columbus, Ohio.

Prothrombin levels of ten patients receiving dicumarol were determined by both the one-stage and the isolation technic. During the first week of therapy there was a discrepancy between the levels obtained by the two technics. After one week of therapy there was an excellent correlation of results, particularly in the therapeutic range where the greatest accuracy is essential. The significance of these findings is discussed.


A case is reported of severe hypoprothrombinemia of unknown cause, accompanied by hemorrhage and terminating fatally.

1. A comparison was made of the changes in prothrombin during clotting, as indicated by the one- and 2-stage methods. 2. By the 2-stage method, progressive disappearance of prothrombin from serum was observed. Prothrombin utilization was slower in human than in dog blood, and was greatly delayed in canine hemophilic blood, platelet-poor human plasma, and in blood clotting in silicone-treated glassware. 3. By the one-stage method, an initial period of hypoactivity in the plasma was followed by a hyperactive phase in the serum. At the peak of hyper-activity, «prothrombin» values were about 180% of the control plasma. In slowly clotting blood, the hyperactive plasma developed less rapidly and persisted for a longer period than in normal blood. The abnormally high prothrombin values in serum obtained by the one-stage test appears to be due to the evolution and persistence of the recently recognized serum factor which accelerates thrombin formation. Apparently this factor does not influence the 2-stage serum prothrombin values.

186 Roller, Physiology and Pathology of Blood Coagulation

This is an excellent summary of the recent developments in our knowledge of the blood coagulation process. Basic factors are considered and interpreted. The relationship between prothrombin, thrombin and the accelerator substances is reviewed in a graphic manner.


A case of true idiopathic hypoprothrombinemia (probably congenital) is reported. Various experiments were performed in order to establish the deficiency as due to prothrombin and not to the known conversion accelerator factors. Plasma adsorbed by barium sulfate was found to be deficient in other substances beside prothrombin.


Correlation between bleeding and prothrombin time is only approximate. Nevertheless, great prothrombin deficiency causes bleeding more frequently than lesser degrees of prothrombin deficiency. Time is an important factor, for patients are much more apt to bleed when prothrombin deficiency has lasted for several days than when it has been present for only about one day.


The authors conclude that prothrombin is promptly utilized or metabolized in the body after injection of prothrombin concentrate, and that the latter is capable of restoring the prothrombin concentration in dicumarolized rabbits to normal.

The determination of the prothrombin time of whole and 12.5 % saline diluted plasma, using rabbit lung thromboplastin and recording results in seconds, is best suited for routine studies of prothrombin activity.


Prothrombin time was determined on 104 samples by a photoelectric technique and also by the one-stage Quick method. The mean of the former was 65 seconds lower than of the latter. By coupling the photoelectric cell of the Coleman spectrophotometer with the first lead of an electrocardiograph, a graphic picture of the clotting reaction is obtained, the resulting curve is caused by the increasing density and decreasing transmission of light at the moment of clotting.


In patients receiving dicumarol the following relationship existed: the rate of degradation of prothrombin converting factor became slower as the prothrombin concentration fell, and the degradation rate was accelerated with the rise of prothrombin concentration.


There are two types of purified prothrombin activators: one type has thromboplastic activity and the second has thromboplastic co-factor activity. Although not too effective separately, together they work rapidly to convert prothrombin. Either activator type can limit thrombin formation experimentally. When both are present in limited quantity, one can increase the rate of prothrombin conversion by addition of thromboplastin or of thromboplastin co-factor. Under these conditions they are quantitatively interchangeable.

Some properties of purified prothrombin and its activation with sodium citrate. Seegers, W.H., R. Mc Claughy, J.S. Fahey. Blood 5, 421 (1950). Dept. of Physiol., Wayne Univ., Detroit, Mich. When examined electrophoretically, prothrombin preparations were found to have 90 % of the protein in one component. The isoelectric point in 1 ionic salt solution is near pH 4.2. By dissolving in approximately 25 ºC concentrated solutions of sodium citrate, purified prothrombin was activated to thrombin. Thrombin thus formed is stable and may be dried from the frozen state, but prothrombin dried in the same manner is unstable; the latter can, however, be dried with acetone.


When hemorrhagic manifestations appear during dicumarol administration, the drug – induced hypoprothrombinemia must be treated immediately; finely dispersed emulsions of vitamin K administered parenterally are advocated in this article.

Corresponding prothrombin determinations by the bedside and one-stage methods were done, using both the same type of thromboplastin as formerly and a newer thromboplastin. With the old thromboplastin the correlation coefficient between the two methods was 810, but with the new type of thromboplastin no direct correlation was observed.

3. Factor V (ac-globulin, labile factor)

Europe:


Two cases of purpura fulminans are described which developed in the course of scarlet fever. One patient died after onset of purpura, the second was saved by exchange transfusion. In the first case factor V was completely lacking in the blood, in the second case factor V was also absent but an antithrombin of the type of heparin antithrombin was found. As far as we know this is the first time such a deficiency of factor V was found in fulminant purpura. In previous observations a considerably prolonged prothrombin time was repeatedly found, which might also be caused by deficiency of factor V.


U.S.A.:


The chemical and/or physical relationship between prothrombin and ac-globulin apparently is very close as evidenced by the inability to denature, adsorb, precipitate or otherwise inactivate completely and at times partially the one, without completely or partially removing or inactivating the other. A method is described whereby oxalated bovine plasma may be rendered free from ac-globulin, but not from prothrombin.


The percentage of labile factor and prothrombin activities and accelerator effect found in serum after completion of the coagulation of blood are in inverse quantitative proportions. A very small percentage of labile factor and prothrombin activity can be found in sera of healthy subjects; in this case high values of accelerator are the rule. Low values of accelerator and a large percentage of prothrombin and labile factor activity are found whenever the formation of thrombin is deficient because of the depletion of either thromboplastin (hemophilia, thrombocytopenic purpura) or prothrombin and labile factor (liver dysfunction). In dicumarol hypoprothrombinemia the available prothrombin is well utilized during coagulation, but in serum the percentage of unconverted labile factor is high and that of the accelerator low.


The authors investigated hemolysis in cases of PNH by complement-antibody reaction. They found that the usual antigen-antibody reaction does not act as complement, but that Seeger’s ac-globulin is the important factor.

If a surplus of thromboplastin and Ca is added to stored oxalated plasma, the prothrombin consumption is low. If one then adds increasing amounts of «labile factor», in the form of diluted, prothrombin-free rat-plasma, the prothrombin consumption rises in corresponding progression. It is therefore assumed that the labile factor as well as thromboplastin and Ca are used in quantitative proportions.

4. Thromboplastin Europe:


Until now the standardization of brain thromboplastin preparations was difficult due to the presence of counteracting substances. Toluidin blue was found to inactivate one of these substances, probably heparin. Another counter-acting substance is removed by keeping thromboplastin at 30° for 80 minutes.


A method is reported to determine the concentration of prothromboplastin in blood.

U.S.A.:


Brain and lung suspensions differ in their influence on blood coagulation (one-stage method). Only brain contains a coagulation delaying substance besides thromboplastin.


5. Platelets

Europe:


Report of 88 cases. Discussion of the disease in general.


Platelet counts (Fonio method) show a regular 24-hour-diagram with a maximum during the day and a minimum during the night. These periodical movements should be taken into consideration in the diagnosis and in judging the effectiveness of therapy.


The extravasal forms of thrombocytes are demonstrated in photographic pictures taken under the electron-microscope.


Based on pictures taken under the electron-microscope, the formation of fibrin, starting from the fibrinogen molecules around the thrombocytes in the normal plasma, is demonstrated.


Starting from clinical observations, which point to the liver as the regulator of the number of thrombocytes in the blood, the authors have found that sodium tauroglycocholate injected i. v. decreases the number of blood platelets in rabbits. Other experiments prove that there is thrombocytoplastic material in the liver. Probably the thrombocytoplastic material is closely related to the active thrombo-plastic factor.


A single dose of ACTH of 25 mg or four divided doses of 6 mg each over a period of 24 hours causes an increase in thrombocytes. The platelet increase is parallel with the one of total leucocytes, whereas the eosinophils and lymphocytes decrease at the same time. These changes were not observed in a patient with Addison’s disease treated similarly.


9 cases of Willebrand’s disease are reported (pseudohemophilia, thrombo-pathia Willebrand-Jurgens).

U.S.A.:


Koller, Physiology and Pathology of Blood Coagulation 191
Atypical secondary or symptomatic thrombocytopenic purpura developing with the use of quinidine sulfate. Collins, D. C. Circulation 2, 438 (1950).

Quinidine sulfate may on rare occasions be the etiologic causative agent of an atypical secondary or symptomatic thrombocytopenic purpura. A case-report of such an occurrence is presented. Three additional case-reports have been collected from the literature.


A patient with thrombocytopenia whose platelets were not only diminished in number but also pathologically damaged, received a blood transfusion from a patient having polycythemia. The platelet count of the latter was about 8 times the normal. The transfused platelets survived and fulfilled their normal physiological functions for 5–6 days. This was proved by the fact that before the transfusion the prothrombin consumption was 0, and after the transfusion it was normal.

After injecting histamin intravenously and after taking several photographs every 3 min. for many hours, the authors concluded that platelets are a natural element of blood and that, when in solution for many hours in contact with glass, they do not change in character.


The electrolytic resistance of the blood clot is markedly reduced in the thrombocytopenic purpura and thrombocytopenia secondary to bone marrow disease as well as in Gaucher's disease.

Following splenectomy for thrombocytopenic purpura, the clot resistance rises and the percentage of clot volume falls in proportion to the rise in platelet count. Although changes in clot resistance occur with marked changes in platelet count and degree of clot retraction, there is no exact correspondence between the level of the platelet count and the clot resistance. This raises questions regarding the functional capacity of platelets to affect clot retraction, or the existence of other factors affecting clot retraction.


In both hemophilic and thrombocytopenic blood the defect of the clotting mechanism reflects a deficiency of active thromboplastin. Addition of thrombocytopenic to hemophilic blood results in a mixture in which the clotting time, clot retraction, prothrombin activity and accelerator effect of serum all become normal.

These findings support the theory that at least two factors are necessary for the formation of active thromboplastin: a plasmatic agent deficient in hemophilia, and a platelet factor defective in thrombocytopenic purpura.


Among 48 human subjects with acute leukemia treated with folic acid antagonists, there were 9 of 25 responding to therapy who had an initial thrombocyto-penia. In 8 cases of acute leukemia there was a return of the platelets to normal levels and the megakaryocytes became more numerous in the bone marrow. In another patient the platelets became elevated to slightly less than normal. The rise in platelets was usually followed by an increase in neutrophilic leucocytes. The regeneration of red cells and hemoglobin gradually responded. The period of remission varied from 21 to 240 days.


Clot retraction is found to depend upon the number of platelets, concentration of thrombin, the surface surrounding the clot, and the cell volume of the blood. The serum expressed from an initial clot contains thrombin and the tendency to thrombosis is aided by continuous formation and retraction of new clots. By reducing formation of thrombin with heparin or dicumarol the likelihood of thrombosis is lessened.

6. Thrombin

U.S.A. and Canada:

When commercial thrombin was incubated with thyrosinase in the presence of phosphate buffer, the blood clotting time was lengthened, showing a marked inactivation of the thrombin.


The authors investigated the possibility of water-soluble vitamins inactivating thrombin. They found that only vitamin C and adermine strongly diminished thrombin activity. When incubated with thrombin, niacin inhibited the clotting ability. While an increase was noted as effect of vitamin C, adermine and vitamin K.


Plasma antithrombin has two separate effects on thrombin. 1. thrombin disposal, determined by finding how much thrombin is left after antithrombin reaction; 2. interference of antithrombin with thrombin – fibrinogen reaction.

(to be continued).