Prevention of Thromboplastin-induced Thrombosis in Rabbits by Means of Plasmin

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Thrombi produced artificially in animals have been successfully treated with the fibrinolytic enzyme, plasmin (10, 22). By direct observation rapid lysis of the thrombus was seen and recanalization of the thrombosed vessels was found in most instances. These experiments were done on isolated segments of the vessels in the periphery of the animals.

Intravascular coagulation in the large central vessels and in the heart can be produced by injection of thromboplastin (6, 11). Death follows immediately after the formation of the thrombus.

It is the purpose of this paper to study the effect of plasmin on fatal intravascular thrombosis produced by injection of large doses of thromboplastin.

Materials and Methods

The *proteolytic enzyme* in blood, plasmin, is formed by activation of its precursor, plasminogen. This activation can be effected by several activators (2). The presence of an activator of plasminogen has been demonstrated in human urine (5). By activating human plasminogen with human urine activator a plasmin preparation is produced which contains only components of human origin (22).

Plasminogen was prepared from human serum by diluting twenty times with distilled water and precipitating the globulin by adding a 1 per cent solution of acetic acid to pH 5.3. After standing for 24 hours at $4°$, the precipitate was dissolved in 0.9 per cent NaCl to a volume equal to $^1/_5$ of the original serum volume and adjusted to pH 7.4 by 0.15 n NaOH. Lyophilized serum preparations or serum obtained from pooled bank blood by recalcification were used.

The *urine activator of plasminogen* was prepared from fresh human urine by precipitating with 3 volumes of ice-cold 96 per cent ethanol. The precipitate was dissolved in 0.9 per cent

NaCl to $^{1}/_{10}$ of the original urine volume and dialyzed overnight against 0.9 per cent NaCl. After centrifugation the supernatant fluid, which contains the urine activator, was lyophilized (5). A highly purified urine activator preparation (17) was kindly supplied by Løvens Kemiske Fabrik, Copenhagen, and this activator was used in the latter part of the investigation.

Since the strength of our activator preparations varied, the activities of the different samples were compared with a potent and stable urine activator preparation (from Løvens Kemiske Fabrik), which served as an arbitrary standard. The fibrin plate method was used for comparing the strength of the samples (4). The minimum amount of the stable urine activator standard necessary for the maximum production of plasmin was determined, and the amounts of the different urine activator preparations were used in accordance with this estimation.

Plasmin was prepared by a modification of the method described by M ü l l e r t z (14). To solutions of human globulin in phosphate buffer (0.1 m, pH 7.6), urine activator dissolved in phosphate buffer was added. After 15 minutes incubation at 37° the mixture was adjusted to pH 1.8 with 0.15 n HCl and immersed in water at 56° for 15 minutes, cooled and neutralized to pH 7.65. By this heating procedure a blood clotting substance, occasionally present in the human globulin, was destroyed. Denatured protein was removed by centrifuging and the proteolytic activity estimated by casein digestion. The increase in optical density (at 275 mμ) of the deproteinized casein solution digested by plasmin is a measure of the strength of the enzyme (M ü l l e r t z [14]). The readings were performed on a Hilger Uvispek spectrophotometer. The solutions used in the experiments were adjusted according to the activity estimated on the standard casein solution. The potency of the preparations varied between 85 and 125 per cent of the value chosen for comparison (optical density 0.300).

Inactive plasmin, used in the control experiments, was produced as described above for active plasmin. The plasmin, after adjustment to pH 7.65, was immersed in boiling water for 15 minutes, cooled and centrifuged. At 100° and pH 7.65 all plasmin was destroyed and this product could neither digest casein nor split fibrin on the heated fibrin plates.

Thromboplastin was prepared from human brain tissue after removing the meninges and superficial vessels (16). The tissue was macerated and a saline emulsion made, which was kept in a refrigerator for 24 hours. The emulsion was centrifuged and the supernatant used as a stock solution of thromboplastin. This stock solution was diluted with 0.9 per cent NaCl to a concentration giving the shortest coagulation time with normal human oxalated plasma as estimated by Owren's prothrombin-proconvertin method. The thromboplastin solution, so produced, was tested on anesthetized rabbits and the minimal amount of a certain thromboplastin batch which would kill the animals by massive coagulation of the blood in the heart and/or the pulmonary arteries was established. The thromboplastin solution decreased in potency with time, and the minimal lethal dose was increased accordingly.

The *injection procedure* of thromboplastin is of importance (6). By rapid injections of the thromboplastin (1—4 seconds) death followed in 1—2 minutes, but by slow injection no fatalities occurred. Rapid administration of thromboplastin was performed through a glass cannula in the jugular vein.

The *fibrinolytic activity of the blood* was estimated after diluting the oxalated blood plasma 10 times and precipitating at pH 5.3 by the addition of acetic acid. The resulting globulin fraction was redissolved in phosphate buffer (pH 7.65) to half of the original plasma volume. The fibrinolytic activity in this solution was then estimated on heated fibrin plates (12).

The *relative fibrinogen concentration* in the blood was measured by the rapid method of Schneider (20). Clot formation in diluted plasma 1/1 to 1/560 in Ringer solution) after addition of thrombin (bovine thrombin, Løvens Kemiske Fabrik, 25—30 units/ml) was compared with clot formation in dilutions of normal rabbit plasma, usually blood plasma taken from the rabbit before the experiment. After estimation of the relative fibrinogen concentration the tubes were stored at 37° for 24 hours and the occurrence of lysis in the tubes followed.

The *prothrombin-proconvertin concentration* was followed by the one-stage assay of Owren. Standard dilution curves were prepared with pooled normal rabbit plasma.

The *whole-blood clotting* time was estimated in the capillary glass tubes. The tubes filled with whole blood, and small pieces of the glass tubes were broken every 30 seconds. The appearance of a red thread indicates that clotting has taken place (18).

In some experiments the dilution of the blood after the injection of solutions of plasmin or inactive plasmin was followed by means of the Hamburger hematocrit value (7). *Proteolytic inhibitors* in rabbit's blood were examined in a few experiments. The inhibitors were estimated on heated plates against plasmin and/or trypsin. The stock solution containing 0.25 mg crystalline trypsin/ml in 1/40 n HCl was diluted to 1/10 in barbital buffer (pH 7.8).

Rabbits weighing about 2—3 kg were used. The animals were anesthetized by intraperitoneal injection of Nembutal sodium (30 mg per kg body weight). The skin in front of the neck was infiltrated with a local anesthetic (0.5 per cent Leostesin-adrenalin) and a median incision was performed. The right external jugular vein and the carotid artery were isolated and a glass cannula inserted. Blood samples for the above mentioned tests were withdrawn from the carotid artery prior to the injection of plasmin, inactive plasmin, or thromboplastin into the vein.

Solutions of plasmin or of inactive plasmin were injected slowly during one to two minutes. The amount of plasmin-solution administered (10—15 ml/kg) depended on the proteolytic strength of the preparation. The amount of inactive plasmin administered to the control animals was equal to the amount of active plasmin (in ml) used in the experimental animals, so that the dilution of the rabbit blood was the same in corresponding experiments.

During the experiments the blood was frequently tested by withdrawing oxalated blood samples (one volume of 2 per cent potassium oxalate to 9 volumes of blood). The rapid injection of thromboplastin (1—4 seconds) was performed at different intervals after the injection of plasmin or inactive plasmin (see below). The animals which survived the thromboplastin injection were usually sacrificed half an hour after the thromboplastin administration and examined by autopsy.

Experiments

1. *Plasmin Experiments:* In order to test the efficiency of plasmin in preventing the fatal effects of rapid intravenous administration of thromboplastin, the rabbits were divided into several groups.

In the first group (three animals) the fibrinolytic activity in the blood after a single injection of plasmin was examined. Results of this experiment indicated that the peak of fibrinolytic activity was found in the first few minutes after the plasmin administration (fig. 1). For five minutes a reasonable activity was still present, but then the activity decreased and after 25—45 minutes no fibrinolytic activity was measurable on the heated fibrin plates. Slight dyspnoea was found immediately after the injections, but this was the only reaction seen. There was no oozing from the wound.

In order to detect a possible protective effect of plasmin on animals which had received a previous lethal dose of thromboplastin, the following experiment was performed. Four animals were rapidly given 1 ml/kg thromboplastin solution followed immediately by 10 ml/kg of plasmin solution. Three of the animals died from intracardial or pulmonary thrombosis, which occurred in spite of the plasmin subsequently injected. Only one animal survived and this was probably due either to a too small thromboplastin dose or too slow injection, since the animal did not respond with severe dyspnoea and convulsions immediately after the injection.
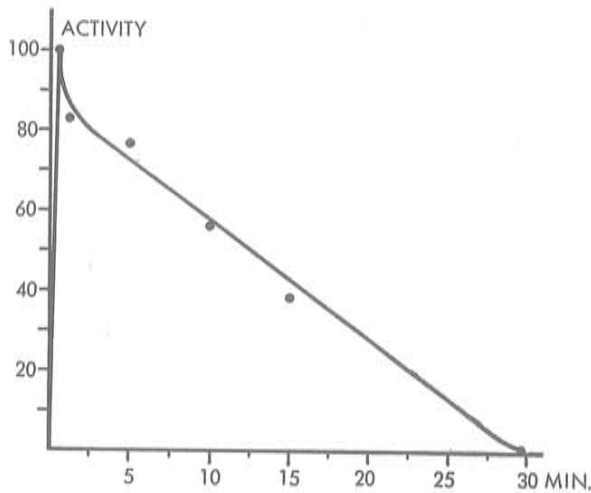

F i g . 1 : Fibrinolytic activity in the blood after a single plasmin injection.
Abscissa: Time in minutes.   Ordinate: Activity in percentage of maximum activity.

The occurrence of intravascular coagulation in blood containing active plasmin was next examined. These experiments were performed on 16 rabbits (table 1). Five to six minutes after the plasmin was given, thromboplastin was rapidly injected. Seven of the animals reacted to the thromboplastin with increased respiration and convulsions. In nine no reaction was seen.

One of the animals (no. 11) died four minutes after the thromboplastin administration. At autopsy there was no intravascular coagulation either in the heart or the pulmonary vessels. The brain was not examined. Only one of the animals reacted in the same way as most of the control animals (see below), i.e., with severe dyspnoea and convulsions. This animal (no. 12) died from an occluding pulmonary thrombus. Two animals (no. 1 and 5) died 90 and 30 minutes

respectively after the thromboplastin injection. The cause of death was in these cases an accidental bleeding from a ruptured carotid artery. A coagulum was found in the right auricle at autopsy in no. 1. In no. 5, lung-infarctions were found.

Table 1

No.	kg.	Plasmin ml.	Thrombopl. ml.	Reaction	Time Cause of Death	Autopsy
1	2	20	4	dyspn. + convl.	90 min. (bleeding)	small coagulum right auricle
2	2.1	27	3.2	no	60 min. (sacrificed)	small lung-infarctions
3	2.2	20	2	no	24 hours (sacrificed)	embolus in a. pulm. from thrombosed jugul. vein. Small lung-infarct.
						infarct. left lower lobe
4	2.3	30	2.7	no	30 min. (sacrificed)	small thrombi in cerebrum
5	2.4	25	2.5	no	30 min. (bleeding)	small lung-infarctions
6	2.5	33	3.8	dyspnoea	60 min. (sacrificed)	small lung-infarctions
7	2.5	33	3.8	no	60 min. (sacrificed)	small lung-infarctions
8	2.6	30	5	no	30 min. (sacrificed)	infarct. right lower lobe,
9	3	39	4.5	no	30 min. (sacrificed)	small infarct. right lung + small brain thrombi
10	3	30	5	dyspn. + convl.	30 min. (sacrificed)	no intracardial or pulmonal thrombosis
11	3	20	7	dyspn. + convl.	4 min. unknown	no intracardial or pulmonal thrombosis (cerebral thrombosis?)
12	3	30	3	severe dyspnoea and convulsions	3 min. pulm. thromb.	occluding thrombi in both pulmonary art.
13	3.2	30	3	light dyspnoea	30 min. (sacrificed)	small thrombi in brain
14	3.5	32	5	no	30 min. (sacrificed)	small lung-infarctions
15	4	52	6	no	30 min. (sacrificed)	small lung-infarctions
16	4	40	4	dyspn. + convl.	5 hours (sacrificed)	small lung-infarctions 5 mm thrombus in right pulm. art. Clot in right ventricle

The other animals — twelve in number — survived the thromboplastin administration and were sacrificed. The autopsy revealed small thrombi either in the pulmonary vessels or in the heart. Also in vessels of the brain thrombi were occasionally found. In rabbit no. 3 a Y-shaped embolus was found in the main stem of the pulmonary artery. This embolus was probably dislodged from the ligated jugular vein immediately before the animal was sacrificed 24 hours after the experiment (thromboplastin-injection). The embolus did not occlude the pulmonary artery completely.

2. *Control Experiments.* Control experiments were performed on 18 other animals (table 2).

Table 2

No.	kg.	Inac. Plasmin ml.	Thrombopl. ml.	Reaction dyspn. + convl.	Time		Cause of Death	Autopsy
1	1.9	25	2.9	dyspn. + convl.	¹/₂ min.		thrombosis	massive intracardial thrombosis + a. pulm. and cerebral thrombosis
2	2	20	2	dyspnoea	30	min.	sacrificed	small thrombi in cerebral vessels
3	2	20	2	dyspnoea	25	min.	sacrificed	small lung infarctions
4	2.1	27	3.2	dyspn. + convl.	1³/₄ min.		thrombosis	massive intracardial coagulation
5	2.2	28	2.6	dyspn. + convl.	20	min.	sacrificed	thrombosis in heart, kidney, and brain
6	2.5	33	3.8	dyspn. + convl.	1¹/₄ min.		thrombosis	thrombosis in heart, lung, and brain
7	2.5	33	3.8	dyspn. + convl.	1³/₄ min.		thrombosis	thrombosis in heart, lung, and brain
8	2.5	20	5	dyspn. + convl.	2	min.	thrombosis	thrombosis in pulm. artery
9	2.5	20	4	dyspn. + convl.	2	min.	thrombosis	thrombosis in pulm. artery
10	2.6	34	3	dyspn. + convl.	1	min.	thrombosis	thrombosis in heart and pulm. art.
11	2.7	27	2.7	dyspn. + convl.	30	min.	sacrificed	small infarct. in pulm. brain and kidney
12	2.8	28	2.8	dyspn. + convl.	1¹/₂ min.		thrombosis	massive thrombosis in heart, pulm. art., aorta, and brain vessels
13	3	30	3	dyspn. + convl.	3	min.	thrombosis	thrombosis in pulm. artery
14	3	30	3	dyspn. + convl.	30	min.	sacrificed	thrombosis in brain vessels
15	3	20	5	dyspn. + convl.	1¹/₂ min.		thrombosis	thrombosis in pulm. artery
16	3.5	35	3.5	dyspn. + convl.	1	min.	thrombosis	thrombosis in heart, and pulm. art.
17	4.5	45	4.5	dyspn. + convl.	1	min.	thrombosis	thrombosis in pulm. artery
18	4.8	48	4.8	dyspn. + convl.	30	min.	sacrificed	small lung infarctions and small thrombi in pulm. art. and brain vessels

Inactive plasmin was injected in the same way as active plasmin. The *thromboplastin* injection followed 5—6 minutes later. Twelve of the animals died 1—2 minutes after the thromboplastin injection. At autopsy massive intravascular coagulation (thrombosis) was found either in the right side of the heart, in the pulmonary arteries or in the vessels at the base of the brain.

Six rabbits survived the thromboplastin injection and were sacrificed. At autopsy intravascular coagulation was also found in these animals (see table 2).

All the control rabbits reacted to the thromboplastin administration with severe dyspnoea and convulsions.

3. *The Fibrinolytic Activity in the Blood.* In all the experiments the fibrinolytic activity in the blood was estimated in the isoelectrically precipitated plasma globulin by the heated fibrin plate method as described above. In some experiments the lysis of diluted plasma clots (modified tube test) also was investigated.

Spontaneous fibrinolytic activity was found in the blood in only one animal of the treated group (no. 11, table 1). In all other animals no activity was recorded in blood samples taken before the plasmin injection.

After the maximum fibrinolytic activity following the plasmin administration the activity decreased. In five of the animals there was a gradual decrease similar to that found in the preliminary experiments with plasmin injection alone (see fig. 1). However, in 10 of the animals a second "peak of activity" occurred 5—15 minutes after the thromboplastin administration (fig. 2), and in an additional animal the same level of fibrinolytic activity continued for 15 minutes.
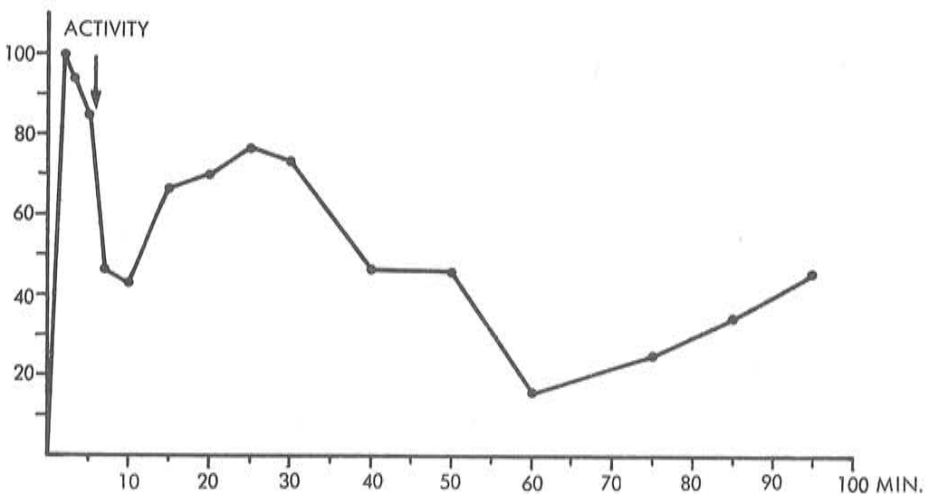

F i g . 2 : Thromboplastin administration (arrow) during plasmin treatment.
Abscissa: Time in minutes.   *Ordinate:* Fibrinolytic activity in percentage of maximum activity.

Immediately after the injection of thromboplastin a steep fall in the fibrinolytic activity was found in three animals. One of these animals (no. 11) died a few minutes later. The remaining two showed an increased fibrinolytic activity after 10 minutes.

After 30 minutes or more, fibrinolytic activity was observed in twelve of the animals. In three cases all activity had disappeared after 20 to 25 minutes. One of the rabbits, which died from thromboplastin injection (no. 12), suffered from severe intravascular coagulation (pulmonary thrombosis) in spite of rather pronounced fibrinolytic activity in the blood at the moment of death. The other plasmin-treated animal that died showed no fibrinolysis after the thromboplastin administration. Fibrinolysis of the coagulum in the tube test was examined in 8 cases. Although fibrinolysis occurred on the heated fibrin in all cases, only in one of them fibrinolysis was found.

Spontaneus fibrinolytic activity was found in two of the control animals (no. 2 and 9, Table 2). After the administration of inactive plasmin a lytic activity (as measured on the heated fibrin) was found in 10 cases. This could be caused by activation of the plasminogen in the rabbits' blood with the urine activator, which is not destroyed completely by the previous treatment.

To confirm this, a solution of the urine activator in the same concentration as used in the activation mixture was given to 3 animals. Although fibrinolytic activity was found in all three cases when blood samples were tested on the heated fibrin, the fibrinolytic activity obtained did not prevent death from intravascular coagulation following injection of thromboplastin. Fibrinolysis in the tubes was found in three of the eleven control animals examined.

Although fibrinolytic activity of the isoelectrically precipitated globulin was found on the heated fibrin in all the plasmintreated animals, lysis of the coagulum as measured by the tube test was seen only once. To explain these discrepancies the rabbit plasma was examined for inhibitory agents against proteolytic enzymes.

Mixtures of plasma from one of the plasmin-treated animals and undiluted plasmin solution were made and the fibrinolytic activity tested on heated plates. No lysis occurred. When the plasma was diluted 1 : 1 with barbital buffer and mixed with plasmin, some lytic activity was found. Similar results were obtained in plasma-trypsin mixtures. The presence of a potent inhibitor against proteolytic enzymes in the rabbit plasma was confirmed.

4. *Coagulability of the Blood During the Experiments.* The initial prothrombin-proconvertin (p-p) determination showed normal values (range 90—140 per cent) in 12 of the plasmin-treated rabbits, moderately decreased concentration (range 70—80 per cent) in 3 rabbits and a low value (46 per cent) in one rabbit. Among the rabbits in the control group, normal prothrombin-proconvertin concentration was found in 10 rabbits (range 90—120 per cent) and values between 70 and 80 per cent in 7 animals.

During the experiments the prothrombin-proconvertin concentration was nearly constant in eight of the plasmin-treated animals. A moderate decrease in p-p concentration occurred in 5 cases. A slight decrease in p-p concentration immediately after the plasmin injection and before the thromboplastin injection corresponds approximately to the increase in plasma volume (measured by the Hamburger hematocrit) caused by the plasmin solution (fig. 3).

Although the prothrombin-proconvertin concentration decreased in 7 cases, the whole-blood coagulation time increased in only 2 of these animals (no. 1 and 4). An increased coagulation time was also found in four cases among the nine animals with normal and constant p-p values. In two of these cases the coagulation time was more than 30 minutes. These changes in coagulability

occurred in 4 cases after the thromboplastin administration and in 2 cases immediately after the plasmin injection.
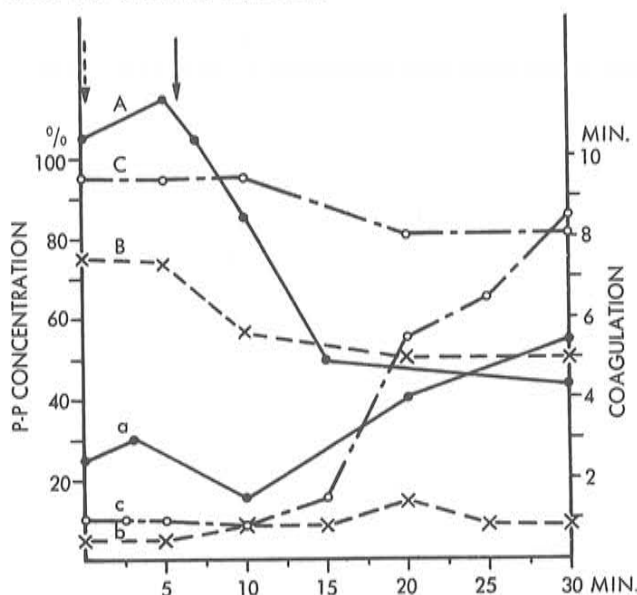

F i g . 3 : Correlation between p-p concentration and whole-blood coagulation time during plasmin treatment (broken arrow) and after thromboplastin administration (arrow).
Abscissa: Time in minutes.   *Ordinate:* p-p concentration and coagulation time in minutes.
A, B, C: Examples of changes in the p-p concentration during experiment.
a, b, c: Examples of changing coagulation time in the same animals as A, B, C during experiment.

In the control group the p-p concentration and the coagulation time could not be followed for any length of time, since most of the animals died a few minutes after the thromboplastin injection. However, a constant p-p concentration was found in 12 of the animals after inactive plasmin administration, and only in 5 cases a moderate fall was recorded. These findings are similar to those in the plasmin group as a fall in the p-p concentration occurred in four cases after the plasmin injection.

In one of the six control animals which survived the thromboplastin injection, the collecting of blood samples failed. The remaining five showed a moderate decrease in the p-p concentration before and after the thromboplastin was injected. The coagulation time was found unchanged and normal in all control rabbits until the thromboplastin administration. Three of the surviving animals showed increased coagulation time (more than 30 minutes) and a fall in the p-p concentration after thromboplastin injection.

The influence on the plasma volume of the plasmin and inactive plasmin was tested on 8 of the plasmin-treated animals and on 13 of the control animals.

An initial normal blood cell volume was found in all but two cases of the plasmin group. One animal in the plasmin group showed increased cell volume and another a rather pronounced decrease in cell volume. These findings correspond approximately to the calculated increase in the rabbits' plasma produced by the fluids administered. However, the dilution of the plasma was not so considerable that a coagulation of the blood was prevented. During the experiments a further increase in the plasma volume was found in four plasmin-treated animals and in four of the control animals which survived the injection of thromboplastin. This was probably due to osmotic action of the hypertonic protein solutions administered (active and inactive plasmin).

The relative fibrinogen concentration in the rabbits' blood was followed by the S c h n e i d e r test for fibrinogen determination. The test was performed on 7 animals of the plasmin-treated group and on 11 of the control group. One in the former group showed a slight decrease in fibrinogen concentration but all others remained unchanged. Similar results were obtained from the control group in blood samples taken before death. But in 7 of the control animals who died immediately after thromboplastin injection, no fibrinogen was found in the blood samples from the inferior cava vein collected at autopsy. Two of those which survived showed only a slight decrease in the fibrinogen concentration at post mortem examination.

5. *Maintenance of the Fibrinolytic Activity.* The effect of a second plasmin administration on the plasmin concentration was also examined (in 6 animals). After the usual plasmin administration, fibrinolytic activity was found
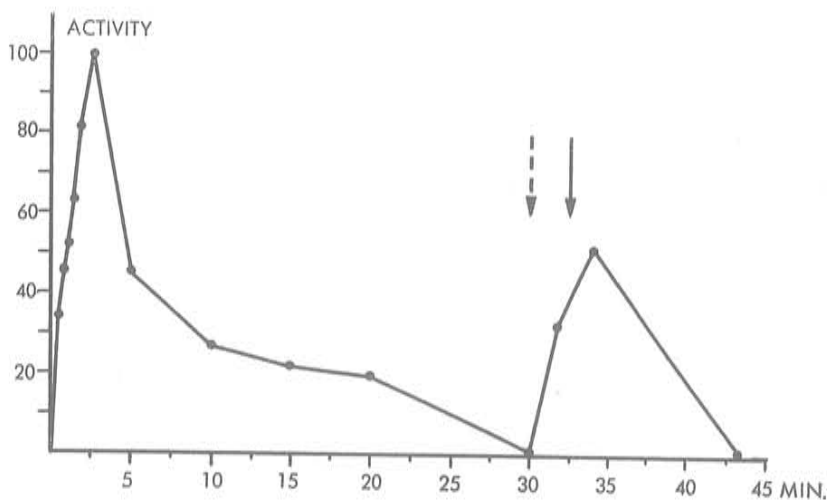

F i g . 4 : Effect of the second plasmin injection (broken arrow) during plasmin treatment.
Thromboplastin injection at arrow.
Abscissa: Time in minutes.   *Ordinate:* Fibrinolytic activity.

in all cases as expected. This activity decreased gradually in the following
30—45 minutes except in one case where no activity could be found after
5 minutes. After the second plasmin injection ($^1/_3$ of the initial amount of
plasmin) a new peak of fibrinolytic actvity occurred in four of the animals
(fig. 4), but no activity was found in the two others. The second administration
was given 30 minutes after the first plasmin injection. One of the rabbits died
from intracardial coagulation shortly after the thromboplastin administration
although a rather pronounced fibrinolytic activity was present at that time.
The remaining 5 animals survived. This includes two animals where no increase
in the plasmin concentration after the second injection of plasmin was demon-
strated on the heated fibrin.

Discussion

The attempt to treat massive intravascular coagulation of the blood (throm-
bosis) by administration of the fibrinolytic enzyme plasmin immediately after
the coagulum was formed (by thromboplastin) failed. The extensive thrombosis
in the heart or pulmonary artery stops the circulation so that contact between
the plasmin and the interior of the blood clot is hindered.

If a certain amount of plasmin is present in the blood at the time of
thromboplastin injection, fatalities seem to be prevented in nearly all cases,
although coagulation in the blood stream is not completely inhibited, since lung
infarctions and other forms of vascular thrombosis were found at autopsy.

Control experiments, where inactive plasmin was used instead of the active
enzyme, indicate that the dilution of plasma by the protein-rich fluids adminis-
tered is not the reason for the different results observed in the treated and
control animals. When intravascular coagulation occurs the plasmin present is
absorbed on the fibrin formed (19, 15, 23). This may explain in the rapid decrease
in the circulating plasmin found after thromboplastin administration as esti-
mated on the heated fibrin. The second peak in activity found is possibly caused
by liberation of plasmin when fibrinolysis proceeds and the coagulum is
destroyed. A certain concentration of plasmin in the blood is probably necessary
to produce thrombolysis. However, in the series with a second injection of
plasmin followed by thromboplastin, fatalities occurred only in one case (in
which fibrinolytic activity was demonstrable) although fibrinolytic activity was
absent in two other cases. An attempt to activate the rabbits' own plasminogen
by means of the urine activator failed in so far as the fibrinolytic activity
obtained (as measured on heated plates) was not sufficient to protect the animal
against intravascular coagulation.

Spontaneous fibrinolytic activity — as seen in control rabbit no. 2 — may be of major importance in the prevention of thrombosis, and this may explain why one of the control animals survived.

Spontaneous fibrinolytic activity in blood has been reported in several cases in the clinic (for references see 1, 8 and 9) and death from bleeding and incoagulability of the blood was found in these patients. However, no oozing of blood from the wounds or defibrinogenation of the blood have been recorded among the plasmin-treated animals. The increase in coagulation time found in both groups was probably caused by the thromboplastin administered (2, 6) and not a result of the plasmin or inactive plasmin given.

In human beings fibrinolysis has been produced by intravenous infusion of streptokinase alone (24). However, this was accompanied by side-effects prob-ably caused by impurities in the preparations used or due to hypersensitivity in the human organism to products from haemolytic streptococci. In the blood of rabbits very little plasminogen is present (3) and therefore the effect of the urine activator is limited. The inhibitors present also play an important rôle in preventing the activation of plasminogen and the action of plasmin. Plasmin in excess must therefore be used.

Summary

1. By administration to rabbits of plasmin produced by activation of human plasminogen with human urine activator, fibrinolysis in the blood was obtained without observable side effects.

2. A single injection of plasmin protects the animals from a fatal intra-vascular coagulation produced by a subsequent thromboplastin administration. Among the control animals treated with inactive plasmin, 2/3 of the animals died from pulmonary thrombosis or massive intracardial coagulation of the blood.

Résumé

1) L'administration de plasmine obtenue par activation de plasminogène humain avec l'activateur isolé de l'urine humaine provoque une fibrinolyse chez le lapin sans autre effet secondaire.

2) Une seule injection protège l'animal contre l'injection intravasculaire habituellement mortelle de thromboplastine. Deux tiers des animaux de contrôle, traités avec de la plasmine inactive, sont morts suite à une thrombose pulmonaire ou coagulation intracardiaque massive.

Zusammenfassung

1. Menschliches Plasminogen wurde durch Urinaktivator vom Menschen zu Plasmin aktiviert. Dieses verursachte bei Kaninchen Fibrinolyse ohne nachweisbare Nebenerscheinungen.

2. Eine Plasmininjektion schützt die Tiere vor einer intravasalen Gerinnung, die durch eine nachfolgende Thrombokinaseinjektion ausgelöst wurde. Von den Kontrolltieren, die mit inaktivem Plasmin behandelt wurden, starben zwei Drittel an Lungenembolie oder massiver intrakardialer Gerinnung.

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