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Fibrinolytic purpura

John B. Maxwell
University of Nebraska Medical Center

FIBRINOLYTIC PURPURA

John B. Maxwell

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I. INTRODUCTION

Recently there has been extensive investigation into a not too common but often fatal hemorrhagic phenomenon which has been observed to be associated with a wide diversity of conditions. It has been observed in such apparently unrelated conditions as abruptio placenta, amniotic fluid embolism, extensive surgery, shock, and cancer (especially cancer of the prostate). The usual laboratory studies of the hemostatic mechanism may show no significant abnormalities. Although normal whole blood when allowed to clot will remain intact in a test tube for days or even weeks, it has been found that blood drawn from patients with this hemorrhagic diathesis will either not coagulate at all, or if a clot forms, will disentegrate and disappear in a matter of hours. It has also been found that the fibrinogen level in the blood of these patients is markedly below the normal level. It has been established that this condition is caused by an upset in a proteolytic enzyme system of the blood with an increase in the activity of the enzyme fibrinolysin, resulting in digestion of not only the fibrin clot, but also fibrinogen, and possibly all protein involved in coagulation. The name "fibrinolytic purpura " has been suggested for this hemorrhagic diathesis. (1)

II. HISTORICAL DEVELOPMENTS

Although most of the discoveries related to the fibrinolytic enzyme system of the blood have been made in the past 50 years, two authors recorded a phenomena, which is directly related, much earlier. In 1769 Morgagni was the first to record an autopsy where the blood was entirely fluid. (2) He thought this was due to dilution by a large quantity of water taken just prior to death. Hunter wrote in 1794, "In many modes of destroying life the blood is deprived of its power of coagulation, as happens in sudden death produced by fits, anger, electricity or lightning, or by a blow in the stomach." (2) The cause of the fluid and incoagulable blood found after certain modes of death was for a long time a matter of much dispute. It was not until 1906 that Morawitz demonstrated that blood from such cases was able to decompose fibrinogen and fibrin. (3)

During the early part of the 20th Century, there were more and more articles reporting the existence of a blood proteolytic enzyme system. In 1893 Lastre observed the phenomenon of clot lysis in dogs who had been bled extensively and gave it the name "fibrinolysis". (4) In 1903, Delezene and Pozerski discovered that normal serum could be rendered proteolytic by treatment with

chloroform. They also observed that serum contains two opposing elements, the chloroform-activated enzyme and an enzyme inhibitor. (4) In 1908 Barker reported that fibrin contained a proteolytic enzyme system and explained his observations on the basis of entrapped mononuclear cells in the fibrin. (5) Jobling and Petersen published a series of articles in 1914 on the nature of the serum anti-enzyme. (5) Abderhalden in 1914 stated that he sometimes found a proteolytic ferment in the sera of guinea pigs and rabbits which he thought was due to the introduction of foreign proteins, such as those due to the ingestion of plants, or to infectious diseases, particularly coccidiosis. (6) Goodpasture in 1914 observed that clotted blood of four patients with atrophic cirrhosis of the liver dissolved within 16 hours when incubated at 37°C, while blood clots of normal persons did not lyse for many days. (7)

In 1918, Yomakawa (6) found that the serum enzyme may be activated in vitro by treatment with organic solvents, such as acetone, alcohols, or chloroform, or by dialysis. He also recognized the presence of an anti-enzyme substance.

Tillett and Garner (8) found, in 1933, that broth cultures of 28 strains of beta hemolytic streptococci, isolated from patients suffering from various manifestat-

ions of streptococcus infections, were able to induce fibrinolysis in normal serum. Plasma of many patients recovered from acute hemolytic streptococcus infections, when clotted in the presence of active cultures, was highly resistant to fibrinolysis. This method of activation has been used subsequently by many other investigators in the study of the serum enzyme.

In 1936 S.S. Yudin described the Russian practice of transfusing with blood obtained from corpses. (9) In this paper stress was laid upon the fact that persons meeting sudden or violent death were particularly useful donors. If in these cases, the blood was withdrawn soon after death, it was found that the blood returned to the fluid state in the course of an hour or two after clotting in the ordinary way, the clots apparently dissolving. Since this fluid blood showed no further tendency to coagulate, the addition of anticoagulants was not required, and it could be preserved in this state almost indefinitely, being used for transfusion when needed. The clot lysis was associated by the Russians with the profound shock experienced before death.

MacFarlane (9) in 1937 observed rapid lysis of clots in 24 out of 29 surgical patients of blood collected immediately postoperatively. He found no rapid lysis in blood collected preoperatively. He stated that exper-

iments suggested that lysis was due to some change in the fibrin, or some substance absorbed by it from the serum, rather than the presence of a free lysin.

In the past 15 or 20 years there have been many reports of the discovery of an increased fibrinolytic activity with or without a bleeding tendency. This has been associated w ith a wide variety of physiologic and pathological conditions. With the frequent report of a high fibrinolytic activity and a low fibrinogen level found in many patients with heretofore unexplainable hemorrhage, the probable etiology, in many of these cases, is fairly well established, and several successful attempts at treatment have been reported.

Even with as much knowledge as has been gained concerning this condition, it apparently is not too well recognized. A recent report describes seven patients with a bleeding tendency of this type, five of which were fatal. No studies for plasma proteolytic activity or hypofibrinogenemia were carried out. (10)

III. FIBRINOLYTIC ENZYME SYSTEM

1. Components:

This system consists of an inert proenzyme, profibrinolysin*, which on occasion may be activated by the kinase fibrinolysokinase, to the active enzyme fibrinolysin**, which in turn may be inactivated by the anti-enzyme antifibrinolysin***. Loomis et al (11) include 2 other factors: 1. antiprofibrinolysin, a naturally occuring plasma or serum compound (s) that blocks conversion of profibrinolysin to fibrinolysin, and 2. antistreptokinase, the naturally occuring plasma or serum compound (s) that may be developed during the immunological response to streptococcal infection and inhibits the particular kinase streptokinase discovered by Tillett and Garner (8). Coon and Hodgson (12) include an antifibrinolysokinase which inhibits fibrinolysokinase shown to be present in serum, certain bacteria, and in the microsome fraction of most animal tissues.

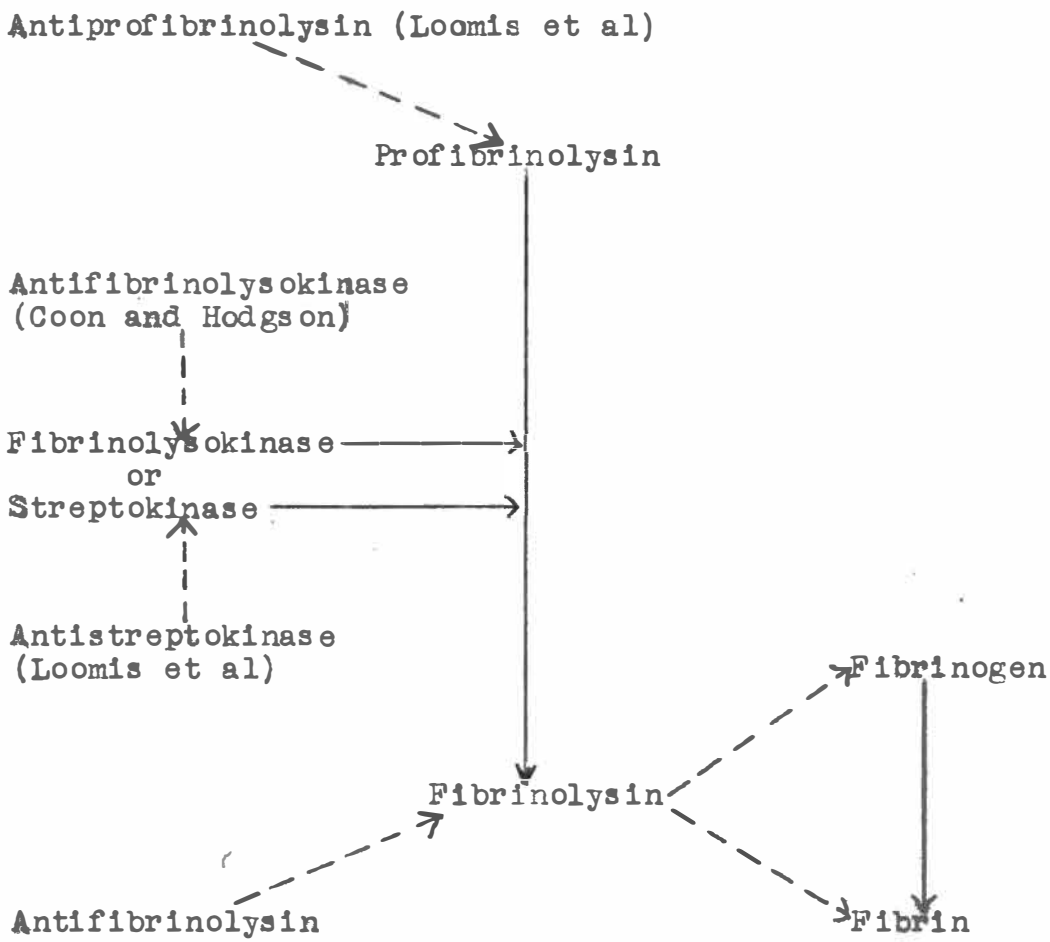
The system is represented diagrammatically in figure I. (Adapted from Coon and Hodgson-12).

* also called plasminogen, serum tryptogen, lytic factor.

** also called plasmin, serum trypsin, serum protease, serum tryptase.

*** also called antiplasmin.

Figure I.


Antiprofibrinolysin (Loomis et al)
Profibrinolysin
Antifibrinolysokinase
(Coon and Hodgson)
Fibrinolysokinase
or
Streptokinase
Antistreptokinase
(Loomis et al)
Fibrinogen
Fibrinolysin
Antifibrinolysin
Fibrin
- - - →Inactivates or digests
——→Activates or forms

2. Description of Components:

Gerheim et al (13) have prepared a purified human profibrinolysin which is nearly 100% pure electrophoreticaly. They found the isoelectric point to be pH 6.1 and found it was a gamma globulin. Other studies by these authors revealed that profibrinolysin contained 13.4% nitrogen, 2.03% carbohydrate, and found 17 amino acids to be present. Permin (14) prepared a rather purified profibrinolysin by separating out the antifibrinolysin by dialysis and then destroying the less stable fibrinolysin by heating to 70°C for five minutes. Most authors agree that profibrinolysin is normally present in serum.

Antifibrinolysin is also normally present in serum associated with the albumin fraction of the plasma according to MacFarlane and Biggs (15). They found inhibitors resembling antifibrinolysin in various tissues, particularly the spleen. There have been no reports of a purified preparation.

Loomis et al (11) have prepared a rather refined fibrinolysin for observation. Their studies showed that fibrinolysin is a euglobulin-water insoluble, saline soluble, non-dialyzable protein enzyme. They state that this enzyme destroys prothrombin, fibrinogen, and fibrin, but does not destroy thrombin. They also found that

fibrinolysin does not clot fibrinogen as some earlier preparations had done. As was stated earlier, Permin (14) found that fibrinolysin is rather unstable and may be destroyed by heating to 70°C for five minutes. MacFarlane and Biggs (15) reported that enzymes resembling fibrinolysin have been found in various tissues, particularly lung and in urine. Huggins and Vail (16) observed that a potent active fibrinolytic agent similar but not identical with plasma fibrinolysin could be isola ted from prostatic fluid.

Some authors believe there are more than one serum protea se. Mole (2) thought that there were at least two distinct serum proteinases as he found that cadaver fibrinolysin proteolysed only fibrin, whereas normal activated serum fibrinolysin proteolysed both fibrinogen and fibrin. Huggins and Vail (16) in studying a potent fibrinolytic agent in prostatic tissue found that dog prostatic fluid destroyed principally fibrinogen while human prostatic fluid destroyed principally fibrin. He used the terms "fibrinogenase" and "fibrinolysin" respectively for these two activities. Results of experiments by Cliffton and Cannemela (17), in using two different potent activators of fibrinolysin, indicate that fibrinogenolytic and fibrinolytic activity may be due to distinct enzymes.

The activating principle, fibrinolysokinase, is not as well understood. Mention has already been made of Tillett and Garner's (8) streptokinase isolated from cultures of certain strains of beta hemolytic streptococci and apparent resistance to it gained by patients recovering from acute streptococcic infections. Cliffton and Cannamela (17) also mentioned a staphylokinase isolated from staphylococci. Coon and Hodgson (12) state that fibrinolysokinase has been shown to be present in serum, certain bacteria, and in the microsome fraction of most animal tissues. Astrup and Permin (18) discovered that animal tissues contained an activator capable of transforming profibrinolysin into fibrinolysin. This activating principle was termed fibrinokinase. The degree of fibrinolysis obtained depended on the organ and the species of animal. The ability of the tissue to activate profibrinolysin was retained undiminished after several weeks in water containing toluene and chloroform as preservatives, and was not dependent on the metabolism of the living cell. It was not found possible to extract the activator from the tissues, but washed suspensions were very active. Astrop and Sterndorf (19) discovered that the fibrinolytic agent in normal urine described by MacFarlane and Biggs (15) is an activator of profibrinolysin rather than the enzyme itself. They

found that the urine activator was completely soluble, while the activator present in the tissues (fibrinokinase) appeared to be bound to the structural proteins. They believe that the urine activator is a physiological fibrinolysokinase chemically different from the fibrinokinase present in tissues.

3. Activation in vivo.

The cause or causes of disturbance in the fibrinolysin- antifibrinolysin balance is essential in understanding the etiology of fibrinolytic purpura. Fibrinolysis has been reported in all degrees of activity, from a normal physiological role, to an increased activity in a wide variety of conditions, to a complete breakdown of the hemostatic mechanism with afibrinogenemia and complete failure to clot.

Most authors have believed that fibrinolysin is not present in normal serum as the active enzyme. MacFarlane and Biggs (20) examined 70 blood samples from 54 normal volunteers and found a weak positive test for fibrinolysis in only one case. Coon and Hodgson (12) state that normal whole blood clots will remain intact in a test tube for days or even weeks. Ratnoff (7) found that normal human blood clots did not

lyse in less than three days, and usually not for at least four days when incubated at 37°C.

Recently, however, others have reported fibrinolytic activity in normal persons. Truelove (21) found that there is progressive diminution of fibrinolytic activity as the interval between collection of the blood and setting up the test is increased. He found that nearly all samples of healthy volunteers at rest show fibrinolytic activity when set up in less than fifteen minutes. Truelove used a more sensitive technique in determining fibrinolytic activity than had been used before. He found that plasma lysed more readily when diluted, and also that thrombin-clotted plasma lysed more readily than that clotted by CaCl. He set up various dilutions of citrated plasma in two sets of three small tubes, the contents of one set being clotted by the addition of thrombin, the other by CaCl, and the tubes incubated for 24 hours at 37°C. He considered it mild fibrinolysis when lysis occured in one or more of the thrombin tubes only, and brisk fibrinolysis when it occured in one or more of the CaCl tubes in addition. Fearnley et al (22) also observed that fibrinolytic activity in the plasma of shed blood falls off with time, the inactivation being in part a function of temperature and of the alkaline shift in pH of shed blood.

Mole (2) believes that fibrinolysin is present normally in the blood stream and presented evidence that endothelium might be the source of fibrinolysin. He suggested that fibrinolysin may have a physiological role if its source is the endothelium. He states, "However much the physical properties of the vascular endothelium make the endothelial surface anti-coagulatory, some deposition of fibrin would be expected. Certainly there is a continual production of fibrinogen by the liver which must involve a continual removal of fibrinogen from the blood stream in some way. Fibrinolysin may therefore be the natural physiological means whereby fibrin deposits are prevented from forming on the vascular endothelium in health."

Astrup and Sterndorff's (19) finding of an activator of fibrinolysin in normal urine suggested to these two authors that the significance of this physiological activator is to keep the urinary system free from harmful effects of clotted blood.

Smith (23) found that normal menstrual discharge contains a fibrinolytic enzyme and also that normal menstruating women had an increased fibrinolytic activity in the circulating blood. He believes that this enzyme may be responsible for the local vascular phenomenon that characterizes menstruation.

The occurance of fibrinolysis in shock was studied by Tagnon et al (25). Of 22 patients studied for fibrinolysis, the following incidence of fibrinolysis was reported:

	No. Of Cases	Fibrinolysis
Burns:		
Shock	3	3
No shock	3	0
Hemorrhagic shock	4	4
Traumatic Injury:		
Shock	1	0
No shock	4	0
"Medical" Shock	7	1

In the three patients with thermal burns in shock the observations on fibrinolysis were repeated over a considerable period of time and it was noted that the fibrinolysis which had been present during the period of shock disappeared after shock had been effectively treated. In addition, hemorrhagic shock was produced experimentally in 13 dogs and fibrinolysis was observed five times. In six dogs with rapid fatal bleeding, fibrinolysis occured three times.

Crosby et al (26) studied the behavior of known clotting mechanisms during febrile reactions following transfusions of compatible whole blood. In addition

to other changes in the coagulation mechanism, it was noted that fibrinogen was halved during the reaction and the fibrinolytic activity became intense. The fibrin in clotted whole blood dissapeared in one hour. Fibrinolysis dissapeared three hours after the chill.

Smith and Smith (27) found that the sera of patients with late toxemia of pregnancy showed a high fibrinolytic activity similar to the normal menstruating women, while normal non-menstruating women and normaly pregnant women showed no activity. They concluded that a factor identical to menstrual "toxin" is present in the circulating blood of menstruating and toxemic women. These observers also have found that there is a stimulation of gonadotropic, as well as adrenotropic hormones, from the pituitary as a part of Selye's "alarm" reaction.

Weiner, Reid, and Roby (28) found that there is as increase fibrinolytic activity in cases of abruptio placenta, and that this increase in activity follows rather than precedes premature separation. Patients with blood loss from incomplete abortion, placenta previa, and post partum hemorrhage from uterine atony were also investigated and found to have normal fibrinogen values and formed normal clots with no increased fibrinolytic activity.

Severe fibrinolysis, in which there has been a hemorrhagic diathesis, has been reported relatively less frequent but still associated with a variety of conditions. There has been some dispute as to the etiology in some cases.

Reid, Weiner, and Roby (29) discovered in a review of the literature that patients with amniotic fluid embolism who survived their initial anaphylactic shock often died a few hours later from post partum hemorrhage. They demonstrated that uncontaminated amniotic fluid collected during labor contained a coagulent that behaved like thromboplastin. Further tests showed that amniotic fluid did not contain fibrinogen, thrombin, prothrombin accelerators, heparin, or fibrinolytic activity. They report a case in a patient with presumptive amniotic fluid infusion, sucessfuly treated by fibrinogen replacement and transfusion, the first to be sucessfuly treated. The tendency toward clot dissolution was particularly prominent in this patient. They observed clot fragmentation at the time when the circulating fibrinogen had been restored to normal limits indicating the presence of a fibrinolysin. They state, "The marked fibrinolytic activity in this instance may well represent the body's reaction to the fibrin

deposition associated with the intravascular clotting precipitated by the thromboplastic action of the amniotic fluid." They believe that a similar mechanism accounts for uncontrolled hemorrhage seen in other obstetrical conditions.

Maloney et al (30) described a case of a hemorrhagic diathesis in pregnancy with premature separation of the placenta. Studies revealed a total lack of fibrinogen and experiments suggested that the lack or destruction of antifibrinolysin was the cause of the afibrinogenemia in this patient. They believe the hemorrhagic tendency in abruptio placenta to be due to activation of fibrinolysis by passage of placental tissue into the circula tion.

Diekman in 1936 (31) in discussing the bleeding tendency associated with abruptio placenta stated that he found subnormal concentrations of fibrinogen in 8 out of 21 cases. He believed the marked decrease in blood fibrinogen was due to actual loss due to hemorrhage and a mobilization of fibrin at the area of placental separation. No studies on fibrinolysin were carried out.

Schneider (32) described 3 cases of severe abruptio placenta in which there was concurrent fibrinopenia. He believed that the fibrinopenia developed secondarily to intravascular fibrin coagulation.. He gave pathological

evidence of intravascular fibrin deposits found in various tissues, especialy the lungs, post mortem. He thought the ultimate causative agent was thromboplastin released by damaged placental tissue.

Stevenson et al (33) described 5 patients with severe abruptio placenta in which there was a hemorrhagic diathesis associated with hypofibrinogenemia. No studies were made of fibrinolytic activity. They believed the depletion of fibrinogen to be due to liberation of thromboplastin into the maternal blood stream from tissues at the abruption site.

Hodgkinson et al (34) also reported a case of abruptio placenta with a hemorrhagic diathesis in which there was hypofibrinogenemia, but no fibrinolytic activity was found. They also believe the hypofibrinogenemia is due to intravascular fibrination, in abruptio. However they found in 2 cases of prolonged retention of a dead fetus in RH isosensitized mothers that there was severe bleeding associated with hypofibrinogenemia and high fibrinolytic activity. They believed the hypofibrinogenemia in the later case was due to fibrinolytic activation.

Recently extensive cancer of the prostate with a bleeding tendency associated with fibrinolysis has been emphasized. Tagnon et al (35) reported 2 patients

with extensive metastatic cancer of the prostate who demonstrated increased fibrinolysis and who subsequently developed a severe hemorrhagic diathesis. Fourteen other patients with this diagnosis were studied with no bleeding tendency and negative tests for fibrinolysis were found. These authors beleived that the cancer itself may have been the source of the enzyme responsible for dissolution of the clot in view of Huggins and Vail's (7) finding of fibrinolysin in prostatic fluid and the absence of shock or state of anoxemia in these 2 patients.

Coon and Hodgson (12) studied 4 patients while in profound shock during cardiac arrest and following resucitation. Each exhibited plasma fibrinolytic activity of varying degrees of intensity and 2 demonstrated the classical picture of fibrinolytic purpura . They associated the fribrinolytic activity with tissue breakdown due to the shock. Patients with extensive cancer of the stomach and bronchogenic carcinoma were also found to have an abnormal but not extremely severe bleeding tendency associated with increased plasma proteolytic activity and decreased plasma fibrinogen levels. They theorized that tissue necrosis, whether it be due to shock, anoxia per se, or cancer, could cause release of of the enzyme activator present in the cell microsome

fraction; this fibrinolysokinase could then convert the precursor to active fibrinolysin. With increasing activation of this enzyme, antifibrinolysin could not antigonize all the fibrinolysin present and fibrin and fibrinogen breakdown would result.

Bennike and Kullertz (36) reported 2 fatal cases of fibrinogenopenia with hemorrhagic diathesis. The first was a cancer of the stomach with metastases. In the second case no definite diagnosis could be established but a marked extramedullary haemopoieses and an aplastic blood picture were conspicuous features. In case 1, an affection of the reticuloendothelial system with a blocking of the formation of fibrinogen (metastatic growth infiltrating lymph nodes, liver, spleen, and bone marrow) was thought to be the cause, no high fibrinolytic activity being found. In case 2 a high fibrinolytic activity was found and thought to be the main cause of the low fibrinogen level.

Ratnoff (37) described a fatal hemorrhagic state associated with excessive fibrinolytic activity in a patient undergoing surgery of cancer of the head of the pancreas.

Friesen and Nelson (10) described massive generalized wound bleeding during operation in 7 cases, 5 of which were fatal. They stated the bleeding, in the

form of an ooze, was refractory to most methods of hemostasis, mechanical and chemical. No studies on fibrinolytic activity were carried out, and they theorized that it might be due to transfusion reactions of the hemolytic type.

4. Activation in vitro:

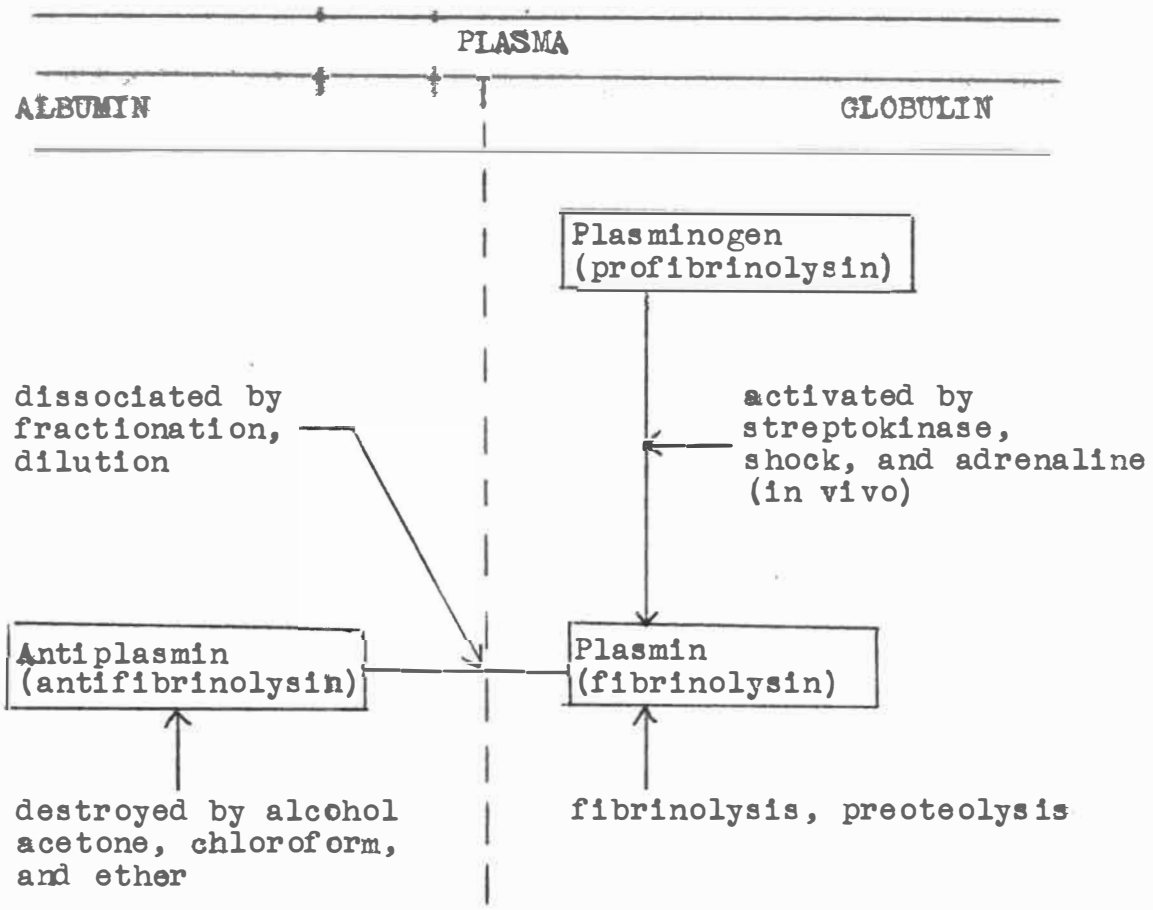
Fibrinolytic activity can be produced in plasma, in vitro, by one of 3 ways; (1) activation of profibrinolysin, (2) destruction of antifibrinolysin, or (3) by separation of the fibrinolysin-antifibrinolysin complex.

Activation of profibrinolysin to fibrinolysin has been carried out in vitro by the action of the exotoxin of certain strains of hemolytic streptococci (8, 11, 15, 17) and staphylococci (17), by tissue preparations (18), particularly lung, heart, kidney, and stoma from erythrocytes (14), by normal urine (19), and by the addition of peptone to serum (38).

Activation of fibrinolysis in serum or plasma with chloroform, alcohol, and acetone has been shown to be due to destruction of antifibrinolysin (8, 15). Yomakawa (16) found that serum protease could be activated by dialysis. MacFarlane and Biggs (15) also found that serum could be activated by separation of the fibrinolysin-antifibrinolysin complex by fractionation. They

summed up the position diagramaticaly as in figure II.

Figure II. (from MacFarlane and Biggs-15)



5. Activation post mortem:

As has already been stated, the observation of incoagulable blood after certain modes of death has been reported for several centuries and has been established as due to fibrinolytic activity. Because of the fluidity of blood after sudden death and the

absence of fibrinolysin after death from infections and cachexia, Mole (12) theorized that this phenomenon was a part of the body's general reaction to injury, there being a failure of this general reaction after protracted illness. Furthermore he found that samples of blood taken from different regions of the body showed a centripetal decrease in activity, limb blood being more active than heart blood. The approximate inverse relationship between the activity of the lysin and the diameter of the vessel from which the sample was obtained suggested that the lysin might be a product of the vascular endothelium. The possible physiological role in preventing fibrin deposition in vessels has already been discussed. Mole further suggested that if one authors finding of "fibrin thrombi on the aortic intima is confirmed and if his interpretation of these thrombi as the initial lesion of atherosclerosis is accepted, there is an obvious connection between the presumptive failure of fibrinolysin to prevent these thrombi and the view that atherosclerosis is in some way the result of a failure of the body's defense mechanisms against the injury caused by the stress and strain of civilized life.

Although Mullertz (3) agreed that a healthy state

of the organism at the moment of death is probably an essential condition for the development of fibrinolytic activity after death, he found that fibrinolytic activity seemed to be related to sudden anoxemia just before death. He thought that under special conditions, anoxemia might produce an increased permeability of the endothelium and thus permit an interaction between profibrinolysin in blood and fibrinokinase in tissue.

6. Relation to histamine:

Because of the presence of an activator in most animal tissues and possible relationship of anaphylaxis and fibrinolysis, it was thought that histamine was the possible activator of fibrinolysin. McIntire et al (39) have shown that homologous antigen will release histamine in vitro or will produce fatal anaphylaxis in vivo without significant activation of fibrinolysin while streptokinase will activate plasma fibrinolysin in vitro and vivo without producing any symptoms of anaphylaxis in vivo or releasing any histamine from the blood cells in vivo. Soicher et al (40) found no significant inhibition of fibrinolysin in vitro by any of eight antihistaminics.

7. Hormonal influences:

Ungar and Damgaard (38), using peptone activated serum and estimating the amount of fibrinolysin and antifibrinolysin with a special method, found that the amount of antifibrinolytic activity in the serum of animals injected with ACTH and cortisone showed a statisticaly highly significant increase. There was no significant increase in four adrenalectomized rats after injection of ACTH showing that the action is mediated through the adrenals. ACTH and cortisone injected in splenectomized animals failed to produce any significant increase in antifibrinolysin. Splenin A injected produced a significant increase in antifibrinolytic activity, the action not being abolished by splenectomy. Splenin B produced the opposite effect. (Splenin A is released into the circulation under influence of the pituitary and adrenal cortex. It decreases capillary permeability, increases capillary resistance, and shortens bleeding time. Splenin B exerts the opposite effect). The authors stated that this action on the antifibrinolytic power of serum appeared to be due to an acceleration of the rate of combination between the enzyme and its inhibitor and not due to an actual increase in antifibrinolysin. The substances concerned act by

catalysing.

Gray and Volkringer (41) found, in contradistinction to Ungar and Damgaard, that their data tended to show that the increased antifibrinolytic activity, observed after administration of certain hormones, is a result of an actual rise in the antifibrinolysin level in the blood, rather than a result of acceleration of combination of the enzyme and inhibitor. They state that the degree of combination between the enzyme and its inhibitor depended on the incubation time and temperature of the reactants. They also found a significant increase in antifibrinolysin titer of blood after administration of ACTH. The injection of thyrotropin and thyroxine also caused elevation of the anti-enzyme titer. They found no significant increase after the injection of cortisone however. Ten days after the removal of the hypophysis or adrenals in rats, the anti-enzyme titer was found to be greatly reduced. Splenectomy did not alter the inhibitor level of plasma. In splenectomized rats ACTH did not produce any change in inhibitor titer, while on the other hand, administration of thyroxine was found to produce an elevation of titer. These authors agreed with Ungar and Damgaard that the influence of the pituitary and adrenals on elevation of the antifibrinolytic level is mediated

through the spleen. (It may be re-emphasized here that MacFarlane and Biggs (15) observed that among all organs the extracts of the spleen had the highest antifibrinolytic activity.) On the other hand, administration of thyroxine to splenectomized rats produced a signigicant elevation of inhibitor titer. Apparently more than one mechanism is involved in the control of the inhibitor level in blood.

Several authors have found that fear, severe exercise, or the injection of adrenalin will cause increase fibrinolytic activity in animals or normal humans. Truelove (21) found that 5 healthy subjects showed increased fibrinolytic activity at 15 and 30 minutes after injection of 1.0 mg adrenaline hydrochloride, but not at 1 hour after injection. MacFarlane and Biggs (15) found that this action of adrenalin can be obtained in the absence of the normal function of the liver, pancreas, spleen, and suprarenal cortex. They also reported in a later article (24) that the addition of adrenaline in vitro to normal blood did not produce fibrinolysis.

IV. DIAGNOSIS AND TREATMENT

1. Diagnosis:

While increased fibrinolytic activity may occur in a wide variety of milder conditions, actual fibrinolytic purpura has been reported only in severer conditions such as surgical, traumatic, or hemorrhagic shock, certain severe obstetrical conditions, and in patients with several types of cancer, particularly cancer of the prostate. In these conditions particularly, should it be suspected in the event of unexplainable bleeding. It should be remembered that it is an acquired condition, and no previous history of bleeding tendency should be expected. It may occur as an uncontrollable ooze from cut surfaces, as a continual vaginal hemorrhage, or spontaneous hemorrhage from the gums and mucus membranes. The two laboratory studies of importance are fibrinolytic activity and fibrinogen level.

Most authors agree that lysis of the clot in less than 24 hours after incubation at 37°C is indication of abnormal fibrinolytic activity. Weiner, Reid, and Roby (28) state that the size and stability of the clot formed by a sample of incubated venous blood is a satisfactory test. In the normal clotting test, the clot that forms is large, binds the majority of red

cells, resists shaking, and is stable after incubation at 37°C for at least 24 hours. When the plasma fibrinogen is less than 50 mg%, initial clotting will occur, but the clot cannot bind red cells and undergoes fragmentation within a few minutes. They believe that if the patient's incubated venous blood clot is stable for 1 hour, enough fibrinogen is present for adequate hemostasis. Another method used by Bennike (36) was described by Permin (14) in the detection of fibrinolysis. A 2-3 mm thick layer of fibrin was prepared in a petri dish from solutions of ox fibrinogen (7ml) and phosphate buffer (pH 6.5, 7 ml) and ox thrombin. On these plates drops of the patients serum are placed and the plates left standing for 24 hours at 39°C. The diameter of dissolved fibrin is then measured.

It seems that Truelove's (21) more sensitive dilution method of determining fibrinolytic activity, which has been discussed, would not be necessary for diagnosis.

The normal value for plasma fibrinogen was found to range from 150-400 mg% by Coon et al (12), most values ranging between 250-300 mg%. Stevenson et al (33) described 10 cases of severe abruptio in which there was hypofibrinogenemia. He stated that those with less than 90 mg% fibrinogen developed a bleeding

tendency. Hodgkinson et al (34) in a study of 3 patients with hypofibrinogenemia with bleeding, found that clots began to appear in one patient when the blood fibrinogen was 78.4 mg% and the bleeding stopped near 100mg%. In another patient clots appeared and bleeding ceased when fibrinogen reached 87.5 mg%. The critical level, below which bleeding occurs, appears to be about 90mg %.

A simplified bedside method for rapid plasma fibrinogen determination has been described recently. (34)

Weiner et al (28) found that there was also a reduction in prothrombin activity in their 4 cases of severe abruptio placenta. This agrees with Loomis' et al (11) finding that fibrinolysin destroys prothrombin. Coon et al (12) also found a depression of prothrombin activity of 30 to 65 per cent by the Quick method, in their cases of cardiac arrest. They state that fibrinolytic destruction of accelerator globulin could produce a change of this magnitude which could not be differentiated by the Quick method from a fall in true prothrombin values.

2. Treatment:

There have been several reports of successful treatment of fibrinolytic purpura. Treatment has consisted of replacement of fibrinogen and other proteins

involved in coagulation which might be proteolysed, attempts at correction of the antifibrinolysin-fibrinolysin imbalance, and treatment of the condition associated with the bleeding tendency.

Maloney et al (30) reported recovery of a patient with severe bleeding associated with abruptio placenta following the administration of large amounts of fibrinogen (as Fraction I Cohn). After the return of clotting time to normal, removal of the uterus was accomplished.

Stevenson et al (33) sucessfully treated 5 cases of abruptio placenta with bleeding tendency with blood transfusions followed by termination of the abruption state through delivery.

Coon and Hodgson (12) controlled the bleeding tendency satisfactorily in 2 patients in profound shock during cardiac arrest and following resucitation, with IV fibrinogen after multiple transfusions (7000-9000 cc of blood)had proved of no benefit. Their source of fibrinogen was antihemophilic globulin.

Reid, Weiner, and Roby (29) reported the 1st case of amniotic fluid infusion to be sucessfuly treated after a bleeding tendency with disolution of clots had appeared. They used fibrinogen replacement and transfusions in their treatment.

Ratnoff (37) transfused a patient with fibrinolytic purpura undergoing surgery for carcinoma of the head of the pancreas with 3000 cc of blood, almost one half the normal circulating blood volume, in an unsuccessful attempt to replace fibrinogen. The fibrinogen level was only 105 mg% immediately after transfusion and only 33 mg% after death.

Weiner et al (34) suggest transfusion of 1500 cc of blood to replace blood loss and increase prothrombin activity plus 2000 to 6000 mg of fibrinogen in the treatment of fibrinolytic purpura.

Hodgkinson et al (34) state that fibrinogen replacement is best accomplished by IV administration of 2000 to 8000 mg of fibrinogen. However fibrinogen is not available commercialy and moreover the virus of infectious hepatitis is concentrated in the fibrinogen fraction making the use of it hazardous. They feel that until preparations of fibrinogen are available commercialy, blood transfusions must be depended on for replacement of fibrinogen. They state that natural regeneration occurs in a matter of a few hours, and it is only necessary to bring the fibrinogen level up to about 100 mg% by transfusion.

Hodgkinson et al (34) also presented some evidence that corticotropin or cortisone may be of value in re-

storing the fibrinolysin-antifibrinolysin equilibrium. Another paper (1) suggests that cortisone and stilbesterol may reduce the activity of fibrinolysin.

V. DISCUSSION

It appears probable that there are a number of factors involved in the mechanism of imbalance of the enzyme-antienzyme system in fibrinolytic purpura. It has been proved in vitro that fibrinolytic activity may be produced either by activation of profibrinolysin to fibrinolysin by the action of tissue kinases, or by destruction of antifibrinolysin.

There is some dispute as to whether increased fibrinolytic activity in vivo is due to an actual rise in fibrinolysin titer or a decrease in antifibrinolysin titer. While most authors seem to assume that the former is true, one author gave evidence that the latter may be true. Ratnoff (42) presented evidence that the speed with which a clot dissolved was related to the deterioration of antifibrinolysin. He found that the concentration of fibrinolysin did not differ between normal persons and those whose clots lysed easily. Furthermore the inhibitory factor of plasma was found to be unstable and deteriorated during incubation at 37°C. Attempts to define the nature of the deterioration were not illuminating, but certain observations suggested that oxidation may be one of the ways that the labile inhibitor is destroyed.

The increase in antifibrinolytic titer obtained by the injection of ACTH, Splenin A, or thyroxin has been discussed. It seems possible that a decrease in antifibrinolytic titer with increase fibrinolytic activity might occur as a result of a reduction in these hormones. Adrenalin is another hormonal regulator, causeing an increase in fibrinolytic activity. The exact mechanism of its action has not been reported, that is whether it causes an actual increase in the enzyme itself or a decrease in the anti-enzyme. It has been shown that it does not activate profibrinolysin to fibrinolysin in vitro and must work through some other unknown factor.

Tissue necrosis or anoxia seems to be another important factor in the etiology of fibrinolytic purpura. The discovery of an activator of profibrinolysin in most animal tissues has led to the theory that tissue damage or destruction, whether due to shock, anoxia per se, trauma, or cancer, may cause absorption of this fibrinokinase into the circulation with subsequent activation of the precursor to active fibrinolysin. It would seem rather paradoxical if nature provided both a coagulant (thromboplastin) and an anticoagulant (fibrinokinase) at the site of an injury, unless the fibrinokinase was absorbed more readily and served to

protect the body from more generalized thrombosis while the thromboplastic activity was localized at the site of injury. In the case of fibrinolytic purpura it is assumed that extensive tissue damage results in the absorption of too much fibrinokinase with the production of more fibrinolysin than can be handled by the anti-enzyme, and fibrin and fibrinogen breakdown results.

In many obstetrical cases, there has been good evidence that the hypofibrinogenemia is the result of intravascular fibrination due to absorption or infusion of thromboplastin at the placental site or in amniotic fluid. High fibrinolytic activity occurs later, if at all, and may only be an additional insult to the bleeding tendency, precipitated by the low fibrinogen level, rather than the actual cause. Some authors believe that the fibrinolytic activity represents the body's reaction to the fibrin deposition precipitated by thromboplastic action. They do not explain the mechanism of this activation, but have found that amniotic fluid does not contain fibrinolytic ativity. However the finding of a high fibrinolytic activity in menstrual discharge, leads one to suspect that uterine tissue may contain a large concentration of the activating factor, and uterine damage may result in absorption of this factor.

Thus it appears likely that there is a normal physiological fibrinolytic activity concerned with the removal of excess fibrinogen and fibrin, not associated with tissue damage. This activity might concievably be hormone regulated. With the occurance of tissue damage, there might be a boost in the fibrinolytic activity from either of two directions; as a result of the release of fibrinokinase from the damaged tissue, or/and a step up in the hormone regulated activity as a part of the general "alarm" reaction. Fibrinolytic purpura may then occur as a result of too extensive tissue damage and/or an abnormaly severe general alarm reaction.

Diagnosis is rather simple if the etiology is suspected in uncontrollable bleeding. A simple bed-side test for fibrinogen level has been reported. A fibrinogen level less than 100 mg % plus the dissolution of the clot in less than 24 hours when incubated at 37°C should establish the diagnosis.

Successful attempts at treatment have been reported, consisting of transfusions, fibrinogen replacement, and the use of ACTH or cortisone. Some authors do not feel that transfusions alone will stop the bleeding tendency, a nd that fibrinogen replacement is essential. Another author believes that since fibrinogen is not available

commercialy, transfusions alone must be depended on to bring the fibrinogen level up above the critical 90-100 mg % level, and that natural regeneration will bring the level up to the normal 250-300 mg% in a few hours.

Experiments have shown that ACTH is probably preferable to cortisone. It is agreed that ACTH causes an increase in antifibrinolytic activity, while there is some dispute as to whether cortisone does. There have been no reports on the use of thyroxine or thyrotropin in the treatment of this disorder, although it has been shown that they also cause an increase in antifibrinolytic activity.

VI. SUMMARY

1. A severe bleeding tendency has been observed associated with a wide variety of conditions including extensive surgery, shock, abruptio placenta, amniotic fluid embolism, and cancer.

2. The cause in most of these cases has been established as due to an upset in a proteolytic fibrinolysin-antifibrinolysin system of the blood, and the hemorrhagic state has been termed "fibrinolytic purpura".

3. It has been shown that animal tissues contain an activator, fibrinokinase, which can convert the proenzyme, profibrinolysin normaly present in blood, to the active enzyme fibrinolysin.

4. It has also been reported that certain hormones injected in animals can cause an increase in fibrinolysin or antifibrinolysin. Adrenalin causes an increase in fibrinolytic activity. ACTH and possibly cortisone cause an increase in antifibrinolysin, the mechanism involving the spleen and the release of splenin A. Thyrotropin or thyroxin also cause an increase in antifibrinolysin, the mechanism not being mediated through the spleen.

5. It is thought that the severe fibrinolytic activity seen in fibrinolytic purpura is due to the

release of fibrinolysokinase in tissue as the result of tissue damage from trauma, or anoxia, or associated with the body's general reaction to injury as the initial phase of Selye's alarm reaction. Possibly both of these factors and more are concerned.

6. Diagnosis is based on the finding of low blood fibrinogen level and lysis of clotted venous blood when incubated.

7. Treatment has been successfuly carried out recently, and has consisted of blood and protein replacement through transfusion, administration of large amounts of fibrinogen, and decreasing fibrinolytic activity by the administration of ACTH or cortisone.

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