The Lysis of Intravascular Thrombi in Rabbits with Human Plasmin (Fibrinolysin)

By Carlo E. Grossi, M.D., Eugene E. Cliffton, M.D., and Dolly A. Cannamela, B.A.

THROMBOPHLEBITIS and phlebothrombosis with their complications, including pulmonary embolus, remain one of the serious problems of surgery. According to recent reports, using postmortem statistics, their incidence has not been significantly reduced, despite conservative and surgical measures.

With the demonstration of the use of streptokinase-streptodornase and trypsin in the lysis of hematomas and purulent exudates, attempts have been made in experimental animals and in patients to produce lysis of intravascular clots using these materials.

Streptokinase produces its lytic effect by activation of a profibrinolysin usually called plasminogen. Many attempts have been made to isolate this latter material for investigation without consistent success. A new method for preparation of this material (plasminogen) has recently been reported. In vivo studies of activated plasminogen (plasmin) in dogs and rabbits have indicated that it is nontoxic and that it effects a marked increase in the lytic activity of the plasma.

The present study was undertaken to establish the effect of this material (human plasmin) on intravascular clots. Thromboses in the marginal veins of the rabbit ear have been a favorite medium for testing the effect of lytic agents. The experience of others, with this method, has served as a basis for further study.

To study the effect of plasmin on thrombi in vivo, it was first necessary to produce them in a standard fashion. Jacques has pointed out the difficulty of producing thrombosis in normal animals. It has been shown that isolation between ligatures of a stationary column of blood in a vein would produce small nonadherent thrombi. Thrombosis has been produced by the injection of thromboplastin into vein segments in dogs, by severe trauma, by infection, and by chemical irritants. O'Neill showed that partial obstruction and interference with the nutrition of the vein in dogs produced clots only after twenty to fifty hours. In our experiments sodium morrhuate was found to give 100 per cent reproducible production of thrombi.

Many studies have been made of the effect of known drugs in causing lysis of preformed clots in experimental animals. Heparin has been shown to have some thrombolytic effect in early thrombi. Tromexan, administered over a long period of time, has been found to promote recanalization of thrombi in rabbits' ear veins, in the femoral vein of dogs, and in the femoral artery of rabbits. Trypsin, administered over a long period of time, has been shown to lyse thrombi.
This is difficult to explain since it is common experience that trypsin produces intravascular thrombosis.\textsuperscript{25, 26} It is possible that this lytic effect of trypsin is due to in vivo activation of plasminogen.\textsuperscript{27} Streptokinase has also been reported to produce lysis of clots in rabbits when used in large doses over a long time interval.\textsuperscript{8}

This report deals with the effects of plasmin (plasminogen activated by streptokinase-streptodornase) on thromboses produced in the marginal vein of the rabbit's ear.

**Materials**

The following substances were used in this experiment:
1. Nembutal veterinary: 65 mg./ml. intravenously for anesthesia.
2. Sodium morrhuate 5 per cent solution.
3. Thrombin (bovine origin).*
4. Streptokinase (SK-SD): streptokinase 100,000 units; streptodornase 25,000 units.\textsuperscript{†}

The enzymes in each vial were dissolved in 10 ml. of sterile saline. Two ml. containing 40,000 units streptokinase and 5000 units streptodornase were added to every 20 ml. of plasminogen used.
5. Plasminogen. This enzyme is prepared in our laboratory from fraction III of human plasma using a previously reported method.\textsuperscript{19}

The potency of our plasminogen varied slightly with each lot prepared. However, it retained its activity when stored for several weeks at 5 to 10 C. The maximum total amount of streptokinase used was 70,000 units. Johnson and Tillet\textsuperscript{11} used 4 to 20 times this amount of SK-SD.

**Methods**

Anesthesia was induced with sodium nembutal (65 mg./ml.) using a ratio of 1 ml. per 5 lbs.

Thrombi were formed in the marginal vein of the rabbit's ear in a standard fashion. A 1 cm. segment of the marginal vein of the ear was isolated from the remainder of the circulation by the application of two bulldog clamps, one proximally and one distally. A number 27 gage hypodermic needle was used to puncture the obstructed vein and blood was aspirated as completely as possible. Sodium morrhuate or thrombin were injected and the vein allowed to refill with blood, then reclamped, and the segment isolated until a clot formed.

Thirty-three rabbits were used in this series. In each rabbit a thrombus 1 to 2 cm. long was produced in the marginal vein of the ear.

Group I: twelve rabbits. One-tenth ml. of thrombin was injected into the isolated segment of the marginal vein. An adherent thrombus was formed in most cases within 15 minutes. This thrombus, unfortunately, did not persist over 24 hours in the majority of the control animals.

Group II: twenty-one rabbits. One-tenth ml. of 5 per cent sodium morrhuate was injected into the isolated segment. A clot formed in 10 to 15 minutes. This thrombus was adherent and persisted in control animals for many weeks.

The administration of plasmin was begun at periods of 1/2 hour, 2, 18, 24, and 48 hours after the production of the clot. Injection of plasmin in the so-called treated group was given into a vein of the opposite ear at the rate of 10 to 15 drops per minute, using an ordinary infusion set. Treated animals received from 30 to 70 ml. of plasmin over a period of 1 to 2 hours. The average amount of plasmin used was 15 ml. per kg. The control animals were given the same quantities of saline at the same rate.

The patency or occlusion by thrombus of the veins of the ear was determined in all cases with a modification of the method of Parke Davis and Co. Thrombin Topical. In a concentration of 1000 units/ml.

\* Parke Davis and Co. Thrombin Topical. In a concentration of 1000 units/ml.

\textsuperscript{†} Varidase (Lederle Laboratories).
Lysis of Intravascular Thrombi with Human Plasmin

cases by observing with transillumination the flow of blood through the involved segment. This means of observation was checked in three ways: (1) by microscopic examination of excised segments of vein, (2) by infrared photographs, and (3) by phlebography.

The coagulation time of the blood was determined at intervals, using samples collected in a small bore capillary tube measuring approximately 0.1 cm. in diameter. The spontaneous clot lysis time was determined by observing the lysis of the clot in the above mentioned capillary tube.

Results

The clotting time and spontaneous lysis time of the drawn blood, in vitro, followed a similar pattern in all animals. The average results are plotted in figure 1. The clotting time was increased from 3 to 5 minutes and returned to normal in 1 to 2 hours. The minimum change was 0 and the maximum 4 minutes. The spontaneous lysis time decreased from >8 hours to <30 minutes, within an hour after the beginning of the administration of plasmin and an active lytic system with a lysis time of <1 hour was present for 2 hours. Clot lysis in the ear vein occurred about 1 hour after the onset of the treatment.

Group I—Clots Produced by the Use of Thrombin (Twelve Rabbits)

In the group where thrombin, 1000 units/ml, was used to produce the clot there were eight treated animals and four controls (tables 1, 2).

A thrombus was produced in all animals. Lysis of the thrombus was total in five animals with thrombi of 2 to 3 hours duration and in the two animals with a thrombus 18 hours old. Partial lysis occurred in the animal with a thrombus more

---

**Fig. 1.**—Line graph indicating average clotting time and clot lysis time (in vitro) of the whole blood of all rabbits in which ear vein clot was treated with plasmin. The time, with the beginning of plasmin injection as 0, is indicated by hours in the ordinate. The bottom transverse sections indicate the time of injection of plasmin and the amount. The middle section contains the line graph for clotting time, with the intervals indicated (2, 4, 6, minutes). The higher the graph the longer the clotting time. The top section contains the line graph for lysis time. Here the time intervals are inverted, since the shorter the lysis time the greater the activity. Thus, the higher the graph, the greater the activity. Normal lysis time longer than 2 hours is indicated by the absence of a lysis time line, before 20 minutes after plasmin injection was started.

The average lysis time of the in vivo clot is indicated by the arrow. Control animals, obviously were not included in this determination.
These animals were treated with saline in amounts equivalent to the plasmin used in treated animals.

TABLE 1.—Result of Treatment with Plasmin in Rabbits where Thrombus Was Produced by Thrombin

<table>
<thead>
<tr>
<th>No.</th>
<th>Weight (lb.)</th>
<th>Anes. (cc.)</th>
<th>Clot length (cm.)</th>
<th>Time clot formed (min.)</th>
<th>Time after clot plasmin given (hr.)</th>
<th>Amt. plasmin (cc.)</th>
<th>Time plasmin given</th>
<th>Time for lysis</th>
<th>Plasmin per Kg. (cc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>4</td>
<td>0.6</td>
<td>1</td>
<td>15</td>
<td>2</td>
<td>30</td>
<td>40 min.</td>
<td>30 min.</td>
<td>16 died</td>
</tr>
<tr>
<td>14</td>
<td>8</td>
<td>1</td>
<td>1.2</td>
<td>18</td>
<td>2</td>
<td>40</td>
<td>35 min.</td>
<td>30 min.</td>
<td>11</td>
</tr>
<tr>
<td>16</td>
<td>9.5</td>
<td>1</td>
<td>1.2</td>
<td>15</td>
<td>2</td>
<td>40</td>
<td>1 hr.</td>
<td>1 hr.</td>
<td>10</td>
</tr>
<tr>
<td>18</td>
<td>4.5</td>
<td>none</td>
<td>1</td>
<td>15</td>
<td>2</td>
<td>40</td>
<td>45 min.</td>
<td>55 min.</td>
<td>15</td>
</tr>
<tr>
<td>20</td>
<td>10.5</td>
<td>none</td>
<td>1</td>
<td>10</td>
<td>18</td>
<td>40</td>
<td>30 min.</td>
<td>75 min.</td>
<td>8</td>
</tr>
<tr>
<td>21</td>
<td>9.4</td>
<td>none</td>
<td>3</td>
<td>15</td>
<td>18</td>
<td>40</td>
<td>1 hr.</td>
<td>75 min.</td>
<td>9 died</td>
</tr>
<tr>
<td>25</td>
<td>2.5</td>
<td>none</td>
<td>1.2</td>
<td>15</td>
<td>2</td>
<td>40</td>
<td>1 hr.</td>
<td>105 min.</td>
<td>14</td>
</tr>
</tbody>
</table>

* Firm clots were present in all at the time plasmin was started.

than 24 hours old. The average amount of plasmin used in these animals was 12 ml. per Kg. The average time in which lysis occurred was 1 hour after the beginning of plasmin administration and clot lysis usually was evident by the time injection was completed. Plasmin was given slowly in order to retain an active lytic system for at least 1 hour.

There were three deaths (12 per cent) in this group. Rabbit no. 21 died twenty-five minutes after receiving 20 ml. of plasmin intravenously. Autopsy revealed some small thrombi in the branches of the pulmonary vessels, and since the thrombus in the ear was lysed, it may be postulated that these thrombi in the lungs were 24 hours old, and related to the thrombin injection when the ear vein clot was formed. The rapid injection of the 20 ml. in this case, coupled with the pre-existing complication caused the animal's death. The clotting time in this animal was not prolonged nor was there a very active lytic system. Rabbit no. 13 died of air embolism one hour after clot lysis. Rabbit no. 25 died twenty-four hours after the lysis of the clot and autopsy revealed pulmonary atelectasis.

In the control group there were two deaths (33 1/3 per cent). In one animal where autopsy showed thrombi in the lungs, death is attributed to thrombin. In the other, thrombin was used to produce a clot which had lysed spontaneously by the next day; thrombin was used again and the animal expired immediately.

TABLE 2.—Control Animals Where Thrombus Was Produced with Thrombin

<table>
<thead>
<tr>
<th>No.</th>
<th>Weight (lb.)</th>
<th>Anes. (cc.)</th>
<th>Clot length (cm.)</th>
<th>Time clot formed (min.)</th>
<th>Lysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>11</td>
<td>0.1</td>
<td>1</td>
<td>15</td>
<td>No clot after 24 hr.</td>
</tr>
<tr>
<td>17</td>
<td>4.5</td>
<td>0.3</td>
<td>1</td>
<td>20</td>
<td>No clot after 24 hr.</td>
</tr>
<tr>
<td>19</td>
<td>9</td>
<td>1.5</td>
<td>1</td>
<td>10</td>
<td>No clot after 24 hr.</td>
</tr>
<tr>
<td>24</td>
<td>8</td>
<td>none</td>
<td>2</td>
<td>15</td>
<td>Died 18 hr. after new inj. 0.1 cc. thrombin</td>
</tr>
</tbody>
</table>

* These animals were treated with saline in amounts equivalent to the plasmin used in treated animals.
LYSIS OF INTRAVASCULAR THROMBI WITH HUMAN PLASMIN

Thrombin produced clots persisted for more than 8 hours in all controls but did not persist for 24 hours in three control animals. Therefore this method was abandoned for the study of thrombi of more than 4 hours duration.

Group II—Clots Produced by the Use of Sodium Morrhuate

Thrombi were produced in the vein in all animals within 15 minutes. In all the controls the thrombi persisted for the three month observation period. Figure 2 shows a photomicrograph of a vein with a 24 hour old control thrombus.

The effect of plasmin on lysis of clots produced by the injection of sodium morrhuate is shown in table 3 and the controls in table 4.

Table 3.—Results of Treatment in Rabbits Where Thrombus Was Produced by Sodium Morrhuate

<table>
<thead>
<tr>
<th>No.</th>
<th>Weight (lb.)</th>
<th>Anes. (cc.)</th>
<th>Clot length (cm.)</th>
<th>Time clot format. (min.)</th>
<th>Time after clot plasmin given</th>
<th>Amount plasmin given (cc.)</th>
<th>Time plasmin given</th>
<th>Time for lysis</th>
<th>Plasmin per kg given (cc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.7</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>5 min.</td>
<td>40</td>
<td>1 hr.</td>
<td>1 hr.</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>6.8</td>
<td>1.3</td>
<td>1</td>
<td>10</td>
<td>25 min.</td>
<td>40</td>
<td>1 hr.</td>
<td>10 hr.</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>0.5</td>
<td>1.2</td>
<td>10</td>
<td>10 min.</td>
<td>40</td>
<td>1 hr.</td>
<td>25 min.</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>4.5</td>
<td>0.6</td>
<td>1</td>
<td>10</td>
<td>2 hr.</td>
<td>30</td>
<td>30 min.</td>
<td>35 min.</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>8.5</td>
<td>1</td>
<td>1.5</td>
<td>10</td>
<td>2 hr.</td>
<td>30</td>
<td>45 min.</td>
<td>1 hr.</td>
<td>7.8</td>
</tr>
<tr>
<td>10</td>
<td>4.5</td>
<td>0.5</td>
<td>1.5</td>
<td>10</td>
<td>2 hr.</td>
<td>30</td>
<td>45 min.</td>
<td>1 hr.</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>4.2</td>
<td>0.1</td>
<td>3</td>
<td>12</td>
<td>2 hr.</td>
<td>30</td>
<td>45 min.</td>
<td>1 hr.</td>
<td>15</td>
</tr>
<tr>
<td>22</td>
<td>8</td>
<td>none</td>
<td>3</td>
<td>10</td>
<td>24 hr.</td>
<td>60</td>
<td>2 hr.</td>
<td>no lysis</td>
<td>16</td>
</tr>
<tr>
<td>23</td>
<td>8</td>
<td>none</td>
<td>1</td>
<td>10</td>
<td>24 hr.</td>
<td>70</td>
<td>2 hr.</td>
<td>partial</td>
<td>19</td>
</tr>
<tr>
<td>27</td>
<td>6</td>
<td>none</td>
<td>1.5</td>
<td>15</td>
<td>24 hr.</td>
<td>40</td>
<td>partial</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>5.5</td>
<td>none</td>
<td>1</td>
<td>15</td>
<td>24 hr.</td>
<td>40</td>
<td>45 min.</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>8.5</td>
<td>none</td>
<td>1.5</td>
<td>10</td>
<td>48 hr.</td>
<td>40</td>
<td>45 min.</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>9</td>
<td>none</td>
<td>1</td>
<td>10</td>
<td>24 hr.</td>
<td>40</td>
<td>1 hr.</td>
<td>75 min.</td>
<td>9</td>
</tr>
<tr>
<td>31</td>
<td>6</td>
<td>none</td>
<td>2</td>
<td>10</td>
<td>48 hr.</td>
<td>40</td>
<td>1 hr.</td>
<td>75 min.</td>
<td>14</td>
</tr>
<tr>
<td>32</td>
<td>5.5</td>
<td>none</td>
<td>1.3</td>
<td>10</td>
<td>48 hr.</td>
<td>40</td>
<td>65 min.</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>5.5</td>
<td>none</td>
<td>1.5</td>
<td>15</td>
<td>48 hr.</td>
<td>50 ml.</td>
<td>1 hr.</td>
<td>90 min.</td>
<td>20</td>
</tr>
</tbody>
</table>
Table 4.—Control Animals Where Thrombus Was Produced with Sodium Morrhuate*

<table>
<thead>
<tr>
<th>No.</th>
<th>Weight (lb.)</th>
<th>Anes. (cc.)</th>
<th>Clot length (cm.)</th>
<th>Time clot formation (min.)</th>
<th>No lysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>6.2</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>Clot after 1 mo.</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>none</td>
<td>1</td>
<td>10</td>
<td>Biopsy of vein</td>
</tr>
<tr>
<td>9</td>
<td>4.2</td>
<td>0.6</td>
<td>1</td>
<td>10</td>
<td>Died 24 hr. later</td>
</tr>
<tr>
<td>12</td>
<td>4.6</td>
<td>0.6</td>
<td>1</td>
<td>10</td>
<td>Clot after 3 mo.</td>
</tr>
<tr>
<td>33</td>
<td>8.0</td>
<td>none</td>
<td>1</td>
<td>10</td>
<td>Clot after 3 mo.</td>
</tr>
</tbody>
</table>

* Treated with saline only.

In all seven animals where the plasmin was begun 2 hours or less after thrombus formation, lysis was complete in 1 to 1 1/2 hours after treatment was started. In the nine animals in which treatment with plasmin was begun 24 to 48 hours after thrombus formation there was complete lysis in four animals, partial lysis in two animals, and no lysis in three animals. When lysis occurred, it took place within 1 to 2 hours. The average amount of plasmin used was 15 ml. per Kg., and it was delivered over a period of 30 minutes to 2 1/2 hours. Figure 3 is a photomicrograph of a vein in which a 24 hour clot had been present, after lysis of the clot by plasmin.

No toxic effects were noted in this group of animals. When the plasmin was given rapidly, as was the case where 20 ml. was given in 2 minutes, no untoward effect was noted. Clot lysis was permanent in the group of animals in which a biopsy was not taken and the clot had been less than 24 hours old. In the 24 to 48 hour old clot group the lysis was permanent only in four of the animals.

In the control group the thrombus persisted and was not affected by the intravenous administration of saline. One control animal died when given a second dose of nembutal and autopsy showed air embolism.

Combined Results in Both Groups

Of the twenty-four treated animals with both methods the clot failed to show any lysis in only three. In three animals the lysis was only partial while in the remaining eighteen it was complete. Table 5 summarizes the results.

Of the twenty-one animals where lysis took place, ten were biopsied and eleven were observed for a period of six weeks. In nine of the eleven animals observed, lysis in the ear vein was permanent.

The average amount of plasmin given was 10 to 15 ml. per Kg. or 3.6 to 5.5 mg. per Kg. The total dose injected was 30 to 70 ml. and was administered over a period of half an hour to 1 hour with no untoward effects.

Table 5.—Lysis of Clots in Animals Treated with Plasmin

<table>
<thead>
<tr>
<th></th>
<th>Treated</th>
<th>Total lysis</th>
<th>Partial lysis</th>
<th>No lysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sodium morrhuate</td>
<td>16</td>
<td>11</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>18</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
Phlebograms were made of some animals before and after the administration of plasmin in order to demonstrate lysis of, or persistence of, the clot in the marginal vein. Figure 4 is a phlebogram of a normal rabbit's ear. Figure 5 is a phlebogram of the thrombosed marginal vein of control rabbit no. 33, where only saline was given after the thrombus in the marginal vein was 24 hours old. The complete obstruction to flow is demonstrated.

In contrast, figure 6 is a phlebogram of rabbit no. 28 taken after lysis of a definite clot by plasmin. The clot in the marginal vein produced by sodium morrhuate was 24 hours old when the treatment with plasmin was started. The free flow of contrast medium is obvious.

Figure 7 demonstrates the block to flow in both directions and the length of the 24 hour old clot in the marginal vein of rabbit no. 30, before plasmin administration. Figure 8 was taken after plasmin was given and shows lysis of the clot with free flow through the vein.

Figure 9 shows the obstruction by a thrombus 48 hours old in rabbit no. 32, and figure 10 the lysis of the thrombus after administration of plasmin.

As previously noted, three or 12 per cent of the treated animals died during the course of the experiment. All three were animals in which the clot was produced.
Fig. 7.—Phlebogram of ear vein of rabbit no. 30. The contrast medium had been injected in the distal vein first and shows the distal end of the thrombus. Contrast medium was then injected in a retrograde direction (needle in place) to show the proximal end. Note the complete obstruction to flow and length of the clot. This thrombus was 24 plus hours old.

Fig. 8.—Phlebogram of the ear of rabbit no. 30 after plasmin administration. Complete lysis of the clot is indicated by the free flow of contrast medium through the vein.

Fig. 9.—Phlebogram of rabbit no. 32 before plasmin administration. Obstruction by the 48 hour old thrombus is seen.

Fig. 10.—Phlebogram of rabbit no. 32 after plasmin administration. Complete lysis of the 48 hour old thrombus is demonstrated by the free flow through the marginal vein.

by thrombin. The same number, but a larger percentage (33 per cent) of the control animals in which clots were produced by thrombin also succumbed. None of the treated animals who survived anesthesia showed any ill effects of the treatment for periods of over three months. Autopsy of the animals that died or were later sacrificed did not show any evidence of pancreatitis or hemorrhage into the body cavities.

**Discussion**

The desirability of a method of rapid lysis of thrombosed vessels is obvious to all clinicians. The rapid lysis of clots in thrombosed arteries would be even more valuable in clinical medicine than the opening of thrombosed vein segments. Not infrequently the desire for discovery of a method of treatment for such seri-
ous dysfunctions leads to premature use of treatment methods and claims for cure.

Even a very careful study of the many publications concerning the fibrinolysin-antifibrinolysin system of blood might lead one to differing conclusions concerning the mechanism of action and effects of these materials. The methods of action and effectiveness of the foreign proteolytic enzymes, when injected into animals or the human patient, further complicate this picture. Several facts must be kept in mind. Different animal species show marked variation in this system which is of great importance in interpretation of results. Even a very careful study of the many publications concerning the fibrinolysin-antifibrinolysin system of blood might lead one to differing conclusions concerning the mechanism of action and effects of these materials. The methods of action and effectiveness of the foreign proteolytic enzymes, when injected into animals or the human patient, further complicate this picture. Several facts must be kept in mind. Different animal species show marked variation in this system which is of great importance in interpretation of results. For instance, dogs normally carry an active fibrinolysin in their blood which may explain in part the difficulty in maintenance of clot formation in this animal. Certain animals, such as the rat, have little active or inactive enzyme, although this may be dependent on failure to use the proper activator. Other animals show variations in the response of their proenzyme to the different activators. The blood of all animals studied contains inhibitors for proteolytic enzymes such as trypsin and chymotrypsin, and these inhibitors are rapidly increased following the injection of these materials. Trypsin itself can activate the pro-fibrinolysin of human blood. Streptokinase itself, an activator of profibrinolysin, is quickly rendered inactive by production of antistreptokinase within the blood.

The use of a new enzyme preparation in this complicated system must be very carefully evaluated and studied in more than one species, before application to human patients is considered.

The present study, combined with previous in vivo and in vitro studies, would indicate that this material, human plasmin, is a potent fibrinolytic material which will rapidly lyse clots in vitro and in vivo in the rabbit. Further studies are being made in dogs to confirm the findings in rabbits reported in this paper.

**Summary**

1. Thrombi were produced in the marginal vein of the ear of rabbits with the use of either thrombin or sodium morrhuate. Sodium morrhuate was found to be most dependable.

2. Plasmin given intravenously with an average dose of 10 to 15 ml. per Kg. was effective in producing a complete intravascular lysis in all instances where the thrombus was less than 24 hours old, and a partial or total lysis in the great majority of animals with thrombi over 24 hours old. This lysis took place within 1 to 2 hours after the injection of plasmin.

3. The intravenous use of plasmin is shown in rabbits to be nonlethal and nontoxic.

**Summario in Interlingua**

Le presente studio esseva interprendite pro determinar le effecto lytic de plasmina (o fibrinolysina) human super thrombos intravascular.

1. Thrombos esseva producite in le vena marginal del aure de conilios per le uso de o thrombina o morrhuate de sodium. Le morrhuate de sodium se monstrava le plus securmente efficace.

2. Plasmina administrate intraveosemente con un dose median de 10 a 15 ml
per kg esseva efficace in producere un completo lysis intravascular in omne casos ubi le etate del thrombo esseva minus de 24 horas e un lysis o total o partial in le grande majoritate del animales in que le etate del thrombo esseva plus de 24 horas. Le lysis eveniva intra un o duo horas post le injection de plasmina.

3. Il es demonstrate que le administration intravenose de plasmina es nonletal e nontoxic a conilios.

REFERENCES

LYSIS OF INTRAVASCULAR THROMBI WITH HUMAN PLASMIN

The Lysis of Intravascular Thrombi in Rabbits with Human Plasmin (Fibrinolysin)

CARLO E. GROSSI, EUGENE E. CLIFFTON and DOLLY A. CANNAMELA