

Early Detection of Deep Venous Thrombosis of the Legs Using I¹³¹ Tagged Human Fibrinogen: *

A Clinical Study

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PREVIOUSLY we have shown that human fibrinogen tagged with I¹³¹ can be incorporated into a developing thrombus.² By this means the thrombus is rendered radioactive and can be detected by scintillation counting.¹ The experimental work was done in dogs, and a few patients were studied. The present report deals with the total experience to date of 75 patients.

Active thrombosis must be in progress for the test to be effective because the injected I¹³¹ tagged fibrinogen must be converted into I¹³¹ fibrin in the clot area to be detected. The test is effective only for thrombosis at and below the inguinal ligament because the scanning is comparing the affected leg with the normal one. It depends upon the differential count between the two legs and progressive change within the former.

The test now has been incorporated into the routine isotope tests on clinical wards. It is thus available on requisition to the isotope laboratory. The test has been found useful not for the full-blown, clinically evident, deep venous thrombosis which is readily diagnosed by clinical examination, but rather for the case with equiv-

ocal signs which may or may not indicate an underlying phlebitis. It has further proved useful in those patients who develop chest symptoms which may indicate a small pulmonary embolus, but of which there is no clinical or radiologic proof; positive results with I¹³¹ leg scan at least prove a site from which the embolus may have arisen and are an indication for anticoagulant therapy. Unfortunately, this method is not applicable at present to pelvic vein thrombosis which is the other possible source of pulmonary emboli. Nevertheless it has proved a reliable guide to anticoagulant treatment.

The third use is in those patients who are particularly prone to develop deep venous thrombosis because of the nature of their illness, e.g., heart failure with congestion, cancer and general debility or a previous history of deep venous thrombosis and who are to undergo operation. These patients can be tested in the postoperative period to discover early evidence of clotting in the deep veins of the leg. Evidence of such clotting can be gained 24 to 48 hours before clinical symptoms and signs appear.

Method

1. The patient is given 0.6 ml. of Lugol's iodine by mouth before the test begins and this is continued three times daily for 4 days. This is to block uptake of I¹³¹ into the thyroid gland.

* Presented before the American Surgical Association, Philadelphia, Pa. May 12-14, 1965.

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Supported by Research Grant of the Life Insurance Medical Research Fund, Grant #G-65-42.

FIG. 1. View of detection system consisting of a scintillation probe, pulse height analyzer and scaler, mounted on mobile stand. Seven counting areas marked off on each leg from the ankle to the groin. Patient lies comfortably in bed.



2. 100 microcuries of I^{131} tagged human fibrinogen * is injected into an arm vein.

3. External scintillation counting is carried out on each leg as the patient lies in bed (Fig. 1). The detection system consists of the scintillation probe, pulse height analyzer and scaler. It is mounted on a mobile probe stand so that the counting procedure can be done at the patient's bedside.

The probe consists of a 2-inch diameter by 2-inch thick NaI(Te) crystal set back in a lead shield so that there is a distance of $4\frac{3}{4}$ inches from the crystal face to the external aperture of the wide angle collimator. The external aperture of the collimator measures $4\frac{1}{4} \times 3$ inches. The pulse height analyzer permits the counting of only 364 kw gamma rays from I^{131} .

Both legs are counted at measured intervals from the toes to the inguinal ligament. There are seven counting areas, four below and three above the knee. A difference greater than 15 per cent between comparable areas of each leg, or a progressive change of over 15 per cent in one, is con-

sidered indicative of an active thrombotic process at that point. With the magnitude of counts per minute recorded, a difference of 15 per cent usually corresponds to three to four standard deviations. It is necessary for the difference to be constant in subsequent readings. The level of significance has been determined by studying 14 normal patients.

The counting procedure begins 1 hour after the fibrinogen is injected to provide a base line, and thereafter it is repeated three times in the day. When a rising count is detected, the counting is continued every 2 hours to confirm findings and follow thrombus formation. As previously reported² a definite diagnosis can be made as soon as 3 hours after the injection of the I^{131} tagged fibrinogen, although a more usual period is 6 hours.

4. As soon as the technician notices an abnormal fibrinogen uptake, he notifies the resident staff on the ward so that anticoagulant therapy may be begun. In cases where the reading is not strongly confirmatory, but is suspicious, the resident is notified that a further report will follow in 2 hours.

* Obtained from Abbott Radio-Pharmaceuticals, Oak Ridge, Tennessee.

TABLE 1. Total Clinical Experience in 75 Patients*

Group	Type of Patient	No.	Positive
I	Normal	14	nil
II	Equivocal symptoms or signs	35	13
III	Possible pulmonary embolism	8	3
IV	Thrombosis prone	18	3
Total		75	19

* Previous study, 26; present study, 49.

Results

The patients have been divided into four groups (Table 1).

Group I. Normal controls, 14. Ages of these patients ranged from 45 to 86 years. Counts between comparable areas on each leg never differed at any one time by as much as 15 per cent. The range was between 1,000 to 5,000 cpm.

Group II. 35 patients, 13 positive. These were patients who had equivocal symptoms and signs of deep venous thrombosis in the legs. These symptoms and signs may have been local or systemic or a combination of both. Patients with positive diagnoses were then treated by anticoagulants in most instances.

Group III. 8 patients, 3 positive. These were patients who had equivocal symptoms and signs suggestive of pulmonary embolism which might have arisen in the legs. All patients recovered normally.

Group IV. 18 patients, 3 positive. These were thrombosis-prone patients who were studied in order that occult deep venous thrombosis might be detected and appropriate treatment instituted early. This group included those with gross varicosities of the lower extremities and previous history of deep venous thrombosis or embolism and patients who were debilitated or had been bed-ridden. Patients with fractured hips should be studied in this way.³

Representative Case Reports

Group I

Case 1. A 65-year-old man was admitted because of migraine headaches. Normal uptake of ¹³¹I tagged fibrinogen, with less than 10% variation between legs at any one time (Fig. 2).

Case 2. A 69-year-old man was admitted with delirium tremens due to chronic alcoholism. Fibrinogen counts were normal except for one reading at a 14% increase in one leg. This reading returned to normal in all subsequent counting and was not considered to be significant.

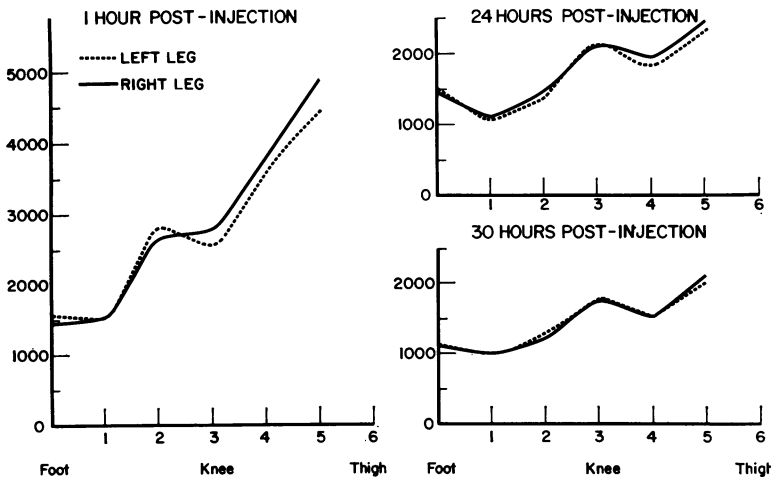
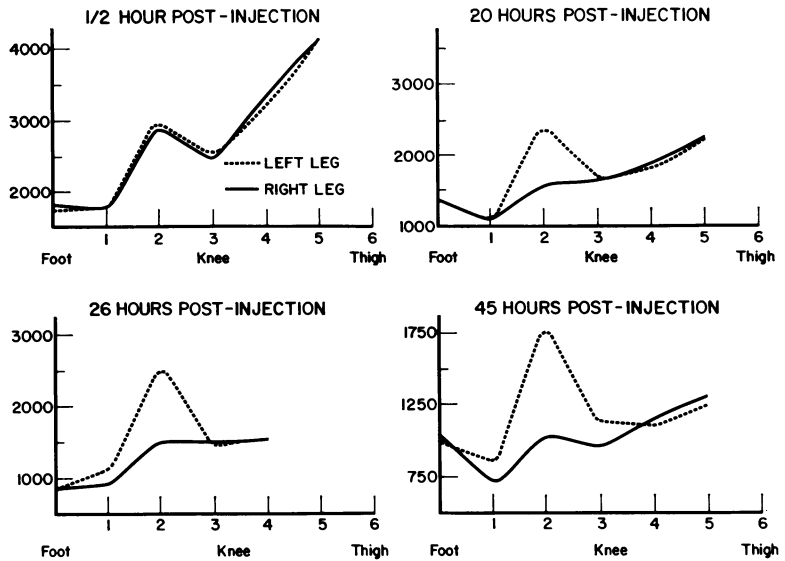


FIG. 2. Example of Group I normal control: Case 1. Less than 8% difference between both legs and no localized rise to one area of one leg.

FIG. 3. Case 3. ^{131}I tagged fibrinogen study was done on the eighth postoperative day and indicates a 75% increase of counts over the left calf.



Group II

Case 3. A 32-year-old woman was admitted with a bleeding gastric ulcer for which she had a Bilioth I partial gastrectomy. Three days postoperatively she developed left calf pain and coughed up blood. Five days later she had some left chest pain and a questionable hemoptysis. On the eighth postoperative day isotope studies showed a 75% increased uptake in the left leg below the knee. The next day anticoagulant therapy was begun. Ten days later she was discharged as well (Fig. 3).

Case 4. A 24-year-old man was admitted with possible deep venous thrombosis in the right leg in which he had local pain, tenderness and some erythema. He was suspected of having an occult malignancy. Fibrinogen studies showed a 45% increase in counts over the right leg.

Case 5. A 58-year-old man had prostatic obstruction for which he had a transurethral resection. He developed local pain and tenderness in the right calf with no systemic findings. Fibrinogen studies were normal, so that no special treatment was instituted and his symptoms disappeared spontaneously.

Case 6. A 72-year-old man was admitted with fracture of left hip which was pinned. He developed local symptoms and signs in the calf with an increased uptake of up to 45% below the knee. Treatment was successful.

Case 7. A 55-year-old woman was admitted with gastrointestinal hemorrhage for which she

had a gastrectomy. Postoperatively the patient developed local signs and symptoms in the left leg. Fibrinogen studies were normal.

Group III

Case 8. A 46-year-old woman was admitted with a history of recurrent pulmonary emboli for which she had a prophylactic ligation of the inferior vena cava. On clinical examination there were no signs of deep venous thrombosis in either leg. However, fibrinogen studies were done on the second postoperative day for academic reasons. Initially the counts were normal, but on the fourth postoperative day counts in the right calf increased by a factor of 50%. Twenty-four hours after the suspected deep thrombotic process was reported, clinical signs and symptoms of pain and tenderness appeared, thus confirming the fibrinogen studies which had given a 24 hour warning. Anticoagulant treatment was begun 5 days after the initial positive fibrinogen study, when deep venous thrombosis was patently evident.

Case 9. A 36-year-old man was a long-standing paraplegic who fractured the shaft of his right femur which was treated by skeletal traction. The patient developed a pulmonary embolism and fibrinogen scanning revealed a 200 to 300% increased uptake over the left thigh area. There was good clinical evidence of a massive deep venous thrombosis involving the common femoral vein. Anticoagulant therapy was instituted but two further episodes of small emboli occurred. For this reason the inferior vena cava was ligated

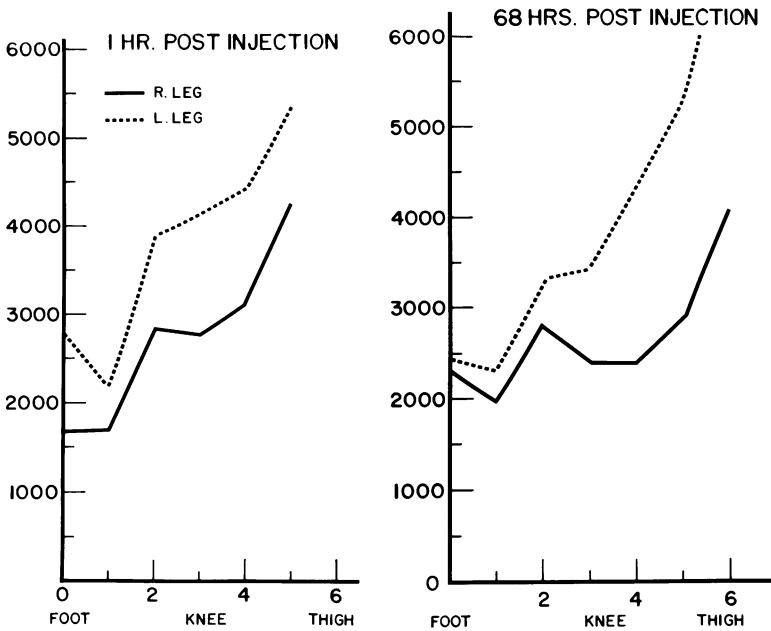


FIG. 4. Case 13 with extensive deep venous thrombosis of the left leg associated with extensive malignancy. Extensive ^{131}I tagged fibrinogen uptake on the left leg throughout its length at 1 hour. Persisting increase of counts over the whole of the left leg at 68 hours.

and at the same time the thrombus in the left common femoral and iliac veins was removed by thrombectomy. Subsequent fibrinogen scanning showed normal readings over the area where the 200 to 300% counts had been recorded. This was proof of the fact that the previous thrombus had been removed and that no fresh thrombus was forming. This was borne out by the clinical course. The patient's swelling in his left leg rapidly and completely regressed even though the inferior vena cava had been ligated. He had been maintained on anticoagulant therapy throughout this period.

Case 10. A 53-year-old man was admitted with cholelithiasis for which he had a cholecystectomy. In the postoperative period he developed chest pain suggestive of a pulmonary embolism. Fibrinogen studies of the legs were entirely normal. Prior to the study the patient had been placed on anticoagulant therapy which was discontinued after only 24 hours. The chest pain cleared up spontaneously. This represents the use of this test as a means of disproving a pulmonary embolism and obviating the needless use of anticoagulants.

Group IV

Case 11. A 68-year-old woman was admitted with a fractured hip which was pinned. She had varicose veins and had been immobilized for some time. Fibrinogen studies remained normal throughout so that no anticoagulant treatment was needed.

Case 12. A 65-year-old man had a partial gastrectomy for a gastric ulcer. He had a history of previous migratory phlebitis. For this reason fibrinogen studies were done. They remained normal throughout the postoperative period so that no anticoagulant treatment was needed and no signs of deep venous thrombosis developed.

A final patient is discussed because there is radiographic and autopsy confirmation of the validity of isotope studies. This patient had florid deep venous thrombosis of the left leg and therefore did not fit strictly into any of the above four groups, although he most approximated Group II.

Case 13. A 93-year-old man was admitted to the medical wards with prostatic obstruction, weakness and a history of "influenza" 3 weeks previously. He was found to have ascites, intra-abdominal metastatic malignancy and edema of the left lower leg. There was tenderness localized to the popliteal area. He was profoundly anemic; the hemoglobin level was 5 Gm./100 ml. Twelve hours later there was swelling of the entire leg with maximum tenderness in the left inguinal area. Femoral pulses were of good volume. The diagnosis was terminal malignancy with venous thrombosis involving the common femoral vein.

Isotope studies (Fig. 4) showed increased uptake over the whole left leg with none of the usual spike over the soleal area. Uptake in the

left leg was 45 to 75% higher than that in the right leg. A venogram showed complete obliteration of the deep veins from the lower calf (Fig. 5A, B) up to the sapheno-femoral junction (Fig. 5C). The patient died 13 days later, and autopsy revealed diffuse carcinoma of the stomach. There were multiple pulmonary emboli and terminal pneumonia with thrombosis of all the main deep veins in the left leg up to the sapheno-femoral junction. The pelvic veins were clear. Isotope studies on the thrombus removed from the sapheno-femoral junction down to the knee showed counts of just over 100 per unit counting length.

Comment

In the 75 patients studied, no false positive and no false negatives have been proved, i.e., no patient who has been reported as positive for deep venous thrombosis has been proved not to have the lesion. Under anticoagulant therapy the positive cases have responded by regression of symptoms as expected. Nor has any case reported as negative subsequently devel-

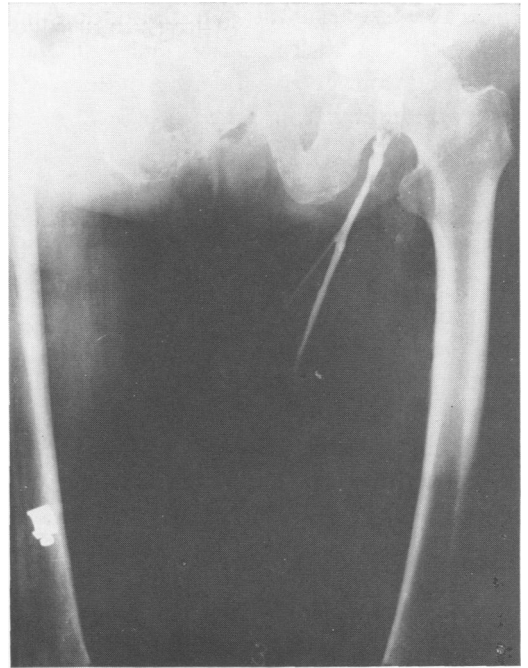


FIG. 5. C. Venogram showing thrombus in the common femoral vein right up to the sapheno-femoral junction. The vein outlined is the long saphenous vein.

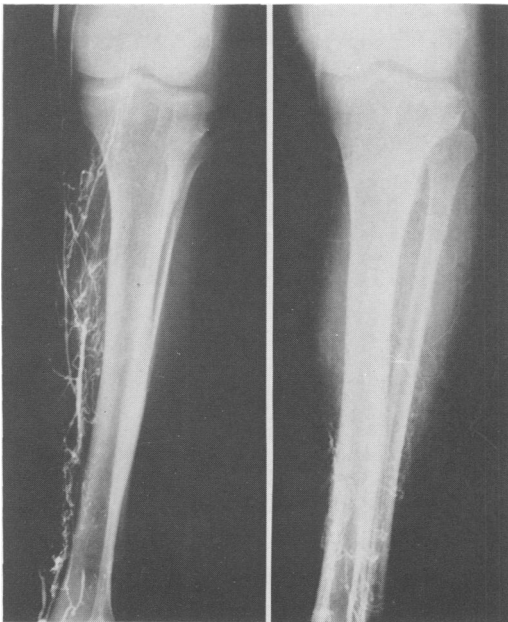


FIG. 5. A. (Left). Case 13. X-ray picture of venogram showing complete obstruction of deep venous system in the calf and popliteal fossa. B. (Right). Further venogram showing obstruction of deep veins beginning at the lower one quarter of the left calf.

oped florid signs of a deep venous thrombosis in the leg or pulmonary embolism. Therefore, the test would appear to be reliable.

The advantages of the use of the I^{131} fibrinogen test are that:

1. It tends to remove the element of uncertainty from the diagnosis of deep venous thrombosis and minor pulmonary embolism.
2. It can anticipate the onset of clinical symptoms and signs of deep venous thrombosis by 24 hours and, therefore, enable anticoagulant therapy to begin early.
3. It can be used to follow thrombosis-prone patients and thus, by treatment, abort severe and florid attack. Blanket prophylactic treatment for this type of patient with anticoagulants is unnecessary.
4. It might be expected that by early adequate treatment of deep venous thrombosis the late sequelae of the postphlebotic syndrome may be prevented or minimized.

5. The test is simple to perform, does not distress the patient and does not aggravate the condition. It can be repeated several times without harm.

Summary

Clinical experience with the use of I^{131} tagged fibrinogen used in 75 patients to study deep venous thrombosis in the legs is reported. Four groups were studied: normal patients, patients with equivocal symptoms and signs, patients with possible pulmonary emboli and patients who were thrombosis prone. 19 positive tests were found. With 14 of the 75 patients serving as controls, 19 of 61 tests were positive.

The test appears to be reliable and causes

no discomfort to the patient. It enables early therapy to be instituted and unnecessary therapy to be obviated.

Acknowledgments

The authors wish to acknowledge the help of Mrs. L. J. McDonald and Mr. A. Seminoff, technicians in the Department of Radiotherapy.

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DISCUSSION

DR. DAVID C. SABISTON, JR. (Durham, N. C.): I have had the privilege of reviewing Dr. Nanson's complete manuscript and wish to commend him for it. He has described an ingenious method for early detection of thrombophlebitis and has carefully documented its indications and usefulness. One of the more interesting aspects of the problems associated with thrombophlebitis is the ultimate fate of intravascular thrombi and emboli. Following numerous experimental and clinical observations, we have become impressed with the phenomenon of thrombosis *in situ* which is frequently associated with pulmonary emboli.

(Slide) In this slide one sees an embolus in the right lower lobe of pulmonary artery. Shortly after arriving at this site intravascular thrombosis occurred both proximal and distal to the embolus and this process could be followed by serial pulmonary cine-scans.

(Slide) After the embolus is removed, repeated serial scans clearly show that the thrombus *in situ* slowly disappears with return of function and blood flow to the involved area of the lung.

I hope Dr. Nanson will comment on any data which he may have concerning the resolution of thrombi, especially in association with this interesting technic which he has described. Also, I would like to ask if he has had occasion to scan the lungs to determine the presence of tagged fibrinogen emboli.

DR. CHARLES G. ROB (Rochester, N. Y.): We have had some experience with this technic, using a method developed by Dr. Schwartz in the De-

partment of Surgery at Rochester, and I would like to show two slides.

(Slide) We have used a slightly different technic, and with a slightly different end in view. We have practiced thrombectomy for deep venous thrombosis fairly widely in our school. Using this technic, you see here the phlebogram on one side and the scan on the other, and this is a reasonable method of detecting visually the thrombus and locating it sufficiently accurately to perform a thrombectomy.

(Slide) This slide is the phlebogram demonstrating the thrombus on the left, and the scan demonstrating the same thrombus on the right.

We believe, therefore, that this method which has been described today by Dr. Nanson is a good preoperative screening method before thrombectomy, and, in fact, is a satisfactory alternate to phlebography in such patients.

DR. ALTON OCHSNER (New Orleans): I think we are indebted to Dr. Nanson for giving us a method of being able definitely to detect thrombi in the extremity. A number of years ago we studied the cases at the Charity Hospital, and we were astounded to find that in 40 per cent of our patients with fatal pulmonary emboli—in going back over the records of these patients—we could find no clinical evidence of an antecedent thrombus, so that any condition which occurs so insidiously (and this is an institution where we were interested in venous thrombosis) is hazardous. Any method that will give us a chance of detecting this at a time when something can be done I think is very worth while.