Fibrinolysin (Plasmin) Therapy in Acute Deep Thrombophlebitis

A Controlled Study

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The magnitude of the literature dealing with deep thrombophlebitis of the lower extremities and its complications reflects not only the interest that this disorder commands among physicians but also the extensive controversy that it has generated. Controversy surrounds even such fundamental problems as the pathogenesis of venous thromboembolism, the natural course of the process, and the adequacy of available diagnostic criteria. When viewed against this background of debate over basic issues, the differences of opinion regarding the effects of various forms of therapy in acute deep venous occlusion are readily understood.

Venous ligation and anticoagulant therapy alone or in combination have attracted strong advocates. This debate over therapy is complicated by the variations in the specific manner in which therapy is applied.

Furthermore the results can be interpreted only after consideration of the criteria used for selection of patients, the specific measures of improvement, and the therapeutic objectives. Since methodologic details obviously influence the results and since identical methods rarely have been used in evaluation of therapeutic agents in thrombophlebitis, the obvious corollary has been a wide divergence in results.

Recently, a new aspect has been added to this already complex therapeutic problem by the development of agents that are capable of acutely dissolving intravascular clot. Such substances have been categorized broadly as "fibrinolytic or thrombolytic agents," since they can induce the lysis of fibrin, the protein which provides the framework of intravascular thrombi.

Materials labeled as "fibrinolytic agents" vary widely in origin, composition, and mechanism of action. All of them, however, act by influencing or supplementing the normal components of the intrinsic fibrinolytic mechanism present in the blood (fig. 1).

During the past several years, 3 fibrinolytic agents (streptokinase, fibrinolysin, and the bacterial pyrogens) have been subjected to intensive laboratory and animal testing with encouraging results. While differences among them require further study, preliminary observations have consistently suggested that fibrinolysin, the bacterial pyrogens, and streptokinase are all capable of inducing dissolution of fresh intravascular clot in man.

We have previously reported in detail investigations of both the therapeutic effect and the toxicity of highly purified human fibrinolysin administered intravenously in man. These studies indicated that this preparation (a highly purified pro-fibrinolysin activated with streptokinase and then further purified) was acceptable for use in human subjects although it was not devoid of side effects, particularly pyrogenicity. Furthermore, this agent appeared to influence favorably the course of peripheral arterial
and venous thrombotic disorders. Carefully controlled studies were necessary, however, to confirm these preliminary impressions of the therapeutic value of fibrinolysin.

The first entity chosen for controlled investigation was acute deep venous thrombosis of the lower extremities. This particular thrombotic disorder was selected for several reasons: (1) it is encountered frequently at the institutions cooperating in this study; (2) any temperature elevation occasioned by fibrinolysin would be unlikely to have deleterious effects upon these patients; (3) the mortality associated with thrombophlebitis is low and would grant an opportunity for follow-up in most instances; (4) some objective criteria exist for determining the therapeutic effect of a given regimen; and (5) the available methods of therapy are not ideal.

In regard to this last point, the ideal therapeutic regimen in patients with acute deep venous occlusion would achieve 4 major goals: the rapid relief of acute signs and symptoms with early return of the patient to normal activity; the prevention of pulmonary embolism; the prevention of permanent residuals such as the postphlebitic syndrome; and the prevention of phlebitic recurrence.

The study reported here is an attempt to ascertain whether a combined fibrinolytic-anticoagulant therapy attains these 4 objectives more adequately than anticoagulant therapy alone. The data presented are derived from the first 62 patients studied.

**Methods of Study**

**Fibrinolysin**

The fibrinolysin preparation used in this study is derived from the euglobulin fraction of the human plasma proteins as pro-fibrinolysin and is activated by small amounts of highly purified streptokinase. Procedures are then employed to obtain an end-product free of detectable streptokinase activity and the material is lyophilized. The precise methods used in isolation, purification, and activation of the material are not available for publication. Studies in our laboratory with the fibrin plate methods of Astrup and Mullertz and Lassen have indicated that the material contains both "activator" and "enzyme" activity. The preparation is standardized by the manufacturer by both fibrinolytic and nonfibrinolytic techniques. In our laboratory, the potency of each lot received is compared with a house standard by a fibrinolytic assay method. The lyophilized material is stable for many weeks at 5 C. It is dissolved in normal saline or 5 per cent dextrose solution just prior to use.

**Criteria for Inclusion of Patients**

The patients in this series include all individuals seen by the authors during a 2-year period in whom unequivocal signs of acute deep venous occlusion of the legs had been present for 10 days or less. All patients with questionable or minimal evidence of occlusion, complicating cellulitis, or mild exacerbation of chronic venous disease were excluded.

The double-blind technic of study was not feasible in this series because of (1) the pyrogenicity of the fibrinolysin preparation and (2) the desire to obtain serial blood samples and other data (electrocardiogram, temperature response, etc.) in those receiving fibrinolytic therapy. Therefore, an alternating technic of controlled study was employed. Each patient was assigned a number in sequence. All even-numbered patients served as controls while all odd-numbered patients received fibrinolytic therapy. No deviation from this sequential assignment was permitted, with 1 exception; namely, in patients who had received anticoagulant therapy for more than 24 hours prior to their referral. The following arbitrary procedure was followed when such patients were encountered: (1) if the protocol for the study had not been followed or adequate records were not available regarding initial and subsequent status of the leg, the patient was eliminated from the series; (2) if the first criterion was satisfied, the patient was assigned a sequential number. If this was an even (control) number, the patient was continued in

*Supplied as Actase-fibrinolysin (human) by the Ortho Research Foundation, Raritan, N.J.*

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this category. If the patient was to be a fibrinolytic case, the patient was reassigned to the control group if significant improvement had occurred prior to the time of referral. Such breaks in sequence were necessary in only 5 instances, since referrals in the early stages of the study usually were made because of failure of response to therapy and, as the study progressed, patients were usually seen within the first hospital day.

**Therapy**

The therapeutic protocol in the control group was as follows: 1. As soon as the diagnosis of thrombophlebitis was established, the patient was placed at bed rest with the legs elevated. Heparin was begun in a dosage of 75 to 100 mg. subcutaneously every 6 hours. Bis-hydroxycoumarin or warfarin was usually administered simultaneously, but heparin was continued until the patient had remained in a 1-stage prothrombin time range of 10 to 30 per cent for at least 24 hours.

2. The patient was permitted to ambulate with elastic bandages approximately 48 hours after the acute phlebitic signs had subsided (i.e., fever; heat, redness, tenderness and turgidity of the extremity). Slight residual edema or increased size of the extremity was not considered a contraindication to ambulation.

3. After 1 full day of uneventful ambulation, anticoagulant therapy was tapered, and it was discontinued within the next 36 hours.

4. The patient was observed for 24 to 48 hours after cessation of anticoagulant therapy and discharged.

5. With recurrence of phlebitic signs or symptoms, the therapeutic regimen was reinstituted. If pulmonary embolization occurred, the patient was kept in bed and on anticoagulant drugs as long as dyspnea, chest pain, temperature elevation, tachycardia, or electrocardiographic abnormalities persisted and the protocol was again followed regarding ambulation, discontinuation of anticoagulant therapy, and discharge.

Exactly the same therapeutic regimen was used in the group treated with fibrinolysin, with the exception that these patients received an intravenous infusion containing 75 to 100,000 units of fibrinolysin over a 3- to 4-hour period as soon as they had been evaluated. The following day, if significant signs or symptoms of phlebitic activity persisted, the patient received a second dose of 50 to 75,000 units over 2 to 3 hours. Thereafter, regardless of response, no further fibrinolysin was administered. Ten patients received 2 infusions; the remainder, 1. Drugs were used to prevent or ameliorate febrile response in most patients and included aspirin, antihistamines, or barbiturates.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Location of Phlebitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fibrinolysin</td>
</tr>
<tr>
<td>Popliteal</td>
<td>13</td>
</tr>
<tr>
<td>Femoral</td>
<td>8</td>
</tr>
<tr>
<td>Iliofemoral</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>32</td>
</tr>
</tbody>
</table>

**Parameters Studied**

The following features of the patient’s course were documented as accurately as possible: onset of phlebitic signs and symptoms; duration of bed rest and anticoagulant therapy; complications of fibrinolytic or anticoagulant therapy; disappearance of turgidity, edema, pain, and tenderness in the involved extremity; date of return of leg size to normal; date of ambulation; date of discharge; pulmonary embolization or phlebitic recurrence; the presence of postphlebitic changes following the acute episode; possible etiologic factors; and location of phlebitic process. The authors personally made daily observations in the great majority of the patients as long as signs or symptoms of thrombophlebitis persisted and also saw virtually all patients in whom either an embolic event or phlebitic recurrence was suspected. The attending physicians were alerted to record daily the status of signs and symptoms throughout the patient’s hospital stay. An attempt was made to follow all patients at regular intervals after discharge.

**Comparability of Groups**

While strict comparability is virtually impossible to attain in a clinical study of this type, the 30 control and 32 fibrinolysin-treated patients appear sufficiently similar to permit valid conclusions regarding differences in therapeutic response.

**Age and Sex**

The mean age of the patients in the control group was 48 years (median 46) and in the fibrinolysin group, 43 years (median 46). There were 16 males in the control group and 15 in the fibrinolysin group.

**Location of the Phlebitic Process**

The location of the thrombotic process (table 1) was defined as follows: (1) popliteal: signs and symptoms limited to the popliteal space and distally; (2) femoral: definite involvement of the thigh as well as below the
Table 2

<table>
<thead>
<tr>
<th>Associated Disorders</th>
<th>Fibrinolysin</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No obvious cause</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Postoperative</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Prior thrombophlebitis</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Varicosities</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Trauma</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Venous catheter</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Postpartum</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

*More than 1 factor was present in some patients.

Table 3

<table>
<thead>
<tr>
<th>Course of Phlebitic Episode in Total Groups (32 fibrinolysin, 30 control patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration in Days of</td>
</tr>
<tr>
<td>Mean (S.E.)</td>
</tr>
<tr>
<td>Phlebitis before anticoagulant therapy</td>
</tr>
<tr>
<td>Pain or tenderness*</td>
</tr>
<tr>
<td>Edema*</td>
</tr>
<tr>
<td>Abnormality in leg size*</td>
</tr>
<tr>
<td>Bed rest*</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Anticoagulant therapy*</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Hospital stay*</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Reported as days after start of anticoagulant therapy.
+Standard error of the mean.
†Level of significance of these differences by the t test; adjusted where necessary for inequality of group variances.

knee; (3) iliofemoral: pain, tenderness, swelling, and turgidity in the inguinal region and thigh as well as below the knee.

Etiology or Associated Factors

The factors associated with thrombophlebitis in a given patient may have a definite bearing upon the speed of recovery, tendency toward recurrence, and incidence of embolization (table 2). There were no striking differences between the 2 groups.

Duration before Therapy

The average duration of signs and symptoms of venous occlusion before institution of anticoagulant therapy was similar in the control and fibrinolysin groups (table 3). However, fibrinolysin was administered on an average of 4.3 days after onset of symptoms, representing an average "lag" period of 1.4 days between institution of anticoagulant drugs and fibrinolysin infusion. This "lag" probably represents a penalty in favor of the control group, since, as mentioned above, no patient who was on anticoagulant drugs when first seen was included in the fibrinolysin group if significant improvement had occurred, but all calculations are dated from the start of anticoagulant therapy.

Results

Prior studies indicated that analysis of the data should take into account 2 important factors: (1) the duration of signs and symp-
or symptoms of active phlebitis (pain, tenderness, turgidity, heat of the extremity, and systemic temperature elevation) had subsided was taken as the starting point. In keeping with the protocol "arbitrary" ambulation represents this figure plus 2 days; "arbitrary" discontinuance of anticoagulant drugs, this figure plus 4 days; "arbitrary" discharge, this figure plus 6 days. Thus, if a patient's phlebitis was inactive on day 3 after start of anticoagulant drugs, he "arbitrarily" would be ambulated on day 5, have anticoagulants discontinued on day 7, and be discharged on day 9.

2. Patients from the 2 groups who met the following criteria were selected for separate analysis: all control patients in whom anticoagulant therapy was begun 5 days or less after onset of symptoms (26 patients); all patients treated with fibrinolysin within 5 days after onset of symptoms and within 24 hours after anticoagulant therapy was instituted (21 patients). Again, both "actual" and "arbitrary" values are reported for duration of anticoagulation, bed rest, and hospital stay.

3. In both the subgroups and total groups, "short-term" and "long-term" results are analyzed separately. The former category includes the response of the involved extremity, the incidence of embolization or recurrence of phlebitis during the first 2 weeks following institution of therapy (or until discharge if the patient was discharged before this time and not seen subsequently), and the status of the extremity at the time of hospital discharge. "Long-term" results include any recurrence of phlebitis or pulmonary emboli that appeared more than 2 weeks after start of anticoagulant therapy. With rare exceptions these represent results in individuals no longer receiving anticoagulant drugs.

We should emphasize that the time intervals reported here are dated from the start of anticoagulant therapy, not from the onset of symptoms, admission, or administration of fibrinolysin. Therefore, day zero is the day on which anticoagulant therapy (heparin) was started.

**Total Group, Short-Term Results (Tables 3 and 4)**

**Subsidence of Pain and Tenderness**

Pain and tenderness were considered to be absent when the Homans' sign and the Lowenberg test were negative, and squeezing or vigorous palpation of the involved areas did not cause discomfort. These are rather stringent criteria, since patients often report they are pain-free while such maneuvers continue to elicit pain. In the control group, pain persisted longer after start of anticoagulant therapy than in the fibrinolysin group.

**Edema**

Edema was defined as absent when all pitting edema had subsided.

**Leg Size Normal**

Calf measurements were made at 10-cm. intervals above the lower border of the internal malleolus. The thigh was measured at 10-cm. intervals above the tibial tubercle. The involved extremity was considered to have returned to normal size when no circumference was more than 2.0 cm. greater than the uninvolved leg. In 3 control patients and 3 patients receiving fibrinolysin, leg size failed to return to normal during hospitalization. There was no significant difference in the remainder of the 2 groups in this time.

**Bed Rest**

Bed rest was longer in the control group than in the fibrinolysin group. Two patients in the control group who died while still at bed rest were excluded from analysis.

**Duration of Anticoagulant Therapy**

The duration of anticoagulant therapy was longer in the control group than in the fibrinolysin group. Two patients were excluded in whom anticoagulant drugs were continued indefinitely for reasons other than thrombophlebitis.

**Duration of Hospital Stay**

The duration of hospital stay after start of therapy for thrombophlebitis was also longer in the controls than in those treated with fibrinolysin.
Table 4
Short-Term Complications in Total Groups

<table>
<thead>
<tr>
<th></th>
<th>Fibrinolysin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite, nonfatal</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Possible, nonfatal</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Possible, fatal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1 (3%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Recurrence of phlebitis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Postphlebitic residual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior venous disease</td>
<td>2/21 (10%)</td>
<td>3/23 (14%)</td>
</tr>
<tr>
<td>Prior venous disease with no residual</td>
<td>0/7</td>
<td>1/5</td>
</tr>
<tr>
<td>Prior venous disease with residual</td>
<td>3/3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>5/31</td>
<td>4/28</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Pulmonary Embolization

Seven control patients (23 per cent) had a history of pulmonary embolization within the 2-week period prior to institution of anticoagulant therapy and a questionable embolic event had occurred in 3 others. In the fibrinolysin group, 9 patients (28 per cent) had suffered a pulmonary embolus during the 2-week period prior to start of anticoagulant drugs.

During the 2 weeks following start of anticoagulant therapy, 3 control patients (10 per cent) had definite evidence of nonfatal pulmonary embolization. One additional control patient suddenly developed tachypnea, cyanosis, and shock on the eighth day of therapy and died. Permission for autopsy was denied and this patient is listed as a “possible” embolus.

In the fibrinolysin group, 1 patient developed aching left chest pain some 5 hours after fibrinolysin infusion. Tachypnea, tachycardia, electrocardiographic and x-ray changes were absent. This “possible” embolus was the only one encountered in the treatment group.

Postphlebitic Syndrome

Patients were classified as having the postphlebitic syndrome at the time of hospital discharge if they showed evidence of deep venous insufficiency such as edema (either persistent or developing only after ambulation), continued abnormality in leg size, dilatation of superficial veins, or aching in the extremity after ambulation. A number of patients had a history of prior venous disease. Since this may have influenced the extent of residual venous disease, these patients are considered separately (table 4).

In the control group, there were 25 patients who had no antecedent history of venous disease. Two of these died prior to discharge. Of the remaining 23, 3 (14 per cent) had postphlebitic residuals at discharge. Two of these were marked and followed iliofemoral thrombophlebitis. The third was of moderate degree and followed a femoral occlusion. Five control patients, all of whom denied prior residual disability, had a history of venous disease. One of these 5 had moderate chronic venous insufficiency at discharge.

In the fibrinolysin-treated group, there were 22 patients with no antecedent history of venous disease. One of these died prior to discharge. Of the remaining 21, 2 (10 per cent) showed evidence of venous insufficiency at the time of discharge. In one, this evidence consisted of a 2.5-cm. discrepancy in leg size that persisted during a 3-week period after a left iliofemoral occlusion. No edema on ambulation or other signs or symptoms were present. The second patient was discharged with slight edema following a popliteal thrombosis. However, pretibial and pedal edema developed after moderate periods of ambulation. Ten fibrinolysin-treated patients had a previous history of venous disease. Three of these had well-documented, prior postphlebitic defects. Evidence of chronic venous insufficiency at discharge was limited to these 3 patients. As far as could be ascertained, the degree of insufficiency increased in 1 patient and had remained unchanged in the other 2.

Recurrence of Phlebitis

In the control group, 2 recurrences appeared within the 2 weeks after therapy was begun, on the twelfth and fifth days. Both patients were ambulatory at the time of recurrence, and one was still on anticoagulant therapy.
Table 5
Duration of Follow-up in Total Groups

<table>
<thead>
<tr>
<th>Duration</th>
<th>Fibrinolysin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>2-4 weeks</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>5-12 weeks</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>13-24 weeks</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>25-51 weeks</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>52 weeks</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Mean</td>
<td>12.3 weeks</td>
<td>16.3 weeks</td>
</tr>
<tr>
<td>Median</td>
<td>6.0 weeks</td>
<td>6.0 weeks</td>
</tr>
</tbody>
</table>

In the fibrinolysin-treated group, no recurrences appeared during this 2-week interval.

Deaths

One "short-term" death was encountered in each group. As mentioned above, the death in the control group occurred suddenly on the eighth day of anticoagulant therapy, presumably due to a pulmonary embolus. The fibrinolysin-treated patient had chronic azotemia and died of progressive uremia 6 days after therapy. The right femoral thrombophlebitis had cleared completely within 3 days. Autopsy revealed a patent left femoral vein and no evidence of pulmonary embolization. Both kidneys were severely hydrenephrotic and virtually replaced by masses of renal calculi.

Total Group, Long-Term Results

The long-term results (after the initial 2-week period) obviously are influenced by the extent of follow-up in the 2 groups. The median duration of follow-up in the 2 groups is the same, whereas the average duration is longer in the controls than in those treated with fibrinolysin (table 5).

Pulmonary Embolization

Of the 24 control patients followed more than 2 weeks, 4 (17 per cent) had one or more episodes of pulmonary embolization (table 6). One of these patients, who had suffered an embolus on the fifth day of anticoagulant therapy, had a second nonfatal pulmonary embolic event 9 months later. She died 3 months later with a third embolic event and congestive heart failure. Permission for postmortem examination was denied. The second patient also had had an embolus during the initial 2-week period. She had several subsequent pulmonary emboli while on anticoagulant therapy, developed intractable cardiac failure, and died 5 weeks after anticoagulant therapy was begun. Autopsy revealed biventricular hypertrophy and dilatation, multiple emboli of varying ages throughout both lungs, and an extensive right iliofemoral venous thrombosis. The third patient, who had recovered uneventfully from her phlebitic episode, entered 10 weeks later with a recurrent phlebitis, evidence of pulmonary embolization, and congestive failure. She died suddenly 7 days after admission. Autopsy showed multiple pulmonary infarctions. The fourth patient was readmitted 8 weeks after the original phlebitic episode with a recurrence of phlebitis, fever, and severe tachypnea. Positive blood cultures and recurrent episodes of embolization characterized his hospital course of 5 weeks. Autopsy revealed thrombosis of the left iliofemoral vein, septic thrombosis of the portal vein, and septic emboli in the liver and lung.

In the fibrinolysin group, 25 patients have been followed more than 2 weeks after onset of anticoagulant therapy. Two patients (8.0 per cent) had nonfatal episodes of pulmonary embolization during the follow-up period—at
Table 7
Course of Phlebitic Episode in "Early Treatment" Subgroups (21 fibrinolysin, 26 control patients)

<table>
<thead>
<tr>
<th>Duration in Days of Phlebitis before anticoagulant therapy</th>
<th>Fibrinolysin Mean (S.E.)†</th>
<th>Control Mean (S.E.)‡</th>
<th>p‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain or tenderness*</td>
<td>3.7 (0.53)</td>
<td>8.0 (1.31)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Abnormality in leg size*</td>
<td>3.6 (0.63)</td>
<td>7.4 (1.44)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Bed rest*</td>
<td>Actual 6.2 (0.78)</td>
<td>10.3 (1.76)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Anticoagulant therapy*</td>
<td>Actual 8.6 (0.94)</td>
<td>12.2 (0.65)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Hospital stay*</td>
<td>Actual 14.4 (2.24)</td>
<td>17.4 (2.77)</td>
<td>&lt;.20</td>
</tr>
</tbody>
</table>

*Reported as days after start of anticoagulant therapy.
†Standard error of the mean.
‡Level of significance of these differences by the t test; adjusted where necessary for inequality of group variances.

3 weeks and 9 weeks, respectively. The former was associated with a phlebitic recurrence. The latter occurred in a patient who had had multiple episodes of venous thrombosis over the prior 2 months and at autopsy was proved to have carcinoma of the pancreas.

Recurrence of Phlebitis

Of the 24 control patients followed for more than 2 weeks, 6 recurrences appeared in 4 patients. One patient developed a recurrence at 17 days with uneventful recovery. In another, recurrence appeared during the third month of follow-up and the patient succumbed to septicemia and pulmonary embolization. The third patient had a recurrence at 1 month and died 6 weeks later with pulmonary embolization and congestive heart failure. The fourth patient had recurrences at 1, 2, and 3 months after discharge but for the subsequent 6 months she had no further complaints other than severe postphlebitic changes of the involved extremity.

In the 25 fibrinolysin patients follow more than 2 weeks, 3 recurrences were observed. One developed 26 days after discharge and was associated with a large, nonfatal pulmonary embolus. Following this admission, the patient had a definite postphlebitic residual. The second patient had a recurrence 10 weeks after discharge and also had chronic venous insufficiency following this episode. The third recurrence was the only one in the opposite extremity in the entire series. This patient had definite persisting abnormalities after the recurrence. The third patient was retreated with fibrinolysin plus anticoagulants; the others, with anticoagulant drugs alone.

Deaths

Four "long-term" deaths (17 per cent) have occurred in the control group during the total period of observation. Recent pulmonary embolism at least contributed to death in all 4, being confirmed at autopsy in 3 and evident clinically in the fourth. In the fibrinolysin group, one "long-term" death is known to have occurred. This patient died of metastatic pancreatic carcinoma 8 months after discharge.

Short and Long-Term Results in Subgroups

In this section, we have compared the 26 control subjects who were started on anticoagulant therapy within 5 days of onset of signs and symptoms with the 21 fibrinolysin patients to whom fibrinolysin was administered within 5 days of onset and within less than 24 hours after anticoagulant drugs were begun (tables 7 to 9).

Composition of Groups

The mean age of control patients was 46.0 years (median 42) versus 49.1 years (median 48) in the fibrinolysin patients. There were 11 men in the control group and 12 in the fibrinolysin group. Duration prior to anticoagulant therapy was 2.1 days in the control group and 2.7 days in the fibrinolysin patients. Location of the phlebitic process remained comparable, as did etiologic factors.

The durations of pain, edema, abnormal leg size, bed rest, anticoagulant therapy, and hospital stay were all shorter in the fibrinolysin-treated than in the control patients (table 7).
Table 8
Short-Term Complications in “Early Treatment” Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Fibrinolysin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite, nonfatal</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Possible, nonfatal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Possible, fatal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Phlebitic recurrence</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Postphlebitic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior venous</td>
<td>2/17 (12%)</td>
<td>3/22 (14%)</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior venous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease with no residual</td>
<td>0/2</td>
<td>1/4</td>
</tr>
<tr>
<td>Prior venous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease with residual</td>
<td>2/2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>4/21</td>
<td>4/26</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (5%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

Pulmonary Embolization

Of the 26 control patients, 5 (19 per cent) had a history of pulmonary embolism during the 2 weeks prior to start of therapy. Two had nonfatal embolic episodes within the first 2 weeks of therapy and another died suddenly with a “possible” embolus. Follow-up beyond 2 weeks was available in 18 control patients. Of these, 3 had subsequent embolic episodes.

Of the 21 fibrinolysin patients, 5 (24 per cent) had had embolic episodes in the 2 weeks prior to start of therapy. During the first 2 weeks after therapy, no emboli occurred. Sixteen patients in this group were followed more than 2 weeks. Two of these patients suffered nonfatal emboli at 3 and 9 weeks after discharge.

Again the figures on embolic incidence may be weighted by the somewhat greater duration of follow-up in the controls, which averaged 15.7 weeks (median 4) versus 9.1 weeks (median 4) in the fibrinolysin patients. That the occurrence of embolization (or recurrence) leading to hospitalization may have conditioned the better follow-up in the control group, however, must also be considered.

Table 9
Long-Term Complications in “Early Treatment” Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Fibrinolysin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Pulmonary Emboli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite, nonfatal</td>
<td>2</td>
<td>(1)*</td>
</tr>
<tr>
<td>Definite, fatal</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Possible, fatal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>2 (13%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Phlebitic recurrence</td>
<td>3† (19%)</td>
<td>4‡ (22%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (6%)</td>
<td>3 (17%)</td>
</tr>
</tbody>
</table>

*Patient included under Definite, fatal.
†One recurrence in opposite leg.
‡Multiple in one patient.

Postphlebitic Syndrome

Four patients in the control group (15 per cent) were left with chronic postphlebitic changes at the time of discharge, including one with a history of prior venous disease that had left no residual. Four fibrinolysin patients (19 per cent) had postphlebitic changes at discharge. Two of these had no antecedent venous disease, while 2 had residuals from prior venous occlusion.

Recurrence

Two “early” recurrences appeared in the 26 control patients versus none in the fibrinolysin group. Six “late” recurrences appeared in 4 of the 18 control patients followed for more than 2 weeks (22 per cent) versus 3 recurrences in 3 of the 16 fibrinolysin patients.

Deaths

One “short-term” death occurred in each group. Pulmonary embolism was the probable cause in the control patient and uremia in the fibrinolysin patient. Of the 3 “long-term” deaths in the control series, 2 were due to pulmonary embolism and embolization contributed to death in the third. The one “long-term” fibrinolysin death resulted from metastatic carcinoma of the pancreas.

Toxicity

As has been our experience in the past, the toxicity accompanying fibrinolysin infusion was limited primarily to temperature elevation.43, 44 Approximately half of the 42 infu-
Incidence of Fever Following Administration of Fibrinolysin

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>No fever</th>
<th>Fever*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Antihistaminic</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Barbiturate</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Aspirin</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

20 (48%) 22 (52%)

*1 F. above baseline temperature.

Maximum Temperature Elevation Following Administration of Fibrinolysin

<table>
<thead>
<tr>
<th>Temperature</th>
<th>No.</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1-1.0</td>
<td>22</td>
<td>52</td>
</tr>
<tr>
<td>1.1-2.0</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>2.1-3.0</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>3.1-4.0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

*Above baseline value.

Table 10
Table 11

sions were followed by a temperature rise of more than 1 F. during the 24 hours after infusion. Various drugs were administered in an attempt to ameliorate or abort the temperature response. The regimens employed included Nembutal by the intramuscular route, 100 mg. just prior to and 6 hours after start of the infusion; aspirin, 0.6 Gm. orally just prior to and every 4 hours after infusion; and Benadryl (75 mg.) or chlortrimeton (6 to 8 mg.) intramuscularly just prior to and every 6 hours after fibrinolysin infusion was begun. The antihistaminic regimen proved the most efficacious, fever appearing in only 2 of the 10 patients treated in this manner (table 10). Observations in a series of some 200 patients treated with the same fibrinolysin preparation also have indicated that the antihistaminic schedules outlined above offer the best means of limiting the incidence and extent of fever.11, 43, 44, 49

The extent of the fever in this series agrees closely with that which we have reported previously, with elevations greater than 4 F. above baseline occurring in approximately 5 per cent of the cases (table 11).

The temperature elevation usually began 3 to 6 hours after the infusion was started, reached a peak at 8 to 10 hours, and subsided in the next 12 to 14 hours in almost all instances. Chills occurred in about one third of the patients who had a febrile reaction. One patient experienced a brief episode of severe epigastric pain that remains unexplained. No bleeding phenomena were noted in any patient within a 4-day period following fibrinolysin. Three patients (2 controls, 1 fibrinolysin), however, did develop bleeding while receiving anticoagulant drugs. One control and 1 fibrinolysin patient had mild hematuria. One control subject developed extensive rectal bleeding which necessitated blood transfusion.

Since fibrinolysin is derived from plasma proteins, some concern regarding possible untoward effects in patients with allergic backgrounds is warranted. In the present series, one patient with a history of bronchial asthma and another with rheumatoid arthritis received the material without significant reaction. One subject with known penicillin sensitivity developed an urticarial rash at the site of infusion. Our total experience now includes a number of patients with bronchial asthma, hay fever, and various "collagen" disorders. These patients do not have a higher incidence of febrile or other reactions than other individuals, with perhaps one exception: of 5 patients with rheumatoid arthritis who received fibrinolysin, 3 had slight to moderate increase in joint signs and symptoms some 24 to 48 hours after infusion. At the present time, therefore, the use of plasmin does not appear to be contraindicated in patients with allergic or collagen-vascular disorders, although observations in subjects with rheumatoid arthritis should be extended in this regard.

Discussion

Theoretically, the combination of an effective thrombolytic drug with anticoagulant therapy should be more effective in the treatment of thrombophlebitis than anticoagulant
FIBRINOLYSIN THERAPY

therapy alone. Acute dissolution of the offending thrombus would promptly relieve venous occlusion and hasten return of the extremity to normal. Fibrinolytic therapy also should reduce the incidence of pulmonary embolization by eliminating the embolic source, particularly since it should be most effective against the relatively fresh thrombotic zones which may be most likely to fragment. The postphlebitic syndrome, a manifestation of chronic deep venous obstruction, should be reduced in incidence and severity if thrombolysis can be achieved promptly.

The possible value of short-term thrombolytic-anticoagulant therapy in reducing the frequency of phlebitic recurrence is less clear. If recurrence is related to the speed or extent of thrombus removal following an episode of venous occlusion, the incidence of recurrence should be lowered by addition of thrombolytic agents. If, on the other hand, recurrence is determined by a primary vascular abnormality or alteration in venous blood flow, or by a hypercoagulable state that persists or returns following the phlebitic event, total clot removal would not alter the tendency toward recurrence. In the latter cases, only prolonged anticoagulant therapy would provide protection against redevelopment of venous thrombosis and its complications.

Several factors other than potency of the drug itself are critical in determining the clinical response to fibrinolysin. 1. The diagnosis of thrombophlebitis (or other thrombotic disorders) must be established as firmly as possible. Fibrinolysin will not influence the course of cellulitis, muscle pain of traumatic or nonspecific origin, or edema due to congestive heart failure, etc. Therefore, patients were not included in this study if the diagnosis appeared equivocal or other explanations for the signs and symptoms were available.

2. An adequate dosage of fibrinolysin must be administered. This condition cannot be fulfilled with certainty at the present time in view of the controversy surrounding the in vivo behavior of fibrinolysin in the plasma and at the level of the clot itself. In the present study, an acceptable dose of fibrinolysin was considered to be one that produces detectable plasma fibrinolytic activity in 90 per cent or more of patients. Previous investigations had indicated that this point was reached when 75,000 to 100,000 fibrinolytic units were administered over a 2- to 4-hour period. Clinical observations also suggested that 1 such dose per 24 hours produced a clinical response in most phlebitic subjects and that repetition the second day often led to further improvement. A third dose rarely altered the course of patients who had not responded to the first 2 infusions. Therefore, in the present study no patient in the fibrinolysin group received more than 2 doses of fibrinolysin. Whether the regimen used in this investigation is excessive or suboptimal cannot be settled at the present time.

3. The age of the thrombus is probably a crucial factor in determining the success of thrombolysis. Obviously, no fibrinolytic drug can dissolve a thrombus that has become organized (i.e., in which fibrin no longer is the predominant component of the supporting framework) or which has been covered by endothelium. The time interval during which a clot remains susceptible to dissolution in a patient with thrombophlebitis is unknown. Studies on experimentally produced thrombi in the dog have indicated that success cannot be expected beyond the first 3 or 4 days. Obviously, these results cannot be transferred directly to man. Experimentally formed clots in the dog may be handled quite differently in terms of organization and endothelialization than a spontaneously formed human clot. Furthermore, venous occlusion in man may often be a progressive phenomenon. A venous thrombus may not be uniform in age and structure, and may contain some portions that are susceptible to lytic agents and others that are not.

Previously, definite evidence of clinical response was noted in a minority of patients when fibrinolysin was administered more than
10 days after onset of phlebitic symptoms. On the other hand, rapid clearing of phlebitis was almost uniformly encountered in those treated within 5 days of onset and in the majority treated between 5 and 10 days. In view of these experiences, patients with phlebitis of more than 10 days' duration were excluded from the present study. In addition, results in those patients treated within 5 days or less were analyzed separately from results in the entire group.

4. The venous clot must be accessible to the fibrinolytic agent. If severe arterial disease coexists in the extremity, delivery of the drug may be unsatisfactory. Also, if total occlusion exists over a long venous segment, thrombolysis is likely to be less successful than when occlusion is incomplete and involves a relatively small zone. These factors are not subject to control but should be considered in evaluating results obtained in specific patients.

5. Adequate anticoagulant therapy should be used simultaneously with fibrinolytic agents if optimum results are to be obtained. Animal investigations have indicated that rethrombosis may follow successful clot lysis unless anticoagulants are used concomitantly. Our own experience has confirmed that a clinical sequence of this type may occur in patients receiving fibrinolysin alone. It should be recognized that the fibrinolytic activity of the plasma following the dosage schedule of fibrinolysin used in this study persists for a rather brief period. Therefore, unless fibrinolysin is repeated or anticoagulants are administered beyond this time, the patient is not protected against the development of thrombosis. Since some thrombotic material, abnormality of the vessel wall, or clotting tendency may persist after acute clot lysis, we believe that a period of anticoagulant therapy should follow use of a fibrinolytic agent. All patients in the fibrinolysin series received such combined therapy.

Having explored the problems surrounding study in this area, we may now turn to evaluation of the results obtained in this particular investigation. Considering first the total series, we find data that strongly suggest that the combined fibrinolysin-anticoagulant regimen is superior to the anticoagulant drugs alone in attaining the "short-term" goals of therapy. Loss of pain and edema as well as the return of leg size to normal all occurred more promptly in those receiving combined therapy. This hastened resolution of phlebitic signs and symptoms carried with it the benefits of earlier ambulation, a shorter period of anticoagulant therapy, and a shorter hospital stay. The superiority of combined therapy is maintained whether actual values or the adjusted "arbitrary" values are considered. Therefore, one of the benefits we hoped to derive from combined therapy was achieved, viz., earlier return of the patient to functional status.

The second objective, prevention of pulmonary embolization, seems to have been achieved although conclusions in this regard must be drawn with caution. Three nonfatal and 1 "possible" fatal pulmonary embolus in the controls during the 2-week period after start of anticoagulant therapy contrast with the single "possible" nonfatal embolus in the fibrinolysin group. Such a low incidence in the latter patients is especially noteworthy when it is recalled that some 28 per cent of this group had suffered an embolus preceding institution of therapy and such patients are especially prone to develop further embolic episodes. The low incidence of embolization in the group receiving combined therapy also indicates that the release of embolic material by fibrinolytic agents seem unlikely.

Attainment of the third objective, prevention of postphlebitic residual, was less clearly influenced by fibrinolysin. The incidence of this complication was quite low in both groups, however, especially in view of the high incidence of femoral and iliofemoral occlusion which characterized the entire series. Definite conclusions regarding the ability of fibrinolysin to reduce the incidence or extent of postphlebitic residuals must be deferred.

The data regarding early recurrence are also rather difficult to interpret. While all
patients receiving combined therapy did escape early recurrence versus 2 recurrences in the controls, the small numbers involved preclude any firm statements on this point.

The "long-term" results of this series are of special interest. It is apparent that even prompt therapy with either fibrinolysin plus the anticoagulant drugs or with the latter alone does not prevent late recurrence of phlebitis or embolism. Indeed, the incidence of late recurrence is rather high in both groups. Pulmonary embolization did occur less frequently in the fibrinolysin group and, while it is tempting to attribute this to therapy, more complete follow-up data in larger series are needed to warrant this conclusion. The redevelopment of thrombosis or embolism can be interpreted in various ways. One may presume that therapy has been ineffective to the extent that thrombotic material remains after the acute episode and serves as a nidus for recurrent formation of clot. On the other hand, local vascular abnormalities may exist which produce moderate degrees of stasis and, alone or in the presence of a temporary thrombotic state, precipitate the original thrombosis and can lead to its renewal. This latter possibility is supported by the investigations of Wessler.53, 54

In terms of over-all mortality, the long-term results also are revealing. The 17 per cent mortality in the controls is a rather imposing figure in view of the limited period of follow-up, especially since embolization was at least a contributory factor in the death of 4 patients and probably the immediate cause of death in the fifth. In the fibrinolysin group, only 2 deaths are known to have occurred—one due to carcinoma of the pancreas and the other due to uremia. While the inference may be drawn that fibrinolysin therapy has reduced mortality due to early and late embolization, again more extensive data must be obtained before such conclusions are justified.

The analysis of the "early treatment" subgroups was carried out to test the hypothesis that the age of the thrombus will influence response of the phlebitic subject to fibrinolysin. If this were so, differences between the fibrinolysin and control subgroups should be greater than those that exist between the two total groups. This expectation appears to be confirmed in regard to "short-term" results, especially in terms of response of the extremity itself. When analysis is limited to those treated promptly, the differences in phlebitic course (table 7) between the control and treated groups become wider and more significant statistically. The absence of either early (within 2 weeks) embolization or recurrence in the fibrinolysin subgroup is also noteworthy, although the incidence of postphlebitic residuals is not appreciably lower than in the controls.

As in the "total groups," however, the apparent superiority of combined therapy is not so evident when long-term results are considered. While embolic incidence and mortality are lower in the fibrinolysin group, these data may be influenced by the follow-up period available in each group. Furthermore, the tendency toward recurrence does not appear to have been diminished in those receiving fibrinolysin.

Finally, in assessing the over-all value of fibrinolysin, we cannot neglect consideration of its toxicity. The present study has confirmed our previous impressions that the febrile response to this agent, while undesirable, does not impair its application in the great majority of patients with acute thrombophlebitis. However, antihistaminic prophylaxis is especially important in patients with underlying disorders that might be unfavorably influenced by a short period of fever or chills (e.g., coronary artery disease). The possible risk of reaction in such individuals must be weighed against the expected benefits. Other theoretic dangers of fibrinolysin therapy, such as embolization or hemorrhage, have not proved of clinical importance. It should be recognized, however, that these statements regarding toxicity of the material apply only to the dosage regimen employed in these patients.

In addition to the information regarding

* Circulation, Volume XXI, March 1960
the effect of fibrinolysin, the present study also supplies some data in an area that is relatively unexplored; namely, the long-term prognosis of phlebitic subjects. The majority of patients with thrombophlebitis recover completely after a relatively short period of bed rest and anticoagulant therapy. In the present series, the morbidity and mortality in both groups would have been extremely low if we had discontinued our observations after a 2-week period or at the time of hospital discharge. Indeed, the results would compare with the most favorable reported in other series regarding incidence of embolization and other complications. When data obtained during follow-up are analyzed, however, the picture is altered. It seems evident that whether combined therapy or anticoagulant therapy alone is used—regardless of the apparent restoration of the phlebitic extremity to a clinically normal state—patients recovered from deep thrombophlebitis have a significant long-term risk of recurrent venous occlusion and pulmonary embolism. Whether this should alter our concepts of management in terms of prolongation of anticoagulant therapy or repetition of fibrinolysin beyond the acute episode requires consideration. Certainly, if further study confirms the data offered here, such a revision may be indicated, since such measures are generally considered unnecessary at the present time. While addition of fibrinolysin to the initial regimen may improve the long-term outlook, acceptance of this as fact must also await further investigation.

Finally, we must emphasize that the fibrinolytic-anticoagulant regimen used in the present study may be less than ideal. Even after many years of widespread use, no criteria for "ideal" anticoagulant therapy with heparin or the coumarin-type drugs have been universally accepted. 23 Therefore, it would seem unlikely that the "ideal" dosage schedule of fibrinolysin, or any fibrinolytic agent, will be generally agreed upon in the near future, especially in view of continued uncertainty regarding the behavior of fibrinolytic agents in vivo.

For the present we must continue to select fibrinolysin dosage on a rather empiric basis supported by experimental data derived from available laboratory methods. As clinical experience expands and laboratory methods improve, it may become apparent that multiple or continuous infusions at higher dosage levels are more effective than those used in the present study. Clinical studies at higher dosage levels are feasible, since we have demonstrated the safety of fibrinolysin in doses well above 100,000 units per 3 hours. 19 Only further investigation will establish whether larger doses than those used here will prove more effective in the treatment of acute deep venous occlusion.

In our opinion, the present study indicates that at least the first few steps have been taken toward the ultimate goal of establishing a method for safely and effectively dissolving intravascular clot in man. It is quite likely that continued research will ultimately lead to development of more ideal thrombolytic agents in terms of ease and administration, absence of toxicity, of precise determination of dosage required to achieve the desired effects.

Summary

Sixty-two patients with deep thrombophlebitis of less than 10 days' duration were studied in controlled fashion. Thirty "control" patients were treated by routine methods including anticoagulant drugs. Thirty-two "treatment" patients received fibrinolysin (plasmin) in addition to control therapy.

The composition of the groups studied and the protocol followed are presented in detail. Comparison of the 2 groups indicates that the addition of fibrinolysin to the therapeutic regimen leads to more rapid clearing of the acute phlebitic episode and may diminish the short-term incidence of phlebitic recurrence and pulmonary embolization. Postphlebitic residuals were encountered with almost equal frequency in both groups.

Greater short-term differences in therapeutic response exist between control and fibrinolysin patients when analysis is restricted to
FIBRINOLYSIN THERAPY

those treated within 5 days of phlebitic onset.

The available data do not permit firm conclusions regarding the apparently favorable influence of fibrinolysin upon the long-term prognosis of phlebitic subjects, but do indicate that recurrence and embolization can be expected in both groups.

The factors that may influence the results obtained with fibrinolytic therapy are discussed and the importance of considering them in studies of this type is emphasized.

Acknowledgment

The authors wish to express their appreciation to Mrs. M. B. Jefferson and Mrs. J. L. Burbank for their technical assistance in all phases of the study; to Mrs. B. B. Beard and Mrs. A. Cohen for their aid in preparation of the manuscript; and to Dr. Luis Nanni, of Rutgers University for his statistical analysis of the data.

Summario in Interlingua

Sexanta-duo patientes con thrombophlebitis pro-funde de minus que 10 dies de duration esseva studiate sub conditiones a controlo. Trenta patientes, representante le gruppo de controlo, esseva tractate secundo le methodos routinari, incluse le uso de drogas anticoagulante. Trenta-duo patientes, representante le gruppo de tractateau, recipieva fibrinolysina (plasmina) a parte le therapia de controlo.

Le composition del gruppos studiate e le technica experimental usate es presentate in detallo.

Le comparation del 2 gruppos indica che le additio de fibrinolysina al regime therapeutice resulta in un plus rapide resolution del episodio phlebitie acute et reduce possibilemente le incidentia a curte vista de recurrentias phlebitie et de embolisation pulmonar. Residuos postphlebitie esseva incontrate in le du gruppos con quasi le mesme frequentia.

Plus notabile differentias immediate in le responsa therapeutice existe inter le patientes tractate con fibrinolysina e le patientes de controlo si le analyse es restringite a casos tractate intra 5 dies post le declaration del phlebitis.

Le datos currentemente disponibile non permitte firme conclusiones con respecto al apparentemente favorabile influentia de fibrinolysina super le prog-nose a longe vista pro le subjectos phlebitie, sed ille datos indica que recurrentias e embolisationes potre esser expectate in ambe gruppos.

Le factores que affice possibilemente le resultatos obtenite per le therapia fibrinolytic es discutiute. Le importantia de prender los in consideration in studios de iste typo es sublineate.

References


**Vesalius**

During Vesalius’ absence from Padua, after the appearance of his book, the storm broke out. The great Sylvius and others thundered against him, reviling him in a free flow of adjectives. Coming back to Padua, after about a year’s absence, he found opposition to his new views strong even there, not the least active among his opponents being his old pupil Columbus. He gave lectures at Padua, offering to test publicly in the dissecting theatre whether his statements were wrong or not. He lectured also at Bologna, and at Pisa, where the enlightened Cosimo de' Medici of Florence would willingly have detained him as professor in the University which he was nursing. But such tokens of encouragement and others like them weighed before him little when compared with the bigoted opposition of so many of his brethren. The spirit shewn by the latter entered like iron into his soul. If the work on which he had laboured so long and which he felt to be so full of promise met with such a reception, why should he continue to labour? Why should he go on casting his pearls before swine? He had by him manuscripts of various kinds, the embodiment of observations and thoughts not included in the *Fabrica*. What they were we can only guess; what the world lost in their loss we shall never know. In a fit of passion he burnt them all, and the Emperor Charles V., offering him the post of Court Physician, he shook from his feet in 1544 the dust of the city in whose University he had done so much, and still a youth who had not yet attained the thirties ended a career of science so gloriously begun.—Sir M. Foster. *Lectures on the History of Physiology*. London, Cambridge University Press, 1901.
Fibrinolysin (Plasmin) Therapy in Acute Deep Thrombophlebitis: A Controlled Study
KENNETH M. MOSER, STEPHEN B. SULAVIK and GEORGE C. HAJJAR

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