

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today  
(1) was not written for publication in a law journal and  
(2) is not binding precedent of the Board.

Paper No. 15

UNITED STATES PATENT AND TRADEMARK OFFICE

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MAILED

BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

APR 11 1995

PAT.&T.M. OFFICE  
BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte CHARLES S. SCHASTEEN,  
KATHLEEN C. DAY  
and  
RORY F. FINN

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Appeal No. 93-3187  
Application 07/495,008<sup>1</sup>

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ON BRIEF

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Before WINTERS, WILLIAM F. SMITH and TURNER, Administrative  
Patent Judges.

WINTERS, Administrative Patent Judge.

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<sup>1</sup> Application for patent filed March 9, 1990.

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Application 07/495,008

DECISION ON APPEAL

This appeal was taken from the examiner's decision refusing to allow claims 1 through 14, all the claims in this application.

Claims 1 and 12 are representative:

1. A method for enhancing tPA mediated clot lysis which comprises administering a lysis enhancing amount of a peptide of the formula:

Ala-Gly-Arg-Ser-Leu-Asn-Pro-Asn-Arg-Val-  
Thr-Phe-Lys-Ala-Asn-Arg-Pro-Phe-Leu-Val-  
Phe-Ile,

with a lysis effective amount of tissue plasminogen activator.

12. A pharmaceutically-acceptable composition comprising a tPA mediated clot lysis enhancing amount of a peptide of the formula:

Ala-Gly-Arg-Ser-Leu-Asn-Pro-Asn-Arg-Val-Thr-  
Phe-Lys-Ala-Asn-Arg-Pro-Phe-Leu-Val-Phe-Ile,

and a lysis effective amount of tissue plasminogen activator.

The references relied on by the examiner are:

Bock et al. (Bock)	4,632,981	Dec. 30, 1986
Mehta et al. (Mehta)	4,790,988	Dec. 13, 1988

Glover et al. (Glover). "Synthetic Peptide Inhibitors of Complement Serine Proteases--I. Identification of Functionally Equivalent Protease Inhibitor Sequences in Serpins and Inhibition of Cls and D." Molecular Immunology, Vol. 25, No. 12, 1988, pp. 1261-1267.

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The issue presented for review is whether the examiner correctly rejected claims 1 through 14 under 35 U.S.C. § 103 as unpatentable over the combined disclosures of Glover, Mehta and Bock.

OPINION

Our deliberations in this matter have included evaluation and review of the following materials:

- (1) the instant specification, including Figures 1 through 5, and all of the claims on appeal;
- (2) appellants' Brief before the Board;
- (3) the Examiner's Answer;
- (4) the above-cited references relied on by the examiner; and
- (5) the excerpt from the Textbook of Medical Physiology, Arthur C. Guyton, Seventh Edition, W. B. Saunders Company, publisher, pp. 76-83 (1986), copy attached as Appendix C to appellants' Brief.

Having carefully considered those materials, we agree with appellants that the subject matter sought to be patented in claims 1 through 14 would not have been obvious at the time the invention was made to a person having ordinary skill in the art

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based on the combined disclosures of Glover, Mehta and Bock. Accordingly, we reverse the examiner's § 103 rejection. For the reasons explained infra, we enter a new ground of rejection under the provisions of 37 C.F.R. § 1.196(b).

#### The Examiner's Rejection

In independent claim 12, appellants recite a pharmaceutically-acceptable composition comprising the combination of a "lysis enhancing amount" of their enhancer peptide and a "lysis effective amount" of tissue plasminogen activator (tPA). Likewise, independent claim 1 recites a method for enhancing tPA mediated clot lysis which comprises administering a "lysis enhancing amount" of their enhancer peptide with a "lysis effective amount" of tPA. Independent claim 9 recites a method for enhancing tPA mediated clot lysis which comprises administering a "lysis enhancing amount" of a pharmaceutically-acceptable composition containing their enhancer peptide and a "lysis effective amount" of tPA.

Having reviewed the examiner's statement of rejection of claims 1 through 14 under 35 U.S.C. § 103, based on the combined disclosures of Glover, Mehta and Bock, we find that the reasons offered in support of that rejection are somewhat fuzzy.

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We refer to the statement set forth in the Answer, paragraph bridging pages 3 and 4. A more clear explanation of the rejection, with supporting reasons, is presented in the "Response to argument" section of the Answer, paragraph bridging pages 4 and 5. There, the examiner summarizes appellants' arguments as follows:

Focusing their arguments on the Bock et al. reference, appellants state that nothing in the patent teaches or suggests the use of the claimed enhancer peptide for the lysis of blood clots. Appellants believe that Bock et al. is strictly limited to the prevention of coagulation and therefore does not teach or suggest the use of antithrombin to lyse a formed clot [emphasis added].

The examiner takes issue with that position and those arguments, concluding that

[i]t is therefore believed that Bock et al. discloses to one skilled in the art that one would reasonably expect that antithrombin III, when administered to the patient characterized by Bock et al. as having an existing blood clot, would participate in lysing a blood clot with t-PA.

See the Answer, page 5, lines 9 through 13.

On these facts, we understand the examiner's position to be that

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(1) Mehta discloses that tPA mediates the dissolution of blood clots by hydrolyzing fibrin;

(2) Bock discloses that antithrombin III (AT III) is useful for lysing blood clots;

(3) the peptide disclosed by Glover possesses the active site of AT III and, therefore, would reasonably be expected to be useful for lysing blood clots;

(4) the peptide disclosed by Glover is identical to appellants' enhancer peptide; and

(5) it would have been obvious to combine tPA and the peptide disclosed by Glover because each material, individually, is known to be useful for lysing blood clots and it follows that the combination would reasonably be expected to be useful for lysing blood clots.

We disagree with this line of reasoning.

As correctly pointed out by appellants in their Brief before the Board, pages 5 and 6, Bock does not disclose or suggest that AT III is a clot lysis agent. We agree with appellants' interpretation of the Bock patent and we agree that Bock discloses using AT III to prevent coagulation but not as a clot lysis agent. Where, as here, the examiner's rejection is predicated on an incorrect factual finding (i.e., a finding that Bock

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discloses that AT III is useful for lysing blood clots), the rejection must fall.

New Ground of Rejection

Under the provisions of 37 C.F.R. § 1.196(b), we enter the following new ground of rejection.

Claims 1 through 14 are rejected under 35 U.S.C. § 103 as unpatentable over the combined disclosures of the Merck Manual, Fifteenth Edition, pages 565-569 (1987), Mehta, Bock, and Glover. A copy of the newly cited Merck Manual reference is enclosed with this opinion.

In discussing the thrombolytic therapy of deep venous thrombosis (DVT), the Merck Manual discloses at page 569 that

[t]hrombolytic therapy using streptokinase or urokinase in tandem with anticoagulants represents a significant advance in the treatment of acute DVT of the popliteal and more proximal veins. Complete or partial dissolution of thrombi will usually occur within 24 to 48 h. Successful treatment restores venous anatomy and thus prevents valvular damage and the complication of chronic venous insufficiency.

As can be seen from a review of the Mehta reference, particularly column 1, lines 40 and 41, tPA is a well-known thrombolytic agent functionally equivalent to urokinase and streptokinase. It would have been obvious to a person having ordinary skill and well

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within the level of skill in this art to substitute tPA for urokinase or streptokinase disclosed by the Merck Manual for use "in tandem" with anticoagulants in the thrombolytic therapy of DVT.

Furthermore, Bock discloses that AT III is an anti-coagulant and reasonably would be expected to be useful in the clinical prevention and management of thromboses. As expressly stated by appellants,

[a]ll of the language which the Examiner points to in the Bock et al. reference shows using AT III as a means to prevent coagulation [emphasis added].

See appellants' Brief before the Board, page 6.

The peptide disclosed by Glover possesses the active site of AT III and, therefore, would reasonably be expected to possess anti-coagulant properties and to be useful in the clinical prevention and management of thromboses. It is undisputed that the peptide disclosed by Glover is identical to appellants' enhancer peptide.

Based on the combined disclosures of those references, we are persuaded that a person having ordinary skill in the art would have found it obvious to combine tPA and the peptide disclosed by Glover for use "in tandem" in the thrombolytic therapy of DVT. As previously discussed, tPA is a known thrombolytic agent, functionally equivalent to urokinase and streptokinase as disclosed by Mehta in column 1, lines 40 and 41. The

peptide disclosed by Glover possesses the active site of AT III and, therefore, would reasonably be expected to possess anticoagulant properties and to be useful in the clinical prevention and management of thromboses. Merely selecting a known thrombolytic agent (tPA) and a known anticoagulant (the peptide disclosed by Glover) for use "in tandem" in the thrombolytic therapy of DVT, per the teachings of the Merck Manual, does not rise to the level of patentability absent a showing of unexpectedly superior results. In so finding, we agree with the examiner's statement of motivation that

[o]ne skilled in the art would have been motivated to employ the smaller active peptide [the peptide disclosed by Glover] in place of the intact enzyme [AT III] because of the advantages of easy synthesis, and less physiological complications because of the small size of the peptide.

See the Examiner's Answer, sentence bridging pages 3 and 4. On this record, that statement has not been disputed by the appellants.

For these reasons, we hold that the subject matter sought to be patented in claims 1 through 14 would have been prima facie obvious based on the combined disclosures of the Merck Manual, pages 565-569, Mehta, Bock and Glover.

According to appellants, Figures 3, 4 and 5 in the specification

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(1) establish that the instantly claimed subject matter possesses unexpectedly superior results, and

(2) serve to rebut the prima facie case of obviousness.

We disagree.

First, Figures 3, 4 and 5 are designed to show that the combination of tPA and the enhancer peptide possesses "synergism," i.e., an unexpectedly greater effect compared with each material used alone. Manifestly, that showing is not designed to compare and does not compare against the closest prior art. Here, the closest prior art is the Merck Manual, Fifteenth Edition, page 569, disclosing thrombolytic therapy in the treatment of DVT using a well-known thrombolytic agent "in tandem" with anticoagulants. The Merck Manual discloses a combined or "in tandem" therapy using a thrombolytic agent and an anticoagulant. Manifestly, the comparison presented in Figures 3, 4 and 5 does not compare appellants' claimed composition against a representative prior art composition containing both thrombolytic agent and anticoagulant. For example, Figures 3, 4 and 5 do not compare appellants' composition against a composition containing streptokinase or urokinase and the peptide disclosed by Glover. Comparative data, to be effective, must compare the claimed subject matter with the closest prior art. Viewing the situation

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in this light, we find that Figures 3, 4 and 5 in the specification do not address the thrust of the new ground of rejection.

Second, in order for a showing of "unexpected results" to be probative evidence of non-obviousness, it is incumbent on appellants to at least establish:

(1) that there actually is a difference between the results obtained through the claimed invention and those of the prior art; and

(2) that the difference actually obtained would not have been expected by one skilled in the art at the time the invention was made.

In re Freeman, 474 F.2d 1318, 177 USPQ 139 (CCPA 1973); In re D'Ancicco, 439 F.2d 1244, 169 USPQ 303 (CCPA 1971). This appellants have not done. Here, the prior art discloses that combination thrombolytic therapy using a well-known thrombolytic agent "in tandem" with anticoagulants

represents a significant advance in the treatment of acute DVT of the popliteal and more proximal veins. Complete or partial dissolution of thrombi will usually occur within 24 to 48 h. Successful treatment restores venous anatomy and thus prevents valvular damage and the complication of chronic venous insufficiency.

See the Merck Manual, Fifteenth Edition, page 569.

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In light of that prior art knowledge, we believe that a person having ordinary skill in the art would have expected excellent results when using "in tandem" a known thrombolytic agent, e.g., tPA, and a known anticoagulant, e.g., the peptide disclosed by Glover. As often stated by our reviewing court, expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected beneficial results are evidence of unobviousness. In re Skoll, 523 F.2d 1392, 187 USPQ 481 (CCPA 1975); In re Skoner, 517 F.2d 947, 186 USPQ 80 (CCPA 1975); In re Gershon, 372 F.2d 535, 152 USPQ 602 (CCPA 1967). Conspicuous by its absence from this record is a statement by an expert in the art, mindful of the Merck Manual disclosure, explaining just why the results set forth in Figures 3, 4 and 5 of the specification would have been unexpected.

It should be apparent from the foregoing discussion that we disagree with the assessment that Figure 3 shows an unexpected result, even to a limited extent. See the Examiner's Answer, paragraph bridging pages 5 and 6. For the reasons discussed above, we find that appellants have not established an unexpectedly superior result or results on this record.

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Conclusion

In conclusion, we reverse the rejection of claims 1 through 14 under 35 U.S.C. § 103 as unpatentable over the combined disclosures of Mehta, Bock and Glover. We enter a new ground of rejection of claims 1 through 14 under 35 U.S.C. § 103 as unpatentable over the combined disclosures of the Merck Manual, Fifteenth Edition, pages 565-569 (1987), Mehta, Bock, and Glover.

The examiner's decision is reversed.

Any request for reconsideration or modification of this decision by the Board of Patent Appeals and Interferences based upon the same record must be filed within one month from the date of the decision (37 C.F.R. § 1.197). Should appellants elect to have further prosecution before the examiner in response to the new rejection under 37 C.F.R. § 1.196(b) by way of amendment or showing of facts, or both, not previously of record, a shortened statutory period for making such response is hereby set to expire two months from the date of this decision.

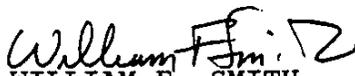
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No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

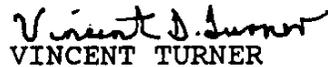
REVERSED 37 C.F.R. § 1.196(b)



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Administrative Patent Judge )



WILLIAM F. SMITH )  
Administrative Patent Judge )



VINCENT TURNER )  
Administrative Patent Judge )

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### Treatment

Therapy of the secondary forms depends on recognition and treatment of the underlying disorder. Mild cases of Raynaud's disease may be controlled by protecting the body and extremities from cold and by using mild sedatives (eg, phenobarbital, 30 mg orally tid or qid). The patient must stop smoking since nicotine is a vasoconstrictor. In a few patients, relaxation techniques, such as biofeedback, may result in vasospastic episodes. Drugs formerly used for treatment have been varied and inconsistently effective. Reserpine 0.1 mg to 0.25 mg orally bid to tid has been commonly used and may decrease the number and severity of attacks, but side effects (eg, depression) may prevent its use. Phenoxybenzamine 10 mg orally tid and methyldopa 1 gm/day orally have been tried with occasional success. The drugs of choice are newer vasodilating agents: prazosin 1 to 2 mg orally at bedtime, and repeated in morning, if necessary, and the Ca-channel blocker nifedipine 10 to 30 mg orally. Reserpine 1.0 mg in 5.0 mL of 0.9% sodium chloride solution injected into the brachial artery q 3 mo may have a beneficial effect on the healing of ulcers. Encouraging reports concerning the effectiveness of pentoxifylline 400 mg bid or tid with meals have appeared in the literature. Research with encouraging results is in progress for the prostaglandins (thromboxane) in the treatment of Raynaud's phenomenon. Phenylbenzamine 10 mg orally tid may be useful. Methyldopa 1 to 2 gm/day or prazosin 8 mg/day may benefit patients with Raynaud's disease. The Ca blocker nifedipine preparations cause vasoconstriction and may induce or worsen Raynaud's phenomenon and are, therefore, contraindicated. Regional sympathectomy is reserved for patients with progressive disability; it often abolishes the symptoms, but the relief may last only 1 to 2 yr. Results from sympathectomy are generally better in patients with Raynaud's disease than in those with secondary Raynaud's phenomenon.

### ACROCYANOSIS

Persistent, painless, symmetric cyanosis of the hands and, less commonly, the feet, caused by vasospasm of the small vessels of the skin. The etiology is unknown, but it is caused by increased tone of the arterioles associated with dilation of capillaries and venules. The disorder usually occurs in women and is not associated with occlusive arterial disease. The digits and hands or feet are persistently cold, bluish, and swollen profusely; they may swell. Cyanosis is usually intensified by exposure to cold, lessened with warming. Trophic changes and ulceration do not occur, and pain is absent. Diagnosis is made from the persistent nature of the findings localized to the hands and feet in the presence of normal arterial pulsations. Except for reassurance and protection from cold, treatment is usually unnecessary. Vasodilators may be tried but are usually ineffective. Sympathectomy is helpful but seldom warranted.

### ERYTHROMELALGIA

A rare syndrome of paroxysmal vasodilation with burning pain, increased skin temperature, and redness of the feet and, less often, the hands. The etiology of primary erythromelalgia is unknown. Secondary erythromelalgia may occur in patients with myeloproliferative disorders, hypertension, venous insufficiency, or diabetes mellitus. The condition is characterized by attacks of burning pain in hot, red feet or hands. Distress is triggered by modest ambient temperatures usually varying between 29 and 32 C (84.2 and 89.6 F) in most patients. Trophic changes do not occur. Symptoms may remain mild for years or may become so severe that total disability results. Diagnosis based on demonstration that the patient's complaints are related to objectively increased skin temperature. Secondary types should be differentiated from the rare

Ch. 30  
 Ch. 30  
 primary disorder, since, in the former, correction of the underlying disorder may relieve the symptoms.

### Treatment

Attacks can be avoided or aborted by rest, elevation of the extremity, and cold applications. Therapy is not always successful. Correction of the underlying disease in specific forms is indicated. In primary erythromelalgia, modest doses of aspirin (600 mg 1 to 4 times/day) may produce prompt, prolonged relief. Avoiding factors that produce vasodilation is usually helpful, and vasoconstrictors (eg, ephedrine 25 mg orally, propranolol 10 to 40 mg orally qid, or methysergide 1 to 4 mg orally q 4 h) may also produce relief.

## VENOUS DISEASES

### VENOUS THROMBOSIS (Thrombophlebitis; Phlebitis)

The presence of a thrombus in a vein.

Other than varicose veins, the most common venous disorders that bring patients to a physician are deep venous thrombosis (DVT), thrombophlebitis, and the sequelae of chronic venous insufficiency: edema, stasis pigmentation, stasis dermatitis, and stasis ulceration. These are usually readily diagnosed except for DVT of the calf, which requires venography or scanning with radioactive fibrinogen. The symptoms of acute thrombophlebitis arise over a period of hours to 1 or 2 days. The disease process is usually self-limited and lasts between 1 and 2 wk; then the acute process subsides and painful symptoms disappear.

The terms *phlegmasia alba dolens* (milk leg) and *phlegmasia cerulea dolens* are applied to extensive thrombosis of the involved extremity (depending on its color). The former term is archaic and is now referred to as iliofemoral thrombophlebitis. The latter term is still used and means a massive venous thrombosis often leading to venous gangrene and eventual death due to underlying disease (eg, widespread malignancy). Eponyms describe thromboses in specific anatomic areas: Mondor's disease refers to thrombosis of the superficial veins over the mammary gland or the adjacent chest wall; Budd-Chiari syndrome characterizes the results of hepatic vein thrombosis. Phlebitis migrans refers to recurrent venous thrombosis, mainly superficial, but occasionally in deep veins of the extremities and other areas usually due to underlying malignancy. Effort (strain) thrombosis occurs in the subclavian vein, secondary to trauma to the vein in the thoracic outlet during unusual physical effort in which the arm is fully abducted. Chemical phlebitis results from intimal injury induced by the introduction of catheters or noxious agents directly into a vein. "Chronic thrombophlebitis" does not exist. (Pelvic vein, mesenteric vein, portal vein, renal vein, jugular-mesenteric vein thromboses, etc., are not discussed here.)

### Etiology

Many factors may contribute to venous thrombosis: (1) injury to the epithelium of the vein, such as occurs with indwelling catheters, injection of irritating substances, thrombocytopenic purpura, and septic phlebitis; (2) hypercoagulability associated with malignant tumors, blood dyscrasias, oral contraceptives, and idiopathic thrombophlebitis; and (3) stasis that occurs in postoperative and postpartum states, varicose thrombophlebitis, and the thrombophlebitis that complicates prolonged bedrest of any chronic illness, heart failure, stroke, and trauma. Prolonged immobilization with the legs dependent while traveling is a risk factor, even in normal, healthy persons.

It is likely that all of these factors play a role, i.e., endothelial injury exposes collagen, causing platelet aggregation and tissue thromboplastin release that, when stasis hypercoagulability is present, trigger the coagulation mechanism.

#### Pathophysiology

Most venous thrombi begin as platelet nidi in the valve cusps of deep veins propagate proximally as a red or fibrin thrombus and fibrin that trap RBCs and arterial lesions. Fibrin thrombi can be prevented from forming or extending by anti-thrombotic drugs (eg, heparin or the coumarin compounds), but the platelet portion of thrombi has not been shown to be influenced by antiplatelet agents, although under intensive study, have not been proven to be effective.

#### Symptoms and Signs

DVT may be asymptomatic or may be manifested over the involved area by variable combinations of tenderness, pain, edema, warmth, bluish skin discoloration, and prominent superficial veins. With deep thrombophlebitis involving the popliteal, femoral, and iliac segments, there may be tenderness and a hard cord palpable over the femoral vein in the femoral triangle in the groin, the medial thigh, or popliteal space over the leg, thigh, and hip areas and lower abdomen. Bedside evaluation will make diagnosis in this clinical setting, but difficulties arise in the diagnosis of DVT of the calf. Since at least 3 main veins drain the lower leg, thrombosis in one will not cause obstruction to venous return, and there is no swelling, cyanosis of the skin, or dilated superficial vein. The patient complains of soreness or of pain on standing and walking that is usually relieved by rest with the leg elevated. On examination, deep calf tenderness can be elicited, but differentiation from muscle pain is often difficult. Pain from straight leg raising (Homans' sign), thereby making this test an unreliable indication of DVT. Loss of peripheral arterial pulses may occasionally accompany massive DVT, but venous thrombosis can also be secondary to acute arterial occlusion.

Superficial thrombophlebitis: A thrombosed superficial vein always can be palpated as a linear, indurated cord; it may be associated with a variable inflammatory reaction manifested by pain, tenderness, erythema, and warmth and may need to be differentiated from acute secondary lymphedema with infection (see below). Palpation of a superficial cord in the leg reflects occlusion of a superficial vein; the inference that this finding, per se, reflects DVT is not justified, since it is seldom the case.

Chronic venous insufficiency in the leg after deep thrombophlebitis is manifested by edema and dilated superficial veins. The patient may complain of fullness, aching, or tiredness in the leg or have no discomfort. This occurs during standing or walking and is relieved by rest and elevation. There is no tenderness over the deep veins to indicate an acute thrombophlebitis, but a history of a previous deep thrombophlebitis is usual not controlled by an elastic support. With time, skin pigmentation appears on the medial and sometimes the lateral aspect of the ankle and lower leg. Further complications include stasis dermatitis and stasis ulceration in these areas. Patients with chronic venous insufficiency may develop varicose veins, but these are secondary to DVT, not often mild, and function as collateral vessels. They should not be excised unless severe.

The symptoms and signs of varicose veins are discussed separately, below.

Physical examination usually can distinguish between acute arterial and venous obstruction. If there is any question, the dilemma can be resolved by noninvasive testing or by arteriography or venography if necessary. A diagnosis of acute DVT cannot be made satisfactorily by clinical findings alone > 50% of the time; Homans' sign should not be relied upon for the diagnosis, and edema may be due to other causes. Specific limb findings (eg, edema, dilated superficial veins), evidence of pulmonary embolism, and the overall clinical setting, including the risk factors mentioned under Etiology (above), permit the physician to estimate the likelihood of a patient having DVT. Noninvasive tests are helpful. If any doubt remains, a venogram should be obtained. Pulmonary embolism can be sought with lung scan or pulmonary arteriogram (see Ch. 39). Overlooking the presence of phlebitis may lead to death from intravascular thrombus by venography or lung scan risks serious hemorrhage.

Contrast venography, as the most accurate diagnostic procedure, is the standard of comparison for every other test. It is widely used, with infrequent complications. Procedures used to locate actively forming DVT include leg scanning, Doppler ultrasound, and plethysmography. Scanning after injection of <sup>125</sup>I fibrinogen is a sensitive screening test for deep calf, popliteal, and distal thigh thrombosis. Doppler ultrasound that the thyroid gland must be blocked, which requires 24 to 36 h, and since the thrombus must be actively forming to incorporate the isotope, heparin must be withheld. Since <sup>125</sup>I fibrinogen appears in blood and exudate, the test is not reliable when healing wounds or hematomas are present in the leg, and it cannot detect thrombi in the upper thigh or pelvis.

Isotope venography is performed by injecting sodium pertechnetate Tc 99m into peripheral vein and scanning the leg with a gamma camera. Although less painful and quick, this method does not give the resolution of conventional venography, but is a valuable alternative in the patient who is sensitive to contrast media.

Noninvasive procedures are less accurate than venography but, in combination, can be diagnostic in 90 to 95% of cases. Doppler ultrasound allows the examiner to scan various segments of an extremity, characteristic alterations in spontaneous flow sounds that occur because of recent complete obstruction of the proximal veins (popliteal and the veins proximal to it). The examiner listens over the femoral vein in the groin, the medial thigh, and the popliteal space. Normal sounds are like a howling wind that waxes and wanes with respirations. Below an obstruction, the respiratory phasicity disappears and abnormal sounds cannot be obliterated by Valsalva or augmented by its cessation. Above an obstruction, augmentation of the venous sound by compressed muscle distally (lower thigh or calf) is lost. For results to be reliable, this method requires considerable training. The test is not reliable in old disease with good collateral circulation. It does not detect thrombi in the calf or tributary veins since these do not cause obstruction to venous return. A negative ultrasound examination is not sufficient to exclude the diagnosis of DVT confidently in the presence of suspicious clinical findings.

Plethysmography, as with ultrasonography, can be used with acceptable accuracy to diagnose thrombotic obstruction of major proximal veins of the extremities. It is not detect calf vein thrombosis. Reductions in venous capacitance and outflow caused by an obstructing thrombus in a proximal vein causes changes in electrical impedance as well as volume and rate of outflow. These changes can be measured with approximately 95% accuracy with instruments using these principles, ie, impedance or plethysmography, plethorheplethysmography, and mercury strain-gauge plethysmography. These methods are noninvasive, relatively inexpensive, require minimum cooperation from the patient, and can be performed well by a trained technician. They

