THE INCIDENCE AND PREVENTION OF POSTOPERATIVE VENOUS THROMBOSIS

T H E S I S

For the Degree of

MASTER OF SURGERY

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University of Cape Town

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Stephen Neal Joffe

Tutius prohibentur mala quam curantur

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1. INTRODUCTION

In the last few years a very high incidence of deep vein thrombosis has been reported in the literature (1 - 8). Venous thrombosis and its sequel, pulmonary embolus account for 12.5% of all postoperative deaths and is the single greatest threat to recovery after surgical operations (9). This study was undertaken to investigate the incidence of postoperative deep vein thrombosis occurring at Groote Schuur Hospital using the newer methods of diagnosis. No previous similar study has been conducted in South Africa. The high risk factors predisposing to venous thrombosis have been assessed and the techniques of diagnosis using Radio-active fibrinogen, Doppler ultrasound and Venography have been studied.

The local findings reported in this study confirmed the high reported incidence. Methods of prevention of venous thrombosis using low does heparin and sodium pentosan polysulphate have been assessed.

2. REVIEW OF THE LITERATURE

I. METHODS OF DIAGNOSIS

II. INCIDENCE

III. PREVENTION

I. METHODS OF DIAGNOSIS

1. Clinical

2. Radio-active I^{125} labelled Fibrinogen.

3. Doppler Ultrasound

4. Venography

5. Limb Impedance

6. Thermography

7. Blood Tests

    a. Platelet Adhesiveness

    b. Fibrin Degradation Products and Other Tests.

DIAGNOSIS

Deep vein thrombosis is a common complication of surgical operations and its sequel pulmonary embolism, is responsible for considerable morbidity and mortality postoperatively.

1. CLINICAL DIAGNOSIS

It is well recognised that many small calf vein thromboses give rise to no symptoms or signs (7). More importantly extensive femoral or iliac vein thrombosis may silently exist, unless shown by special investigation or by the presentation of pulmonary emboli (10, 11).

Not only is deep vein thrombosis often overlooked, it is also frequently diagnosed when none is present (10). As many as two thirds of patients showing deep vein thrombosis are not suspected on clinical grounds despite careful examination. Furthermore, in patients in whom the clinical diagnosis of venous thrombosis had been made, the diagnosis might be falsely positive in 25 to 50% of cases (7). The most important symptom is a feeling of heaviness or continuous dull pain in the calf. This sensation is aggravated by muscular contraction or the erect posture. The signs of unilateral ankle oedema, increased girth around the calf, tenderness of the calf, pre-tibial venous dilatation and increase in the tension of the calf muscles are the classical clinical diagnostic features of venous thrombosis (12, 13). The rare presentation of ilio-femoral venous thrombosis in the severest form is a phlegmasia caerulea dolens after a sudden onset of acute pain, is characteristic. There is a diffuse oedema of the whole of the lower limb including the thigh, calf and ankle with associated tenderness (14).

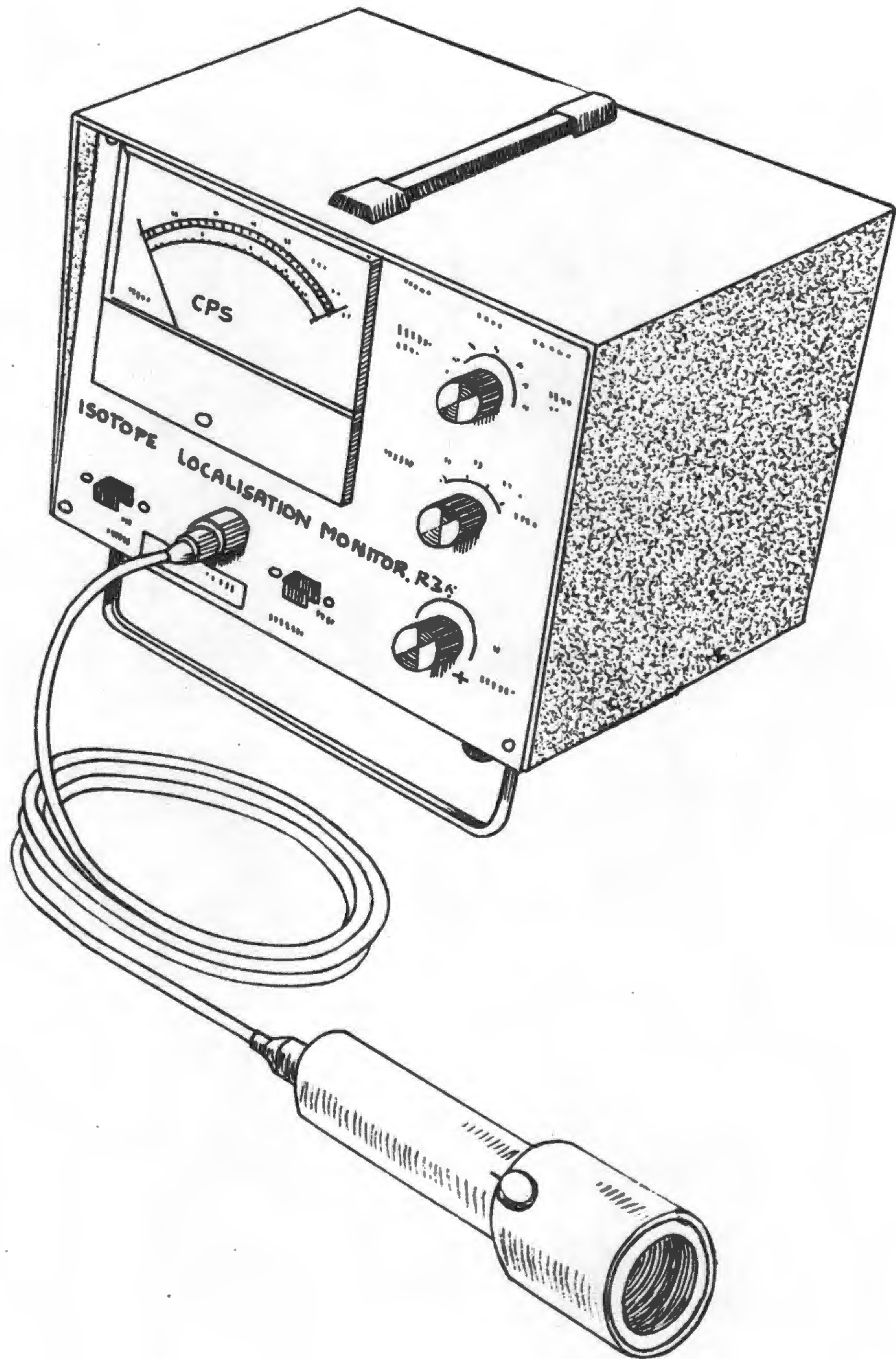
Temperature chart analysis can detect half of those patients developing clots in the legs. If the patient is afebrile, any venous thrombosis present is more likely to be of a short duration and therefore less likely to extend into the more proximal vessels (15).

2. RADIO-ACTIVE I^{125} LABELLED FIBRINOGEN TECHNIQUE

This technique was first described in 1960 by Hobbs and Davies (16), and their work was followed by the studies of Atkins and Hawkins and of Nanson in 1965 (17, 18). The accuracy of the technique used in a prospective manner was finally established in 1968 by comparison with phlebography by Flanc et al (19), at King's College Hospital and by Negus at The Middlesex Hospital (8). The technique depends on the fact that human Fibrinogen, labelled with a suitable isotope, is incorporated into the forming thrombi and a concentration of the isotope can be detected by a suitable external counter. Iodine $^{-125}$ is used in preference to Isotope I^{-131}, because of its longer half life (60 days as compared to 8 days) which facilitates storage and also ensures an adequate blood concentration during the 7 or 8 day period of monitoring.

Measurement of radio-activity is made with a scaler using a collimated scintillation counter designed to measure a field of 10 cms diameter and 3.75 cms depth. A single channel pulse height analyser is used, the lower level corresponding to 5 kev. and the upper to 50 kev. More recently a small portable ratemeter called the Isotope Localisation Monitor 235, D. A. Pitman Ltd. (Fig. 1) has been introduced at a relatively inexpensive price. The Pitman Ratemeter, which is portable, appears to be as accurate as a scaler except at very low count rates which may occur five to six days after injection of labelled fibrinogen.

FIGURE 1. RATEMETER (PITMAN MODEL 235 ISOTOPE LOCALISATION MONITOR) AND SCINTILLATION COUNTER


CPS
ISOTOPE LOCALISATION MONITOR. R3

Technique of Patient examination

The thyroid uptake of radioactive iodine is blocked by administration of 150 mg. potassium iodide which is given orally 24 hours before the injection of the isotope-labelled Fibrinogen and is continued daily for the following two weeks. One hundred microcuries of I^{125} Human Fibrinogen, obtained from a small pool of hepatitis-free donors, is then injected intravenously and counts of radio-activity are made at selected points on the lower limb and the activity of each is recorded. All measurements are made in the ward with the patient lying supine in bed, and the legs elevated 10° above the horizontal in order to avoid venous pooling. The points of measurement on the legs are indicated in figure 2a and b. The distance between these points depends on the size of the collimator used. With the scaler counts are made at 10 cms intervals. If a smaller collimator is used such as the Pitman Ratemeter, it is necessary to perform counts at 5 cms intervals. Daily counts are made over the precordial area as well as over points on the limb, and activity at each point on the limb is expressed as a percentage of the heart count measured on the same occasion. This method eliminates the need for calculating biological or radioactive decay. With the Pitman Ratemeter, the radio-activity at each point on the leg can be expressed as a percentage of the heart count by simple use of a control that adjusts the precordial counts to a figure of 100% (Fig. 3). This obviates calculation and greatly simplifies measurement. The count at any one point on the limb, expressed as a percentage of the heart rate, measured on the same occasion, is compared with the count at the same point on the previous day and is also compared with adjacent points on the same limb and with the corresponding point on the opposite limb. Comparison with phlebography by Negus (8) has shown that a rise of 15% in the count rate using the scaler (28), and 20% using the Pitman Ratemeter,

indicates the presence of venous thrombosis, provided that the rise in the activity persists and increases on the succeeding day. The figure of 15% applies to the detection of calf thrombosis. The baseline counts in the thigh are higher and a proportionally greater increase in percentage activity is required for diagnosis.

Advantages

This technique has the advantage that it is a simple one, causes no discomfort to the patient, and is suitable for repeated monitoring. It is therefore particularly useful in prospective studies of the natural history of postoperative venous thrombosis (8, 19).
The I^{-125} fibrinogen technique can also be applied to research into methods of prevention of deep vein thrombosis. It has been used by a number of workers as an objective method of diagnosis in controlled trials of preventing deep vein thrombosis (6, 20, 21, 22, 23) as well as evaluating methods of treating venous thrombosis (24).
It is furthermore a reliable screening method for detecting thrombi in the lower leg and thigh (10).
In the diagnosis of the early suspected case, the technique is between 80% and 92% accurate (25, 26), but care should be used in interpreting the result if the patient has had symptoms or signs suggestive of deep vein thrombosis for more than 5 days.
In the diagnosis of the suspected case, it takes 6 hours for the radioactive fibrinogen to be concentrated sufficiently for detection with a scintillation counter, and a definite diagnosis is not possible for 24 hours (10, 28).

Limitations

i. This technique is useless for the diagnosis of thrombi in the upper femoral or iliac vessels, and is only reliable up to 10 cms of the inguinal ligament (10, 28).

ii. It is unreliable in the presence of healing wounds because these take up fibrinogen, and it cannot therefore be used after operations to the lower limbs (10).

iii. It is not quite as accurate in the diagnosis of established thrombi (10, 25, 26).

iv. It is inaccurate if gross oedema is present, such as in congestive cardiac failure because the fibrinogen diffuses out (10).

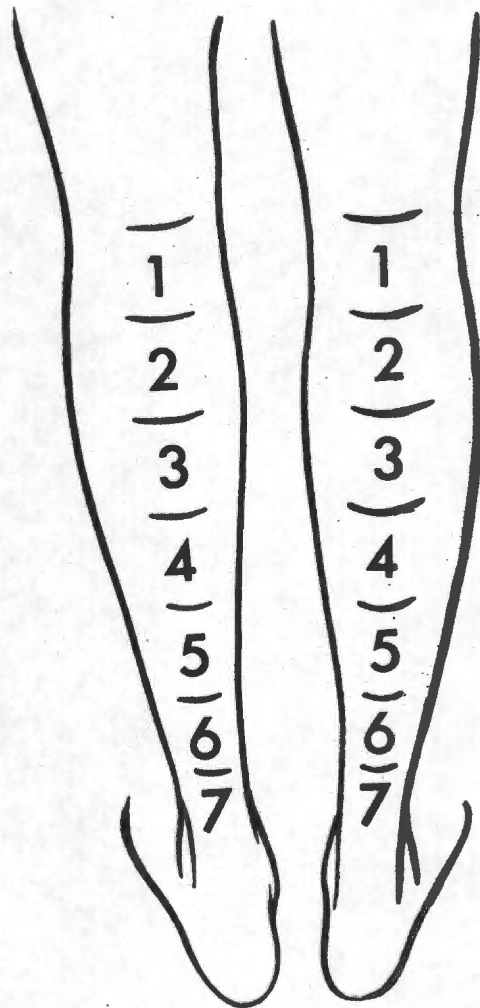
v. Pregnancy is a contraindication.

vi. It is expensive, time consuming and requires a trained technician(27).

vii. Is a possible risk of serum hepatitis but no cases seen in 800 patients studied by Kakkar (26).

In summary the use of I^{-125} fibrinogen is a simple, accurate, portable, non-invasive method of detecting deep vein thrombosis in the patient postoperatively.

FIGURE 2A POSITIONS AT WHICH RADIOACTIVITY IS MEASURED


1
2
3
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6
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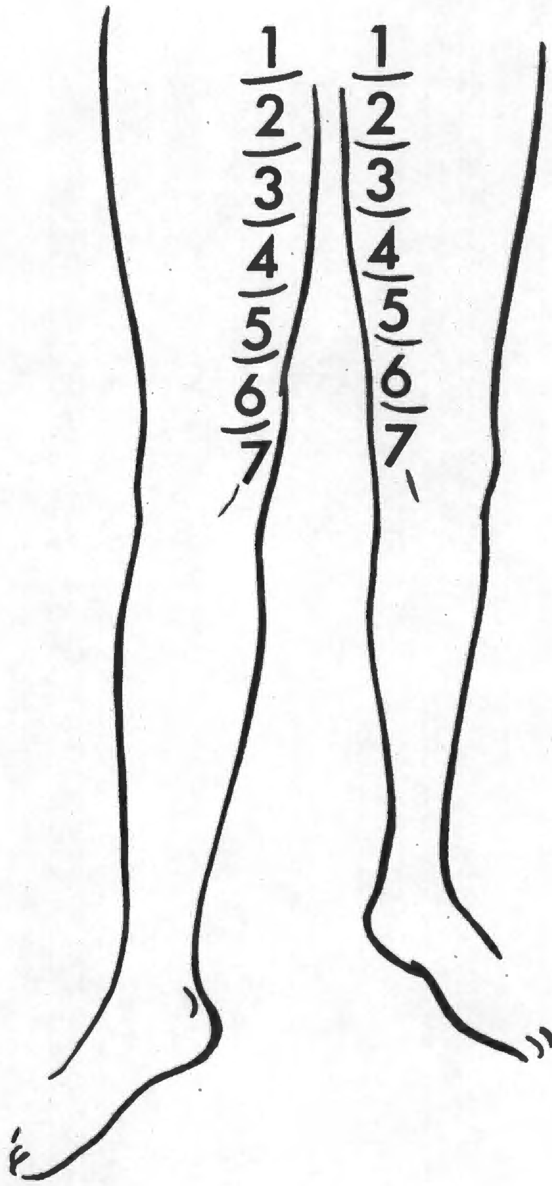
5
6
7

FIGURE 2B POSITIONS AT WHICH RADIOACTIVITY IS MEASURED


1
2
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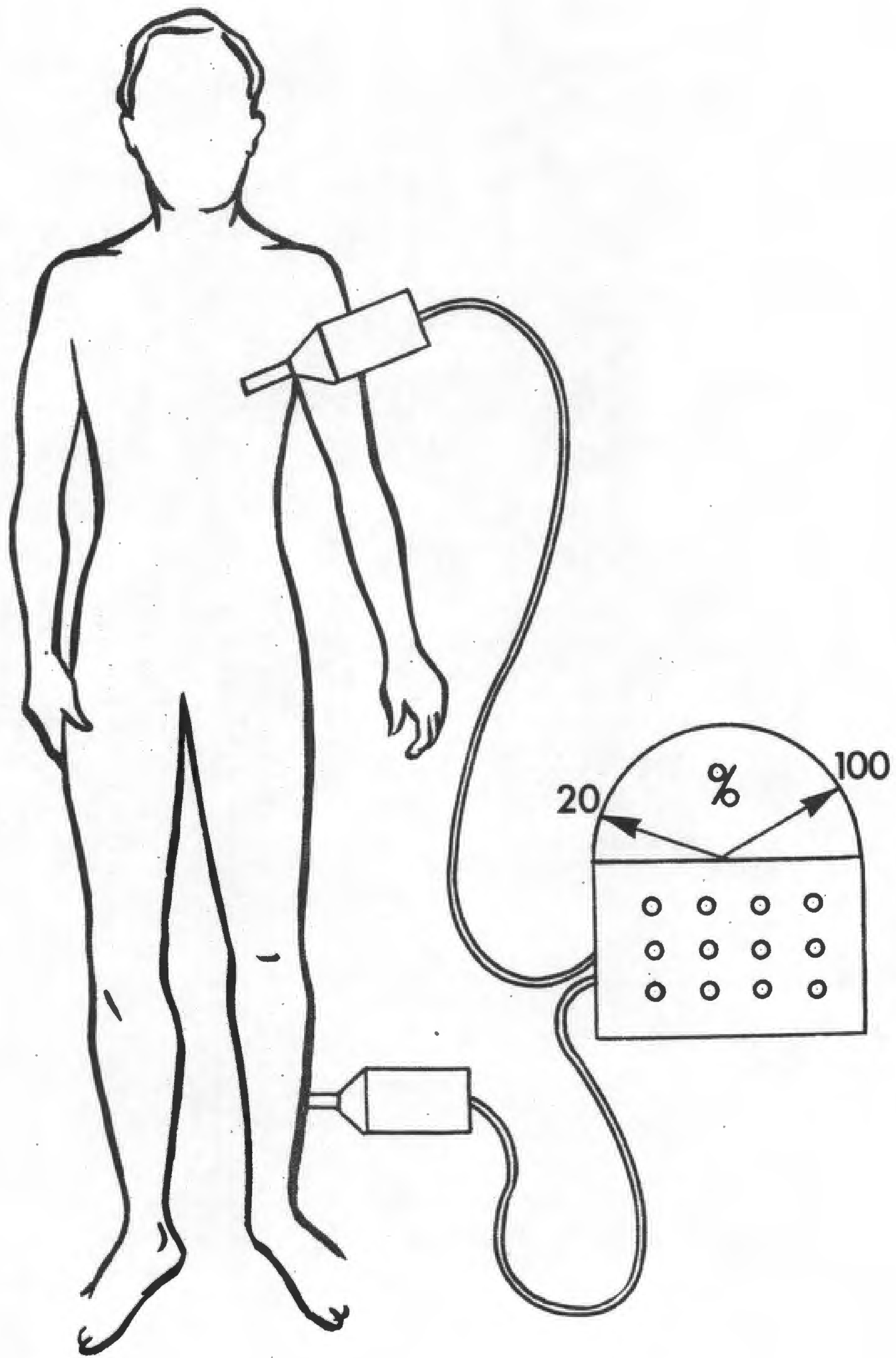
6
7

FIGURE 3. PRINCIPLE OF RATEMETER.
READINGS ON LINEAR SCALE ARE
DIRECT PERCENTAGE OF HEART COUNT


20
%
100

3. DOPPLER ULTRASOUND TECHNIQUE

The use of ultrasound for the diagnosis of venous thrombosis was first described by Strandness in 1967 (29) and Sigel in 1968 extended this application, using a machine operating at 5 mega Hertz (30, 31). Both teams were able to directly determine the presence of deep venous flow from calf to groin. The technique was further modified by Evans and Cockett in 1969 who changed the transmission frequency to 2 mega Hertz (32). This increases tissue penetration and allows direct examination of the iliac veins and inferior vena cava. The machine used is a Sonicaid D205M (fig. 4) Sonicaid Limited, Sussex, which has the advantage of simplicity of operation, is portable, inexpensive, and totally safe to the patient. The machine consists of a transmitter operated at 2 mHz, a receiver, an audioamplifier, and a loudspeaker contained in a case approximately 30 x 20 x 7.5 cms and weighing 3 kg. which can easily be carried from bed to bed. A transducer containing 2 ceramic crystals, one of which emits ultrasound and the other acting as a receiver, is connected to the cabinet by a detachable lead. Usually the examiner listens for a "whoosing" sound, although if desired, permanent recording called a Dopplergram can be obtained by connecting a lead from a pen-recorder to the transmitter, or alternatively the examiner can listen through a set of head phones.

When a stationary column of blood is examined, the reflected signal is identical to the transmitted and no sound is heard from the loudspeaker. However, when moving blood is examined, there is a shift in the frequency of the reflected signal proportional to the velocity of flow, due to the Doppler effect. This shift in frequency is within the audible range and with suitable amplifications can be heard. The presence of moving blood is therefore indicated by a sound, while in venous obstruction there is silence.

Sigel (30, 31) showed that if a squeeze was applied to the leg distal to the site of the transducer, an augmentation of venous flow velocity would occur and a roar or "whoosh" would be heard from the loudspeaker. This he termed the Augmentation wave or A wave. An A wave indicates the presence of deep venous flow between the site of squeezing and the transducer.

Technique of patient examination

Patient examined in bed in the ward, sitting propped up and flexed with the hips at 45° or more. The lower limbs are straight and the ankles supported to allow good passive filling of the calf veins (10, 33). The transducer is applied to the skin overlying the vein to be examined, using a suitable coupling medium such as olive oil. The transducer is sited over femoral vein 10 cm. below the inguinal ligament, the common femoral vein, the external iliac vein, and over the inferior vena cava (33) and popliteal vein (34).

To produce "A-waves" the leg is squeezed by hand over the upper thigh along the line of the superficial vein, over the mid thigh, over the lower thigh at the level of the adductor canal and calf. In patients with painful calves, the squeeze is applied using a calf pressure unit (10). This has enabled more accurate examinations, less discomfort to the patient, and elimination of occasional false positive results achieved on hand squeezing. Permanent visual recording of the sounds heard may be made by attaching the lead of a pen-recorder to the back of a Sonicaid D205M cabinet.

The femoral artery is first located with the transducer by the characteristic pulsatile sound of major arterial flow, and the transducer is moved medially over the femoral vein.

The calf is squeezed, until the venous flow is detected by the presence of a roar. This is the so-called Augmentation or "A-wave", described by Sigel (30, 31). Similar observations can be made with the transducer over the inferior vena cava, the iliac veins, the femoral vein or the popliteal vein, thus localising the site of any obstruction. Obstruction is indicated by the absence of a sound, although with practice one could recognise a diminished sound compared with the other leg or with what is recognised as normal (10, 34, 35, 36). For the purposes of this study however, thrombosis was only diagnosed by the absence of a sound. Patency of the inferior vena cava and iliac veins can be assessed by applying the Doppler probe over the common femoral vein during hyperventilation. Absence of obstruction is indicated by a wave-like roar corresponding to the respiratory excursions (30, 31).

Advantages

Patient examination with ultrasound is very rapid, it is possible to examine a patient fully in two to three minutes. This means that all the patients in the ward of 30 beds can be screened in just over an hour. Ultrasound will detect thrombus in the popliteal or more proximal veins, that is an anatomical region where deep vein thrombosis is a potential hazard to the life of the patient and is a useful screening method (38).
Should there be any doubt in interpretation, the simplicity of testing allows repeated examination with minimum inconvenience. Evans (10, 33) suggested patients screening twice weekly as being feasible and sufficiently reliable for regular use. Ultrasound examination had proved particularly useful in

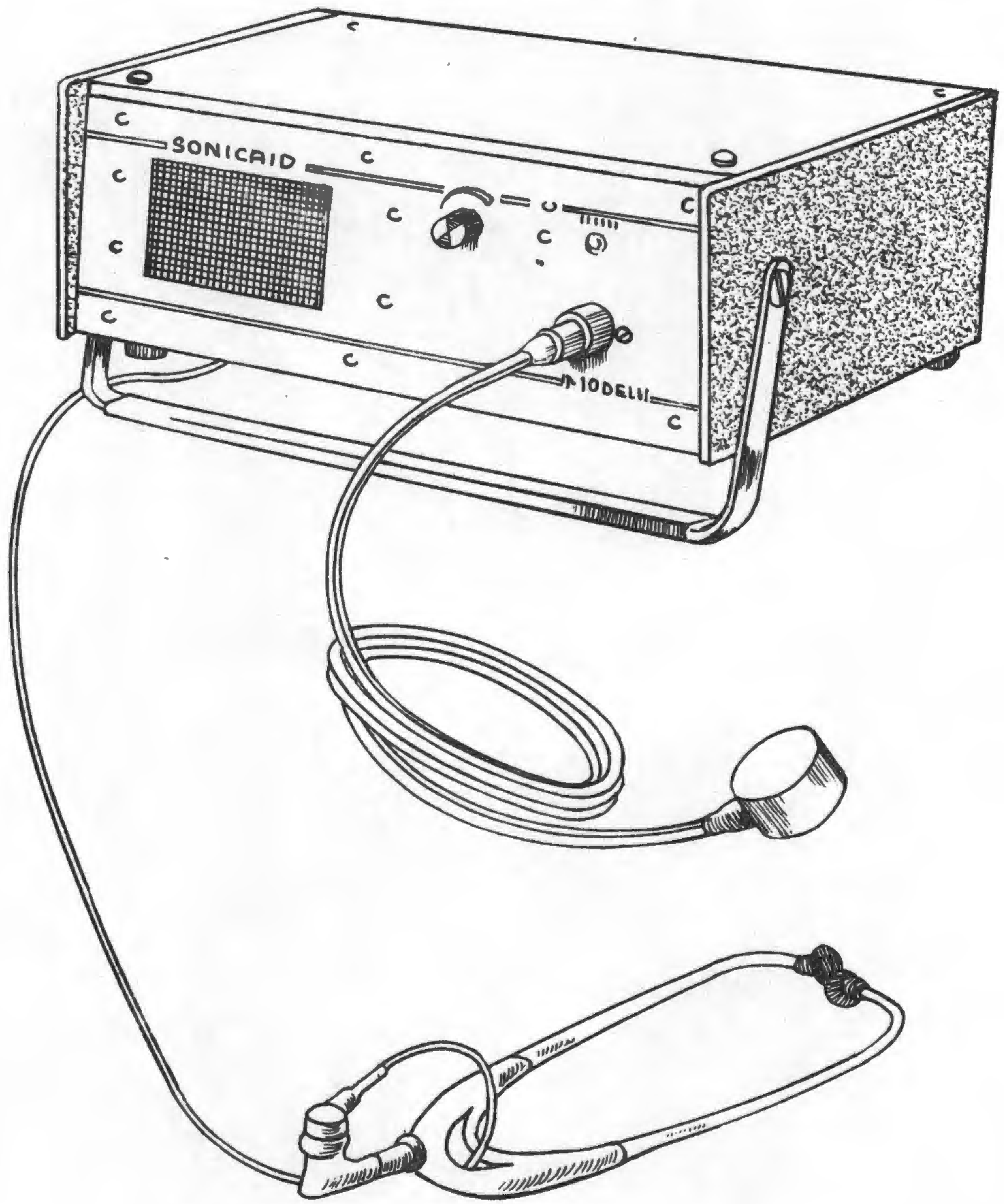
assessing collapsed patients, when massive pulmonary embolism is a possible cause (10). In a small series, evidence of venous obstruction has been found in one or both legs of all patients sustaining a massive pulmonary embolus.(10). Following thrombectomy, ultrasound can be used to monitor the patency of veins and detect reocclusion. In pregnancy the deep venous system can be assessed without hazard to the foetus. Ultrasound assessment is also indicated after lower limb surgery, and in oedematous limbs when other forms of investigations may be difficult to perform or interpret (10, 33, 37).

Limitations

Ultrasound examination will not detect minor calf vein thrombosis. However, if a thrombus propagates to the popliteal veins it will be detected (10, 36). If a major vein is only partially occluded the thrombus may be over looked. Again, if there is a good collateral flow through a venous obstruction, thrombosis may be overlooked without careful siting of the transducer as already described (10, 34, 35).

In summary the Doppler ultrasound is a simple, portable, quick, non-invasive method of detecting deep vein thrombosis in the patient postoperatively.

FIGURE 4. SONICAID D205 M DOPPLER ULTRASOUND


SONICAID

4. VENOGRAPHY (PHLEBOGRAPHY)

Venography of the lower extremities was first reported by Berberich and Hirsch in 1923 (39). During the 1930's lower leg phlebography was introduced as a routine clinical method (40, 41, 42, 43). The procedure, however, lost its popularity, mainly due to technical inadequacy which gave rise to diagnostic pitfalls (44, 45). Many improvements in the technique of venography have been described (41, 44, 46, 47), and as knowledge of the dynamics of flow of venous blood and of contrast material has increased, the reliability of the technique has improved (40). Venography is being increasingly used to confirm or exclude suspected deep vein thrombosis and to plan treatment to prevent pulmonary embolism (48-54). Radiologists and clinicians often feel that the examination is technically difficult to perform and interpret and that it is time-consuming, unpleasant and dangerous for the patient. However, experience of over 600 examinations by Lea Thomas (50) suggests that phlebography can usually be rapidly carried out, causing little or no discomfort to the patient, is free of significant complications, and requires only standard radiographic equipment. With a little experience a thrombus can be recognised or excluded with certainty. Furthermore, phlebography provides information not only about the presence of a thrombus, but also its exact position, size and whether it is loose or adherent to the vein wall. Loose thrombus may be shown to be locked in by more proximal adherent thrombus, and unable to embolise. This information is unobtainable by any other diagnostic method (50).

Technique

A tilting screen table equipped with an undercouch tube, television and an automatic exposure device, is most convenient. A useful film format is a 35 cm x 35 cm. film, which may be divided into three parts. Each leg is examined separately. The patient lies supine on the table and a self-fastening rubber tourniquet is applied around the ankle to distend the foot veins. A No. 20 gauge 25 mm. disposable needle is bent at its hub so it lies flat against the dorsum of the foot. It is introduced percutaneously into a vein towards the more lateral side of the foot, in order to avoid too direct communication with a long saphenous system. The needle is directed towards the toes, that is, in an upstream direction. A second tourniquet is applied above the knee to trap the contrast medium in the calf veins.

The table is tilted 20° downwards and the leg internally rotated to separate the images of the tibia and fibula. A syringe containing 50 ml of the contrast medium, Meglumine Iothalamate 60%, is connected to the needle by polyethylene tube and a hand injection is bagun under television control. The ankle and above-knee tourniquets are tightened and the table tilt increased until deep venous filling is noted on television. It is not part of this technique to occlude totally the superficial venous system as thrombus can arise from the superficial veins (55), and also contrast from the long saphenous vein allows filling above an obstructed portion of the femoral vein. Upstream injection helps to fill the deep veins as the contrast medium passes through the communicating veins in the foot directly into the deep venous system (56). Two exposures are made, one

below the knee and one including the knee in the postero-anterior projection. Filming is started about half-way through the injection and judged by television screening. A third exposure is made with the legs externally rotated so that the lateral aspect of the calf lies flat on the table top. In this lateral projection the calf muscle sinusoids are not obscured by tibia and fibula. The leg is then again internally rotated and the upper tourniquet removed. Further exposures are made from the popliteal vein to the inferior vena cava. The patient is asked to perform a Valsalva manoeuvre and the common femoral vein is filled with contrast in order to show the profunda vein as far as a competent valve. Good filling of the upper femoral and iliac vein is obtained by the injector applying firm pressure in an upward direction to the calf while the exposure is being made. This procedure may also outline the lower part of the inferior vena cava.

For adequate demonstration of the iliac veins and lower inferior vena cava, a modification can be employed without the use of ankle tourniquet, and with firm upward pressure being applied to calves on both sides after bilateral 50 ml injection of contrast medium given simultaneously. A valsalva manoeuvre may enable internal iliac to be demonstrated as far as a competent valve (50).

Intraosseous Venography

This is indicated if there is obstruction to the proximal part of the deep venous system and the full extent of the thrombus has not been adequately demonstrated. The examination is painful and therefore requires a general anaesthetic.

Often a combined technique with a percutaneous femoral injection of contrast medium on the non-obstructed side and a pertrochanteric injection on the other side is used. Bilateral injections are always required to show the inferior vena cava adequately.

Separate iliac phlebography and inferior vena cavography is only required in about 5% of the patients, as these veins are sufficiently well shown by foot injections in the remainder. A standard bilateral examination demonstrating the whole venous system from the ankle to the inferior vena cava requires 200 ml of contrast medium, but double this amount may be required occasionally if doubtful areas have to be re-examined.

Complications

Contrast medium is known to damage the intima and predispose to thrombosis (50), but this can be avoided by thoroughly clearing the veins with normal saline at the end of the examination. In an obstructed venous system, contrast medium may be trapped in the foot causing tissue damage (52). Careful aseptic precautions are necessary to prevent local sepsis and with intraosseous phlebography there is always a danger of osteomyelitis. The use of the Valsalva manoeuvre has been criticised as predisposing to pulmonary embolism (57) but Lea Thomas has not encountered this complication (50). The use of calf pressure is also open to criticism as this may dislodge fresh thrombus. The pressure used is probably no more than that produced by the patient involuntary contracting the calf muscles, and it is used clinically to assess calf tenderness and is a standard part of the Doppler Ultrasound technique.

The contrast medium, Meglumine Iothalamate 60%, is painless on injection and produces little discomfort to the patient apart from a bursting sensation in an obstructed venous system. The relatively large quantity of contrast medium which may be necessary in some patients has not resulted in any complication (50).

Interpretation of Venograms

Unequivocal deep vein thrombosis shows as well-defined filling defects in an opacified vein which presents a constant appearance both on screening and serial films. Loose thrombus appears as a cylindrical or rounded translucent defect separated from the vein wall by thin white line of contrast medium. Obliteration of this white line indicates adherence or fixity of the thrombus to the vein wall. When a thrombus obstructs a vein or segment of the vein completely, no contrast medium surrounds it, but the veins above and below and the collaterals are filled with contrast. The full extent of the thrombus must be shown in all instances and this may be at different sites in the same leg. As a thrombus ages it retracts, develops a thicker rim of contrast around it, and its surface is more clearly defined. A vein may remain permanently occluded and be bypassed by collaterals or the thrombus may organize leaving an irregular, often reduplicated lumen and destroyed valves. Study carried out by Lea Thomas and McAllister (51), suggested that the usual sequence of events following thrombosis was for the thrombus to remain free for the first week and over the next fourteen days to become adherent to the vein wall and then contract. An obstructed vein may recanalize after several months or it may remain permanently occluded. Recanalization more frequently occurs in the calf veins than the ilio-femoral veins (50).

Appearances that may be confused with thrombus

Most filling defects are due to normal structures such as the valves and artifacts which may result from underfilling, dilution and streamlining of contrast which can be excluded by the screening technique (50).

Limitations and value of venography

The main disadvantage is the need for skilled medical personnel, possible difficulty of venepuncture and is time consuming with a definite though small morbidity (40, 50).
The practical advantage of venography over the use of ultrasound and radioactive fibrinogen is that it not only demonstrates the presence of a thrombus, but also shows its exact site, extent and degree of fixity. A thrombus shown to be loose represents a potential hazard from embolization.

The choice between surgical or medical treatment may be assisted, for if the thrombus is loose, it should probably be removed surgically. If adherent, surgical removal may be impossible or partially successful with intimal damage and rethrombosis (48, 49, 58).

In summary, venography gives diagnostic confirmation of the presence of venous thrombosis from the ankles to the inferior vena cava.

5. IMPEDANCE PHLEBOGRAPHY

Measurement of electrical impedance (59) depends upon the fact that when a constant electrical current flows through part of the body, changes in local blood volume alter the electrical impedance. Measurement of the voltage thus gives an indirect assessment of changes in local blood volume.

Normally the venous blood volume in the leg varies slightly with venous pressure changes due to respiration. When venous thrombosis is present, the respiratory venous volume changes are diminished and can be detected by impedance measurements.

Technique

The testing procedure is simple, but technical detail is important. A Codman 1 PG-100 Impedance Phlebograph by Codman and Shurtleff (59) and a Minnesota Impedance Cardiograph, Model 303 (61) are available for recording the measurements. Circumferential electrodes are placed at fixed points on the lower limb and baseline recordings are made with subject breathing quietly and then during deep inspiration, holding his breath for at least 5 seconds and then breathing passively.

The most useful measurement on the tracing is the height of impedance change associated with deep inspiration which is expressed as a percentage change in the baseline impedance (59, 60, 61).

Advantages

Impedance phlebography would appear to be a useful non-invasive, simple screening technique, but should be checked by venography in almost all cases until its accuracy is improved (63).

Limitations

It cannot be carried out in patients unable to lie quietly, cooperate or hold their breath for five seconds.

The accuracy for detection of a recent thrombosis is from 53% (61) to 68% (63) although Mullick (59) initially reported better results.

It is incapable of detecting minor calf thrombosis and will probably not detect partial venous occlusion in the early stages of thrombosis or total venous occlusion in presence of adequate collaterals (10, 62).

In summary, impedance phlebography appears to have similar limitations as the Doppler ultrasound and is not as reliable due to difficulty with interpretation of results.

6. THERMOGRAPHY

The use of infrared photography, to detect "hot spots" which can be produced by thrombophlebitis (64) has been suggested in the diagnosis of deep vein thrombosis. As yet there has been no systematic study of its usefulness and no comparison of its accuracy with venography.

7. BLOOD TESTS

A number of blood tests have been considered as aids to detecting venous thrombosis.

a. Platelet Adhesiveness

It was suggested that a rise in platelet adhesiveness accompanies deep vein thrombosis and may appear before physical signs become apparent (65, 66). This phenomenon was not confirmed by Negus (67).

b. Fibrin Degradation Products and Other Tests

Ruckley et al (68) found that serum fibrin degradation products were not helpful in detecting deep vein thrombosis but Fletcher found a correlation in the high risk group (71).
Fibrinogen-fibrin related antigen was found significantly elevated in patients with postoperative deep vein thrombosis but the highest levels were recorded in those with associated systemic complications (69).
Mansfield (70) found an earlier and more severe reduction in the fibrinolytic activity in patients developing postoperative deep vein thrombosis.

It appears, that the changes observed in the plasma fibrinogen, blood lysis time, serum F.D.P, platelet count and platelet adhesiveness, taken alone or together, fail to discriminate between the patients with deep vein thrombosis and those without. The changes are probably a sequel to a major surgical operation and the 'hypercoagulable state' is probably the result rather than the cause of the high incidence of postoperative venous thrombosis (72).

II. INCIDENCE OF DEEP VEIN THROMBOSIS

1. Introduction

2. Magnitude of Problem

- death certificates
- hospital sampling
- hospital statistics

3. Frequency

1. Clinical Incidence
2. Post Mortem
   - Deep vein thrombosis
   - Pulmonary embolism
   - Increasing?
3. Newer Methods of Diagnosis using
   - I^{125} fibrinogen,
     Doppler ultrasound and
     Venography.

1. Introduction

Deep vein thrombosis and its sequel pulmonary embolus are'how perhaps the single greatest threat to recovery after surgical operations." (9)

Thrombo-embolic disease kills 5,000 people in Britain annually (73) and contributes to 12.5% of all postoperative deaths (4). It is therefore a serious cause for concern.
The problem should be considered as (i) the early mortality and morbidity and (ii) late mortality and morbidity.

2. Magnitude of the Problem

- death certificates
- hospital sampling
- hospital statistics

The importance of deep vein thrombosis and pulmonary embolism has to be judged by their incidence and the effect on the morbidity, mortality and prognosis of patients undergoing surgical operations. Pulmonary embolism has been described as "the most acute pulmonary illness encountered in a general hospital, as one of the commonest lethal processes seen at necropsy and the third commonest non lethal affliction after pneumonia and chronic emphysema." (74).

The reported incidence of deep vein thrombosis and pulmonary embolism varies considerably but the figures must be considered in relation to their source and potential accuracy. Published figures based on <u>death certificates</u> are unquestionably underestimated.

For England and Wales in 1967, the Registrar-General's figures were 2,426 for "pulmonary embolism and infarction", and 2555 for "other venous embolism and thrombosis." (75)
From the Registrar General's figures making appropriate corrections, pulmonary embolism mentioned as a cause of death in about 21,000 death certificates in England and Wales during 1967 (76).

Another approach to determine the prevalence of thrombo-embolism is based on hospital sampling. Number of inpatients with various underlying diagnosis in hospitals in England and Wales were investigated by the Hospital Inpatient Enquiry. In 1963 the number with either pulmonary embolism and infarction or with other "venous embolism and thrombosis" was assessed as 12,502 (77), but this is much too low for reasons similar to those which apply to the published analysis of death certificates (76).

From hospital statistics in the United States a reasonable estimate of the number of diagnosed cases of pulmonary embolism and venous thrombosis seems possible.
Data from reports issued by the Commission on Professional and Hospital Activities (PAS) shows that among 5.05 million patients discharged from their participating hospitals in 1966 (all short term hospitals), there were 19,054 patients in whom the diagnosis was listed either as pulmonary embolism and infarction or other venous embolism and thrombosis; 28,799 patients with a diagnosis of phlebitis and thrombo-phlebitis of the lower extremeties.
In 1966 "short-term" cases admitted to United States hospitals

totalled 28.5 million, and assuming that the frequencies of the diagnosis of thrombosis and embolism were the same as in the PAS participating hospitals, the following figures can be calculated. For 1966, the total cases of pulmonary embolism in US hospitals was about 106,000 and the total cases of phlebitis and thrombophlebitis was about 182,000. In round figures thus there were approximately one quarter of a million patients with diagnosed venous thrombosis or embolism in US hospitals in 1966. These estimates exclude patients in nursing homes or custodial care institutions and those treated at home (76).

The third approach to establishing the prevalence is from hospital statistics, to multiply the mean hospital rates of fatal and non fatal embolism by the number of inpatients. A reasonable overall estimate of the incidence of fatal embolism based on necropsy studies is about 5 per 1,000 inpatients and for non fatal embolism about 10 per 1000 inpatients (76). For England and Wales with 4.2 million hospital inpatients, this would give about 21,000 fatal and an additional 42,000 non fatal cases of pulmonary embolism. From the United States with 28.5 million short-term inpatients, this would give 142,000 fatal and an additional 285,000 non-fatal cases of pulmonary embolism (76). These figures are greater than the estimates made by Coon and Willis (77) from the US of about 47,000 deaths from pulmonary embolism as a sole cause, and three times as many contributing to death. The number of persons with clinical thrombosis is also difficult to assess. Those with the diagnosis of thrombo-phlebitis in the US hospitals in 1966 were estimated at 182,000 (76).

3. FREQUENCY OF DEEP VEIN THROMBOSIS

1. Clinical Incidence
2. Post Mortem
3. Newer Methods of Diagnosis

1. Clinical Incidence

In a review of the literature Bruzelius (79) found the postoperative frequency varied from 0.6 to 3.5 per cent. Clinical thrombosis was found in 12 to 15% patients with fractures or soft tissue injury to the lower limbs (80, 81). Barker in 1941 studied 158,200 medical, surgical and gynaecological patients, and found an overall incidence of deep vein thrombosis in 0.95%, of these 0.5% developed pulmonary embolism, and 0.2% were fatal (82). Sevitt (78) in a combined clinico-pathological study in 1961 estimated that as many as 2 out of 3 deep vein thromboses were symptom-free, and found no clinical evidence of venous thrombosis in 50% of patients dying of pulmonary embolism (11). The insensitivity of clinical diagnosis was suspected in 1941 by Welch and Faxon who found that only 5% of fatal pulmonary emboli had clinical evidence of deep vein thrombosis (101). McLachlin (88) in 1962 compared the clinical physical signs of thrombosis with post mortem findings and found that

- ankle oedema - was reliable in 80%, but Gibbs (89) in 1957 found that it was 100% reliable if there was occlusion of the ilio-femoral or ilio-caval veins.

- local tenderness - was reliable in 50% of cases
- positive Homans' sign - was reliable in 8% of cases
- pyrexia and tachycardia - was very unreliable
- late pain - was perhaps the most important symptom

Furthermore the signs of thrombosis may be present in the absence of a thrombus (4).

2. Post Mortem Incidence of Deep Vein Thrombosis

The incidence of deep vein thrombosis reported at necropsy ranges from 27 to 80%. See Table I. Some differences are related to the completeness or otherwise of venous dissection and in most series the frequency will range from 44 to 65%. (76, 86, 89, 90). The incidence does not seem to depend upon the sex or directly on clinical diagnosis and the evidence indicates the likelihood of thrombosis is similar in medical, surgical or traumatic cases with other factors being similar (76). The frequency of thrombosis in any series of post mortems depends on the ages and survival period (bed rest) of the patients(76). This explains at least some of the differences reported in the table and also differences in the frequency between e.g. those dying from fractured neck of femur (83%), head and chest injuries (37%) and burns (60%). The lowest figure was associated with a large proportion of cases with short survival, the very high rate is related to relatively long survival period combined with advanced age. Survival and prolongation of life may also be related to therapy which would then indirectly influence the frequency of thrombosis. From the 11 published series in Table 1 of 2,460 patients the overall incidence of deep vein thrombosis at post mortem was 56%.

Table 1. Incidence of Deep Vein Thrombosis of the Lower Limbs at Post Mortem

References	Number of necropsies	Nature of Case	Percent with deep Vein Thrombi	Notes
Rössle (83)	324	Consecutive miscellaneous cases over 20 years old	26	Cases of sudden death without preceding bedrest
Neumann (84)	165	Miscellaneous	60.6	Dissection of deep thigh and calf veins.
Putzer (85)	370	Miscellaneous	27	Calf veins only examined
Hunter (86)	351	Medical and Surgical	52.7	Dissection of deep thigh and calf veins
Hunter et al. (86)	200	Medical and surgical	59	Dissection of deep thigh and calf veins
	200	Medical and surgical	44	
Greenstein (87)	100	Miscellaneous mainly Medical	51	Calf veins dissected
McLachlin (88)	100	Male subjects over 40 years old	34	Dissection of deep thigh and calf veins
Gibbs (89)	253	Medical, surgical, and traumatic	59	Dissection of deep thigh and calf veins.
Sevitt and Gallagher (11)	39	Elderly patients with fractured neck of femur	80	Dissection of deep thigh and calf veins

(Continued) /.....

References	Number of necropsies	Nature of Case	Percent with deep Vein Thrombi	Notes
Sevitt and Gallagher (78)		Fractured neck of femur	83	Dissection of deep thigh and calf veins; cases without pulmonary embolism; frequency of thrombosis related to duration of bedrest and age over 45 years.
		Other fracture of femur	86	
		Fractured pelvis or spine	75	
		Head or head and chest injury	37	
		Other injuries	43	
	92	Total trauma cases	66	
	33	Burns	60	
	125	Trauma and burns	65	
Roberts (90)	108	Medical and surgical	53.7	Dissection of deep thigh and calf veins.
TOTAL				
11 Series	2,460		56%	

Pulmonary Embolism at Post Mortem

Table II gives the findings from 16 published series of the incidence of pulmonary embolism at post mortem.

In some series the total incidence may represent major embolism rather than the fatal incidence because the pathological criteria for fatal emboli may vary between pathologists.

The overall frequency ranged considerably from 1.8% (94) to 67% (99), but in most embolism was found in 10 to 30%.

Pulmonary embolism which was fatal or contributing to death, the range was also very wide from 2% (93) to 25% (89), but was generally 3 to 10%.

The frequency is influenced by many factors which include the amount of detailed dissection and histological confirmation (99, 100), and preceding clinical composition of the patients (76).

Authors (86, 87, 88, 98, 99) who present figures drawn from incidences are agreed on three points.

i. Thrombosis of leg veins when it occurs, is bilateral in a high proportion. Often a thrombosis is extensive in one leg and slight in the other i.e. clinically manifest or clincially silent respectively.

ii. Pulmonary emboli which are fatal or non-fatal are almost never found in the absence of a peripheral source of thrombosis in the limbs, if these limb veins are properly dissected out.

iii. Untreated pulmonary embolization tends to be a repetitive and recurring process.

TABLE II INCIDENCE OF PULMONARY EMBOLISM AT POST MORTEM

References	Number of Necropsies	Nature of Case	Percent with Pulmonary Emboli: Fatal or Contributory to death	Percent with Pulmonary Emboli: Total Incidence	Notes
Brenner (91)	100	Miscellaneous	-	13	Macroscopic emboli
				19	Microscopic emboli; special histological study
Hampton (92)	3500	Miscellaneous	3.5	9	10 year retrospective necropsy analysis
	400	Miscellaneous		14	Specially studied cases
Hunter (86)	200	Medical and Surgical	3.5	15.5	Two series analyzed; special study for venous thrombosis
	200	Medical and Surgical	5.5	19.5	(See Table I)
Greenstein (87)	175	Mainly medical	Several	18	Special study for venous thrombosis
Cohn and Walsh (93)	4875	Miscellaneous	2 to 2.4	6	10 year retrospective necropsy analysis
Pulvertaft (94)	4750	Miscellaneous	-	1.8	20 year retrospective necropsy analysis; average age 57 years
Zimmerman (95)	5588	Miscellaneous	3.2	6.1	Included children (40 percent); 17 year retrospective necropsy analysis; trauma cases not included.

Continued/...

References	Number of Necropsies	Nature of Case	Percent with Pulmonary Emboli		Notes
			Fatal or Contributory to death	Total Incidence	
McLachlin (88)	100	Miscellaneous all males older than 40 years	-	19	Special study for venous thrombosis and embolism
Gibbs (89)	198	Medical and non-operative surgical	3	8	Special study for venous thrombosis and embolism
	43	Surgical operative	25	37	See also Table 1
Coon (77,96)	1346	Cardiac	-	24.7	10 year retrospective necropsy analysis
	3045	Noncardiac		9.0	
	4391	Total	9.0	13.8	
Sandritter (97)	51350	Miscellaneous	3.9	11.0	Retrospective necropsy analysis 1905 to 1955
Morrell, Truelove and Barr (98)	2807	Miscellaneous 1952 - 1956	-	4.9	Retrospective comparison with regard to increasing frequency of embolism
	2390	Miscellaneous 1957 - 1960	-	9.5	
Roberts (90)	108	Miscellaneous	14	25	Special study of thrombosis and embolism
Braconier (99)	1106	Miscellaneous	8.2	22.4	Fatal embolism equivalent to 0.56 percent of cases admitted
Freiman (100)	61	Consecutive adult necropsies (average age 67 years)	-	64	Recent, organizing, and organized emboli; special study with detailed dissection of lung arteries and histology.

Is Pulmonary Embolism Increasing?

The number of deaths from pulmonary embolism are greatly underestimated by the international method of recording based on medical certification, nevertheless published figures show an increase since 1946, especially rapid from 1952 and still continuing (75).

The graph in Figure 5 though imperfect and selective, suggests a genuine rise in the frequency of fatal pulmonary embolism in England and Wales since the end of the Second World War.

Morrell et al (98) reached a similar conclusion, of a real increase on the basis of a retrospective analysis of records from two general hospitals in Oxford from 1952 to 1961 in which 90 percent were confirmed at post mortem.

3. Newer Methods of Diagnosis

The incidence of postoperative deep vein thrombosis using I^{125} Fibrinogen in 10 different centres gave an overall incidence of 30% as shown in Table III. However, it must be stressed that the I^{125} - Fibrinogen is for the diagnosis of the calf and lower thigh venous thromboses and not the upper thigh or pelvic.

FIGURE 5 ANNUAL DEATHS FROM PULMONARY EMBOLISM IN ENGLAND AND WALES
From Registrar-General's Reports (75)

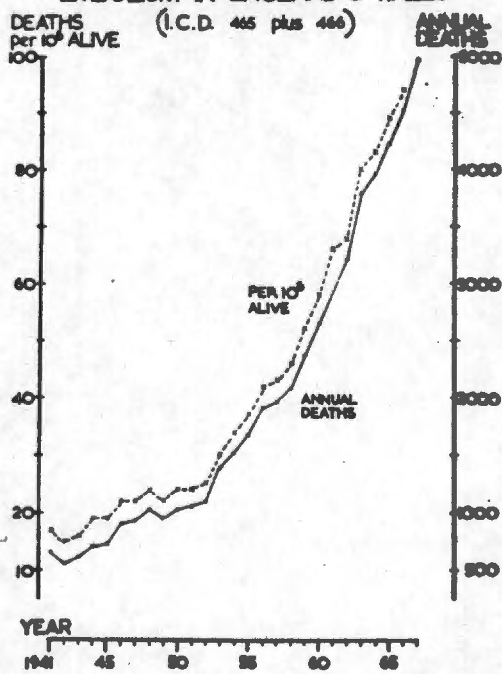

ANNUAL DEATHS FROM PULMONARY
EMBOLISM IN ENGLAND & WALES
(I.C.D. 465 plus 466)
DEATHS
per 10^6 ALIVE
ANNUAL
DEATHS
100
80
60
40
20
10
5000
4000
3000
2000
1000
500
PER 10^6
ALIVE
ANNUAL
DEATHS
YEAR
1941
45
50
55
60
65

Table III

Incidence of Deep Vein Thrombosis diagnosed with I^{125} Fibrinogen Technique

Author	Type of operation	Number of patients	Age	Thrombi	%
Flanc in 1968 (19)	Elective Surgery	65	> 40	23	35.4
Negus in 1968 (8)	Major Surgery	93	> 50	32	34.4
Kakkar in 1969 (24)	Elective Surgery	132	> 40	40	30.3
Browse and Negus in 1970 (6)	Moderate or Major Surgery	110	> 40	23	20.9
Lambie in 1970 (7,23)	Major Abdominal and Hip Surgery	111	> 40	49	44.1
Hedlund in 1971 (103)	Transvesical Prostatectomy	31	> 50	11	35.5
Rosengarten in 1971 (20, 104)	Elective Surgery	38	> 40	12	31.6
Tsapogas in 1970 (105)	Major Surgery	20	> 40	6	30.0
Becker in 1971 (102)	Transvesical Prostatectomy	30	> 50	10	33.3
	Cholecystectomy	60	> 50	9	15.0
Kemble in 1971 (4)	Major Surgery	280	> 40	80	28.0
	TOTAL	970			30.0%

Evans and Cockett (32) in 1969 compared ultrasound, clinical diagnosis, phlebography and I^{125} Isotopic studies. Of 19 legs thought clinically to have deep vein thrombosis, 8 were positive by ultrasound compared with 10 positive by phlebography or isotopic studies. In 19 clinically normal legs, two were positive by ultrasound compared with three positive by phlebography or isotopic studies. Similar results were obtained by Evans (33) in a series in which there were no false positives. In McIlroy's series (38) in 322 legs, 16 were positive giving an incidence of 5%. In this series only half the patients who were though to have deep vein thrombosis on clinical grounds were shown to have a positive deep vein thrombosis by ultrasound. More significantly however, over 50% of those which were shown to have deep vein thrombosis by ultrasound, were judged clinically to be negative. Yao (35) examined 50 patients with chronic swollen legs, of 15 patients with normal ultrasound findings, 13 had normal patent iliac veins on iliac phlebography i.e. 80%. Thirty-three patients who had abnormal ultrasound findings were found to have complete or incomplete iliac vein thrombosis i.e. 100% diagnosis.
He felt that the Doppler ultrasound method was of special value in selecting patients with swollen limbs for radiological investigation. Strandness (34) used the Doppler ultrasound in 112 patients who presented with clinical evidence of deep vein thrombosis. Result of ultrasound tesing programme was confirmed in 67 venograms in 53 patients and by operation an additional 4 patients. The correlation of Doppler ultrasound with venography was 93%. The Doppler ultrasaund is useful for occlusion in the ilio-femoral and femoro-popliteal segments of veins. Negative examinations occur with venous occlusions confined to the small veins of the calf (10, 34).

The incidence of deep vein thrombosis occurring in fractures of the hip or lower extremity as diagnosed by Venography is shown in Table IV. The overall incidence in 356 cases from seven centres was 48%.

Venography gives the most reliable and accurate incidence of postoperative deep vein thrombosis and confirms the clinical, I^{125} fibringgen and Doppler ultrasound methods. It visualises the whole venous system from the ankle to iliac and even inferior cava (50).

Table IV Incidence of Deep Vein Thrombosis Diagnosed by Phlebography

Author	Injury	Diagnosis	Number of Patients	Age	Thrombi	%
Ahlberg in 1968 (106)	Hip fractures	Phlebography	99	>50	44	44
Borgström in 1965 (107)	Hip fractures	Phlebography + Autopsy	25	>50	14	56
Hamilton in 1970 (108)	Hip fractures	Phlebography	38	>50	18	48
Hjelmstedt and Bergvall in 1968 (109)	Tibial fractures	Phlebography	43	>40	24	56
Johnson in 1968 (110)	Hip fractures	Phlebography	25	>50	13	52
Myhre and Holen in 1969 (111)	Hip fractures	Phlebography	55	>50	22	40
Stevens in 1968 (112)	Hip fractures	Phlebography	71	>50	28	40
		TOTAL	356			48%

III. PREVENTION OF POSTOPERATIVE DEEP VEIN THROMBOSIS

Preoperative, Peroperative, Postoperative

INTRODUCTION

1. SIMPLE MEASURES TO IMPROVE BLOOD FLOW THROUGH THE LEG VEINS.
2. ELECTRICAL STIMULATION OF THE CALF.
3. MOTORISED FOOT MOVER FOR RHYTHMIC PASSIVE MOVEMENT OF FOOT.
4. PNEUMATIC COMPRESSION OF CALF.
5. ORAL ANTICOAGULANTS.
6. HEPARIN -
   a. Full Dose
   b. Low Dose

      Subcutaneous, intramuscular or intravenous.
7. DEXTRAN -
   a. Dextran 40
   b. Dextran 70
8. SODIUM PENTOSAN POLYSULPHATE "TAVAN - SP 54"
9. MISCELLANEOUS -
   a. Antiplatelet agents
      1. Aspirin
      2. Hydroxychloroquine Sulphate
      3. Dipyridamole.
   b. Endogenous Fibrinolysis -

      Phenformin and Anabolic Steroid

Introduction

The new diagnostic methods have disclosed a high incidence of postoperative deep vein thrombosis (4, 19, 26, 28) . Many of the thrombi form on the operating table and within the first 24 to 48 hours (26). This new information assists in defending methods for the prevention of deep vein thrombosis.

The prevention must be subdivided into

1. Preoperative - which is by far the most important,
2. Interoperative - or peroperative and
3. Postoperative measures.

Virchow's Triad (113, 114) despite extensive investigations into the aetiology and pathophysiology of deep vein thrombosis is still valid (115) and consists of i) slowing of venous blood flow i.e. stasis.
ii) changes in blood coagulability and
iii) vessel intimal damage.

Methods of prevention of deep vein thrombosis have been slow to develop for two reasons, because

a. the aetiology is poorly understood, therefore attempts at prophylaxis are difficult and
b. problem of objective assessment within the past, when many erroneous claims were made and later discredited.

The number in many series are too small to make definite conclusions, although the general impression conveyed in several studies are that the complications are less frequent

in the treated group.

The significance of clinical studies may lie in the incidence of the major complications such as pulmonary emboli rather than a total incidence of deep vein thrombosis.

All the methods of prevention to be discussed are aimed at preventing and treating one or more of the factors involved in Virchow's Triad (113).

1. SIMPLE MECHANICAL MEASURES TO IMPROVE BLOOD FLOW THROUGH THE VEINS.

The evidence that simple prophylactic measures are effective in reducing the incidence of deep vein thrombosis is conflicting. Some workers say it is of value (116, 117) while the others deny this (118, 119). Unfortunately these conclusions are based on physical signs which are quite inadequate in the diagnosis of venous thrombosis (19). In a study by Flanc (120), 65 patients received conventional prophylactic measures and the incidence of deep vein thrombosis was 35%. More intensive measures, designed to protect the legs from pressure and to promote venous flow during and after operation were used in 67 patients. The incidence of deep vein thrombosis in this group was 25% and the difference was not significant (P=0.25). However in elderly patients undergoing a major operation there was a significant reduction in the incidence of venous thrombosis from 61% in the control group to 24% in the test group.

Prophylactic Measures

a. Before operation controls seen by physiotherapists on the day before operation and were taught to do active leg exercises and static quadriceps contractions. Thick below knee elastic stockings were fitted and worn throughout the patient's stay in hospital and the patients were instructed to perform exercises constantly, but with special vigour for five minutes in every hour. The foot of the bed was elevated to 23 cms on blocks and a foot board placed in the bed so that plantar flexion could be performed against resistance.

b. During operation elastic stockings were worn and pressure on the calves was prevented by the use of specially devised Sorbo-rubber stands. After the operation, the legs were kept elevated by this stand while the patient was carried to the ward, and until they are conscious and able to perform active leg exercises.

c. Postoperative period.
Patient was seen by the physiotherapist twice a day until allowed to walk. They were encouraged to move their legs vigorously and to push against the footboard. Patients were constantly reminded of their exercise schedule of 5 minutes in every hour by the nursing staff. All patients were instructed in deep breathing exercises before and after operation. A period of intensive physiotherapy does cause an increase in spontaneous resolution of the thrombus which has been shown by I^{125} Fibrinogen (2.5 instead of 6 days) (120).

Results however show that leg exercises as performed twice daily in the surgical wards in many hospitals do not prevent thrombosis (120).

Leg elevation during and after operation does not reduce the incidence of deep vein thrombosis in patients undergoing elective surgery over the age of 40 years. The incidence was 31% in the control group and 33% in patients in whom the legs were elevated (20).

Study carried out by Sigel et al (121) showed that elastic stockings in inactive recumbent patients increased the femoral venous flow velocity during periods of compression up to 3 hours. This increase in blood flow velocity persisted up to 30 minutes after removal of stockings. Compression reduced the fluctuation effects of respiration on the venous flow, resulting in a more constant flow. Their findings indicated that elastic compression of the lower extremities produced increased venous flow velocity and decreased venous pooling which may reduce the recurrence of venous thrombosis. However Rosengarten (20) showed that compression stockings (Tubi-grip) did not prevent deep vein thrombosis after operation.

2. ELECTRICAL STIMULATION OF THE CALF

Doran (122) showed that the velocity of the venous blood flow in the leg reached its lowest level during operation and he felt that this was the most important period to try and increase it. The velocity of venous blood flow could be increased by stimulating the calf muscles with an intermittent galvanic current. Doran and White (123) reported the results of a clinical trial of the effect of this method on the incidence of deep vein thrombosis and pulmonary embolism. Their results were encouraging but not entirely acceptable because the diagnosis of deep vein thrombosis was based on physical

signs, a method of assessment which has been shown to be notoriously unreliable (19). In a prospective trial carried out by Browse and Negus (6), electrical stimulation of the calf muscle of one leg was used in 110 patients undergoing major surgery. Deep vein thrombosis was detected by means of the I^{125} fibrinogen uptake test in 9 of the stimulated legs and 23 of the unstimulated legs. Analysis showed a statistically significant reduction in the incidence of deep vein thrombosis. This finding was confirmed by Nicolaides (124) using optimal electrical stimulation. However in a study by Moloney (125), of 285 patients and Dejode (126) in 64 patients undergoing major surgery, there was no signficant difference in the incidence of deep vein thrombosis.

The instrument used is called a "Thrombophylactor" produced by Rank Precision Industries and Stanley Cox Medical Equipment, England. The difficulties encountered are to have the precise control of the site and intensity of the stimulus needed. Furthermore it depends on the anaesthetic condition, for if the patient is curarised, then it is ineffective. Cases of skin erythema and blistering have been recorded.

In summary, electrical stimulation of the calf probably results in a negligible difference in the incidence of postoperative deep vein thrombosis.

3. MOTORISED FOOT MOVER FOR RHYTHMIC FLEXION OF THE FOOT

Passive flexion of the foot has several advantages, it mimics active contraction by producing compression of the calf veins, the flexion can be precisely controlled in terms of rate and amplitude, it will not produce electrical interference, and its effects were not markedly dependent on the anaesthetic condition of the subject (22). The machine consists of a foot board which is attached in the region of the ankle. The foot is held in contact with the board and controlled oscillations are produced by electrically driven crank mechanism. Roberts showed that the peak femoral blood flow could be increased twice its normal value and that its pulsatility could be increased eleven-fold (127).

The passive flexion is begun with induction of the general anaesthetic and continued throughout the entire operation and can be continued postoperatively. In a series of 41 patients, there was a decreased incidence of early thrombosis by 77% (22). However the study was too small for any definite conclusions and requires further investigation. The mechanism of decreasing the incidence of deep vein thrombosis by this method is unknown, but it may be due to an increase in the pulsatile venous flow or just increase in the volume of blood flow (127). The machine produces a continuous dorsal and plantar flexion at 50 cycles per minute at the amplitude of 20° to the vertical (22).

4. PNEUMATIC INTERMITTENT COMPRESSION OF THE CALF

Calnan designed a tubular legging which compresses the calf and foot at 40 mm. Hg pressure intermittently three times a minute (21).

The pneumatic pressure is generated from a standard electrical pump which is almost silent and could hang at the end of the bed. From their initial studies, they concluded that intermittent compression of the calf muscles, rhythmically altered volume of blood flow in veins of the leg. Thus mimicing the normal calf muscle pump (21).

A study undertaken by Hills with a modified apparatus consisting of a single piece of P.V.C. legging incorporating the foot and calf in a unitory design, was carried out in 100 patients (128). The electric pump inflated each leg alternately so that a compression at 40 to 45 mm Hg. for one minute was achieved followed by relaxation for one minute. The apparatus was applied preoperatively at the time of giving the premedication, continued peroperatively and for one day postoperatively. They found that in patients suffering from malignant disease there was no decrease in incidence of deep vein thrombosis. In those patients not suffering from malignant disease, there was a decrease in the incidence. They concluded that it was a safe, effective and practical method of preventing postoperative deep vein thrombosis. In their study both legs were used and the patients were divided into two groups (128). Sabri carried out a study in which one leg of each patient was used as a control. Their results in 39 patients showed that the increase in the pulsatility of the venous flow in the leg was a potent prophylaxis against deep vein thrombosis (129).

In Summary, these mechanical methods are aimed to reduce the thrombi occurring during the operation and within the first 48 to 72 hours postoperative by preventing stasis of blood in the lower limbs.

Simple mechanical measures are inadequate alone; electrical stimulation has complications and the results are inconclusive (22, 126).

The motorized foot mover and pneumatic intermittent compression of the calf appear to be effective but further studies are necessary (22, 128, 129).

5. ORAL ANTICOAGULANTS

Pinto showed that if sodium warfarin was given with the premedication there was no decrease in the incidence of deep vein thrombosis in patients undergoing hip surgery (130). The probable reason for this negative result was that it takes 48 to 72 hours for oral coagulants to take effect. However, in the study by Lambie (30) in which 30 mgs of sodium warfarin was given 36 hours preoperatively and subsequent doses were adjusted with prothrombin time, he found that 12 out of 40 patients developed deep vein thrombosis, six of which were extensive, six minor and bleeding was a definite complication.

In summary, oral anticoagulants such as Warfarin probably have no place in the prevention of deep vein thrombosis even if given preoperatively and have the risk of side effects.

6. HEPARIN

Many reports have appeared in the literature in the last three years on the use of heparin even given intravenously, intramuscularly or subcutaneously (1, 3, 5, 131, 133, 134). Various studies have been undertaken using high dose heparin which alters the clotting and prothrombin time or small (low dose heparin) which does not affect the prothrombin or clotting time, but appears to increase the quantity of naturally occurring inhibitors of coagulation (135, 136, 137). Anticoagulation in full heparin doses increases the risk of bleeding both at operation and postoperatively, and thus is an impractical proposition (138, 139). Kakkar et al (131) reported the use of small dose subcutaneous heparin in 1971, as concentrated aqueous calcium heparin ("Calciparine"), which is in a solution of 25,000 units per cc. They gave 5,000 units of heparin two hours preoperatively and in first 24 hours postoperatively, followed by 12 hourly injections for the next five days. In their study, the incidence of deep vein thrombosis decreased from 26% to 4%. Sharnoff (140) who began this work 10 years before showed that this treatment largely prevented fatal pulmonary emboli.

Mechanism of Action

In the dosage used heparin increases the circulating level of two naturally occurring inhibitors of coagulation i.e. antifactor Xa and antithrombin III and reduces platelet adhesiveness (135, 136, 137).

Clinical studies

The ability of subcutaneous low dose heparin to prevent postoperative deep vein thrombosis, has now been assessed in a number of well controlled trials in which I^{125} fibrinogen tests have been used to detect thrombosis (See Table V). In all the trials, the incidence of positive tests indicating deep vein thrombosis, was much lower than the controls. In William's trial (5) the difference was somewhat obscured by the high incidence of positive tests after prostactectomy in both treated and controlled groups. However, in the study by Gordon-Smith (9), there was no evidence of thrombosis in 6 patients who had retro-pubic prostatectomies. Furthermore, the total incidence of positive tests treated for only one day after operation did not differ significantly from that in patients treated for five days (9). However, in the patients who had malignant disease, the incidence of positive tests was reduced only by the longer period of treatment (9). The largest and most recently published trial by Nicolaides (133) has provided the first clear link between the incidence of positive fibrinogen tests and that of thrombi extending dangerously into the proximal veins. Such a thrombus was found in 9 patients in the control group and none in the heparin-treated group, a highly significant difference. None of the patients in the trial developed signs of pulmonary embolism, the 9 patients with the extending thrombi were treated with anticoagulants (133). Relatively few positive tests for deep vein thrombosis were also found in a series of 133 patients considered to be a high risk of postoperative thrombosis by Kakkar (1), all of whom received low dose heparin. The results were similar between the

patients who had benign or malignant disease (1). However, positive tests were seen in 40% of 50 patients having operations for fractured neck of the femur (1). The failure of low dose heparin to protect patients with femoral neck fractures or cardiac infarction is plausibly explained by the activation of factor X, which follows tissue damage. Once this has occurred, much higher doses of heparin are required to neutralise it (141).

Dose

Low dose subcutaneous heparin is given in dose of 5,000 units one or two hours before operation and 12 hours thereafter for 5 to 7 days by deep subcutaneous injection (131).

Complications

No complications were reported by Kakkar (131) and Williams (5). Wound haematomas developed in four percent of treated patients in Gordon-Smith's study (3), but in a larger trial by Nicolaides (133), they occurred with equal frequency in the controls and treated patients. Troublesome bleeding was reported in two trials, the incidence being 1 out of 123 patients treated (133) and 3 out of 222 (1).

In all four patients there were other factors which may have been partly responsible.

Bruising at the injection site did not give rise to many complaints, even when doses of 7,500 units were given 12-hourly (142).
In some trials, calcium heparin was used because it apparently causes less local bleeding (1, 131). In others, sodium heparin

caused haematoma at the injection site in only 6 out of 222 patients, and in 4 of these the injection was given incorrectly (3, 133).

Conclusion

Low dose subcutaneous heparin in the dose of 5,000 units one or two hours before operation and 12 hours thereafter for 5 to 7 days lowers the incidence of postoperative deep vein thrombosis after most major operations. Prophylactic effects have not been found in patients with fractured neck of femur or with cardiac infarction, presumably because in these conditions the dose of heparin is too small to neutralise the factor X, which has been activated by previous tissue damage. Lowering the incidence of deep vein thrombosis, as shown by the radioactive fibrinogen tests, is likely to reduce that of pulmonary embolism, but this can be proved only by large-scale studies. The treatment is safe, cheap and simple to administer.

TABLE V - DETAILS OF FIVE TRIALS USING LOW DOSE SUBCUTANEOUS HEPARIN IN PREVENTION OF POSTOPERATIVE DEEP VEIN THROMBOSIS

Authors	Regimen	Case Material	Design	No	Incidence of positive ^{125}I-fibrinogen tests (%)	Statistical Significance
Kakkar (131)	5000 u 2 hr before operation and 5000 u 12-hourly for 5 days	herniorrhaphies	2 series treated consecutively	27 controls 26 treated	26) 4)	$p < 0.05$
Williams(5)	10,000 u hr before operation and 2500-5000 u 6-hourly for 7 days	major operations in patients over 50 years	allocation to treatment groups by birth year	29 controls 27 treated	41) 15)	$p < 0.03$ (Fisher's exact test)
Gordon-Smith (3)	5000 u 1 hr before operation and 5000 u 12 hrly. for 1 or 5 days.	major operations in patients over 40 years	random allocation to treatment groups	50 controls 52 treated 1 day postop 48 treated 5 days postop	42) 13)) 8)	$p < 0.01$ -))$p < .0001$ insignificant) -))
Kakkar (1)	5000 u 2 hr before operation and 5000 u 12-hourly for 7 days	(a) major operations in patients over 40 years	double blind comparison. heparin v. placebo	39 controls 39 treated	42) 8)	$p < 0.001$
		(b)elective major operations in 'high risk'patients	series without controls	133 treated	10	
		(c) emergency operations for fractured neck of femur	series without controls	50 treated	40	

Continued/.......

Authors	Regimen	Case Material	Design	No.	Incidence of positive ^{125}I-fibrinogen tests (%)	Statistical Significance
Nicolaides (133)	5000 u 2 hr before operation and 5000 u 12-hourly for 7 days	major operations in patients over 40 years	random allocation to groups	122 controls 122 treated	24) 0.8)	$p < 0.0001$

7. DEXTRAN

a. Dextran 40 ("Rheomacrodex")

b. Dextran 70 ("Macrodex")

Dextrans are polysaccharides produced by bacterial interaction on sucrose. The two clinically available dextrans are Dextran 70, which has an average molecular weight of 70,000 units ("Macrodex") and Dextran 40, with an average molecular weight of 40,000 units ("Rheomacrodex"). For surveys of the metabolism and excretion of dextran as well as other biological effects not connected with antithrombotic properties, there has been an extensive review on this subject given by Ingelman (143).

The antithrombotic effects of dextran are well documented both clinically and experimentally but its mode of action is still a matter of discussion. It may be due to an effect on the coagulation mechanism, the platelet function, the vessel endothelium, fibrinolysis or on blood flow (115).

The antithrombotic effects of dextran cannot be explained by its anticoagulant properties (115). From investigation it appears that dextran has a depressive effect on platelet function, and this may be the main cause of a slightly increased bleeding time reported by some authors (115, 144). Whether dextran has any fibrolytic properties is still a matter of discussion (145). Gelin noted the improvement of blood flow and a counteraction of postcapillary venous stasis (146). Kockenberg in 1961 published the first report on the clinical use of dextran for the prevention of postoperative thrombo-embolism in general surgery (147).
A review of the results in most of the clinical trials is given in Table VI.

TABLE VI REVIEW OF CLINICAL TRIALS WITH DEXTRAN IN PREVENTION OF POSTOPERATIVE THROMBOEMBOLISM

Author Year	Kind of surgery No. of cases	Type of Dextran	Duration of treatment	Thromboembolism % Control	Dextran
Kockenberg 1962 (147)	General Surgery 199	Macrodex	1 day	32	10.9
Ahlberg 1968 (106)	Hip Surgery 198	Macrodex	3 days	44.4	19.7
Johnsson 1968 (110)	Hip Surgery 52	Macrodex	12 days	52	4
Sawyer 1968 (148)	General Surgery 103	Macrodex	6-8 days	13.4	5.9
Elsner-MacKey 1969(149)	General Surgery 818	Macrodex	4 days	12.4	3.8
Hartshorn 1969 (150)	General Surgery 203	Dx 75	3 days	20	16
London 1969 (151)	General Surgery 100	Macrodex	4 days	34	14
Atik 1970 (152)	Hip Surgery 70	Dx 70	5-10 days	15.5	2.0
Everts 1970 (153)	Hip Surgery 36	Dx 40	13 days	46	22
Kakkar 1970 (154)	General Surgery 90	Dx 70	2 days	47	55
Stadil 1970 (155)	General Surgery 850	Macrodex	2 days	10.3	3.8

In 1968 several papers were published reporting good prophylaxis using dextran in connection with orthopaedic and general surgery (147,110). In patients with hip fractures the average incidence of venous thrombosis was about 50% and dextran could decrease these complications by 80%. All patients were checked with phlebography.

A conclusive study was reported by Lambie et al 1970, in which 80 patients over the age of 40 years were operated on for major gynaecological surgery and divided randomly into two groups (23). One group was treated with Warfarin Sodium and the other group received Dextran 70 in saline.
The diagnosis of deep vein thrombosis was made using labelled fibrinogen. In the warfarin group 6 major and 6 minor thromboses were diagnosed, and in the dextran group there were no major, and only 4 minor thromboses (23).

From Table VI it will be seen that dextran 70 appears superior to dextran 40 in preventing venous thrombosis. This is probably due to the antithrombotic properties, rather than improved blood flow and plasma volume expansion (115).
The most conclusive report is that from Jansen (115) in which 901 cases were studied in a double blind trial.

Postoperatively the patients were followed clinically with bedside examinations of the lower extremities. In all cases of even slight suspicion of venous thrombosis ascending phlebography was performed. In the 901 cases studied, 301 were in the control group, 304 in the dextran 70 group and 296 in the dextran 40 group. In the control group, 10% of the cases developed postoperative deep vein thrombosis which was

confirmed on phlebography. (6 pulmonary emboli, 5 major emboli). The incidence in the dextran 70 group was 5.9% (18 cases, 4 with pulmonary emboli, 1 major embolus.) In the dextran 40 group 4.4% (13 cases, no emboli). Jansen concluded that the difference in incidence of thrombosis between the dextran groups and the control group was statistically significant. The prevention seemed to be most effective with dextran 40. There was no statistically significant difference however between the two dextran preparations. Further analysis of the results showed that the preventive effect was most pronounced in 489 patients with an operation time of 1 hour or less. In the remaining patients with an operation time of more than one hour, the effect of 500 ml of dextran was no longer significant, probably indicating that the dextran dosage used was insufficient in such cases.

In a later study, when the test solutions were given the day after operation, the frequency of postoperative thrombo-embolism was equal in all groups (115). Jansen concluded from his study that the administration of 1 single unit of 500 ml of dextran in the course of an operation of one hour or less, was a simple and safe way to decrease the incidence of thrombo-embolic complications, in general surgery (115).

Side effects induced by Dextran

1. Increased bleeding tendency during the operation was not observed in the trial by Jansen (115).
2. Acute reactions to dextran infusion have been reported and the Swedish Adverse Drug Reaction Committee have collected 64 cases from an international survey (156).

3. Dextran is contraindicated in patients with congestive cardiac failure, bronchospasm or renal failure (115).

8. SODIUM PENTOSAN POLYSULPHATE "TAVAN-SP 54"

This is a polysaccharide, synthetic heparin-like sulphated polyanion. Several studies have been undertaken which show that it causes an inhibition of platelet aggregation, is anti-thrombotic, and acts as a clearing factor (157). The only clinical trial using Tavan-SP 54 was published by Kraft in 1962 in the prevention of postoperative deep vein thrombosis (158). The dose used was 50 mg intramuscularly 12 hourly starting on the evening of the first postoperative day.

Results

In 3,752 cases of patients treated prophylactically over a period of four years, an incidence of less than 1% of deep vein thrombosis, and of these 0.08% were lethal.
The control incidence of deep vein thrombosis was 3.15%, and of pulmonary emboli 1.5% , with a mortality of 0.3% over a seven year period comprising 15,000 operations. However the diagnosis of deep vein thrombosis and pulmonary emboli were on a clinical basis which by todays standards are inacceptable. The remaining work on the use of Tavan-SP 54 has been done in animals (157).

9. MISCELLANEOUS

A. Antiplatelet agents

These are relatively free from side effects and therefore may have a more important role than anticoagulants.

1. Hydroxychloroquine Sulphate

This had been shown to decrease platelet aggregation.
Initial work was done by Knisely (160) in 1941 and Madow (161) in 1960 when it was used as an anti-malarial drug to decrease the red blood cell sludging. In the two groups studied by Carter (159) in 1972 the one was diagnosed clinically and the other by phlebography with a statistically significant decrease in the incidence of deep vein thrombosis and pulmonary emboli. The dose was 200 mgs of hydroxycholoroquine sulphate intramuscularly with the premedication and then 8 hourly intramuscularly or orally until discharged (159).
There were no complications, but the group was small and one awaits further results.

2. Dipyridamole

This initially showed some promise, but has now been shown to be unsatisfactory (161A).

3. Aspirin

A report by Steering Committee of a trial sponsored by the Medical Research Council, done as a double blind randomised study of the effect of aspirin on postoperative deep vein thrombosis (162).
There were 303 patients over the age of 27, who were admitted to four hospitals for elective surgery and received

either 600 mgs of Aspirin or a placebo during the 24 hours preceeding operation and on the first 5 postoperative mornings. Deep vein thrombosis was diagnosed by I^{125} fibrinogen uptake tests and the results showed <u>no</u> significant difference between the treated and placebo groups (162).
A smaller trial using 600 mgs, 4 times a day was also undertaken but the incidence of deep vein thrombosis remained unaltered.

B. <u>Stimulation of endogenous fibrinolysis pharmacologically</u>

After surgery there is a period of reduced fibrinolytic activity, the so called "fibrinolytic shut-down" (163). It has been shown that administration of Phenformin and Ethyloestrenol increases endogenous blood fibrinolytic activity as measured by the clot lysis time (164). The study by Brown (165) in 1971 in which two groups of 27 patients were studied, one group was given six weeks of preoperative, followed by 10 days of postoperative treatment with Phenformin 50 mgs twice daily and Ethyloestrenol (an anabolic steroid), 4 mgs twice daily, and the other was not. Their results showed an increase in the fibrinolytic activity by the clot-lysis time and an increased level of fibrin-degradation products. This could be a useful method of prevention and a trial has now been undertaken by Brown (165). The disadvantage is however, that the patient must be prepared 6 weeks before surgery.

<u>Summary</u> of drugs used in the prevention of postoperative deep vein thrombosis.

Many studies have been undertaken. If the efficacy of low dose subcutaneous heparin is confirmed in our own patients then a turning point would have been reached in the prevention of postoperative deep vein thrombosis.
Coumadin, aspirin and dipyridamole are ineffective and dextran appears to have a place in selected patients.

3. MATERIAL

THE TOTAL NUMBER of patients included in this study were 298 patients.

Sub-division of patients into

1.	CONTROL GROUP IN GENERAL SURGERY	130
2.	NEUROSURGERY	23
3.	OPHTHALMOLOGY AND OTOLARYNGOLOGY	31
4.	CALCIUM HEPARIN TRIAL	54
5.	SODIUM PENTOSAN POLYSULPHATE TRIAL	60

CONTROL GROUP IN GENERAL SURGERY

All patients in the control group underwent an operation requiring a general anaesthetic. Ninety percent of the patients were over the age of 40 years and were to undergo a major elective surgical procedure. A major operation was defined for the purpose of the trial as any surgical procedure performed under general anaesthesia which lasted more than 30 minutes and which would be followed by at least seven days in hospital. Patients excluded from the trial were those undergoing surgery to the lower limb and those undergoing left mastectomy, because of the difficulty in radioactive fibrinogen counting.

NEUROSURGICAL PATIENTS

In this group all patients who were undergoing any neurosurgical procedure and spinal operations were included. Similar criteria with the procedure being performed under general anaesthetic lasting more than half an hour and the patient being in hospital for longer than 7 days. All patients included in this series were over the age of 21 years.

OPHTHALMOLOGICAL AND OTOLARYNGOLOGY PATIENTS

These patients were selected provided that they had to undergo general anaesthetic lasting more than half an hour with at least 3 days postoperative hospitalisation.

PROPHYLAXIS OF DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM WITH SUBCUTANEOUS CALCIUM HEPARIN

The criteria for inclusion in this co-operative trial associated with King's College Hospital, London were that the patients

i. age over 40 years undergoing a
ii. major elective surgical procedure.

Patients excluded were those undergoing

i. emergency surgery. Those receiving
ii. heparin for any reason. Those undergoing
iii. surgery to the lower limb, or
iv. left mastectomy.

Two groups of patients were studied. One group received prophylactic subcutaneous heparin and the other group would act as a control. Patients were allocated to a group on a computerised basis of randomly allocated envelopes, which contained a slip on which was printed "treatment" or "control". The proformas and calcium heparin was obtained from the Calcium Heparin Trial Centre at the Department of Surgery, King's College Hospital Medical School, London, where Dr V. Kakkar is conducting a multicentre trial of prophylactic subcutaneous heparin.
A total of 54 patients received prophylactic subcutaneous heparin.

Calcium Heparin

Patients in the treatment group received subcutaneous heparin in the dose of 5,000 units, 2 hours preoperatively and 8 hours after this for the first 6 postoperative days (a total of 7 days treatment). If, at the end of the 6th postoperative day, the patient was still confined to bed due to any condition (e.g. infection) Calcium Heparin was continued in the same dosage until the patient was fully mobile. The time of administration of the drug postoperatively was adjusted to correspond with the ward drug-rounds, provided an 8 hour interval between injections was maintained. The injection was given using a 26 gauge needle, into the subcutaneous tissue of the anterior abdominal wall. A fold of skin was raised and the needle inserted at right angles to the skin. After injection the needle was withdrawn at the same angle. Other sites e.g. arms and thighs were not used for the injection. One sheet of the proforma was provided on which administration of the Calcium Heparin by the nursing staff was recorded. This record was of vital importance to the trial as evidence that the drug had been given.

SODIUM PENTOSAN POLYSULPHATE OR "TAVAN-SP 54"

Patients were admitted to this trial who were undergoing elective major general surgical operations under general anaesthesia. Patients were allocated consecutively into control and trial groups.

A. The first part of the study was undertaken using high dose of Tavan-SP54 in which 100 mgs was given 2 hours preoperatively and then 100 mgs was given 6 hourly by intramuscular injection. However, due to complications of bleeding this was changed.

B. A second study was made using low dose Tavan-SP 54, in which 50 mgs was given 2 hours preoperatively and then 50 mgs was given 12 hourly by intramuscular injection. A total of 60 cases were admitted to this trial, 12 to the high dose and 48 to the low dose of Tavan-SP 54.

4. METHOD OF DIAGNOSIS OF DEEP VEIN THROMBOSIS

1. CLINICAL

2. RADIO-ACTIVE FIBRINOGEN

3. DOPPLER ULTRASOUND TECHNIQUE

4. VENOGRAPHY

1. CLINICAL

The classical signs of deep vein thrombosis were sought daily, and included calf tenderness and swelling, oedema and duskiness of the ankle and Homan's sign.
The temperature chart was noted and the patient was directly questioned as to any evidence of pulmonary emboli such as chest pain, shortness of breath or haemoptysis and the chest was clinically examined.

2. RADIO-ACTIVE I^{125} LABELLED FIBRINOGEN TECHNIQUE

The thyroid uptake of the radio-active iodine was blocked by giving 100 mgs of potassium iodide orally 24 hours before the injection of the isotope labelled fibrinogen and daily thereafter or by the intravenous injection of 20 cc's of a 10% solution of sodium iodide if the patient was taking nil per mouth.
This was followed by injection of 100 microcuries of I^{125} Human Fibrinogen, obtained from a small pool of hepatitis-free donors from the Radiochemical Centre, United Kingdom Atomic Energy Authority, Amersham, England, and was injected intravenously. All measurements were made in the ward with the patient lying supine in bed, with the legs elevated 10^0 above the horizontal in order to avoid venous pooling.
Counts were made at selected 5 cm interval points on the lower limb and the precordial activity was also noted. Daily counts were made. Activity at each point on the limb was expressed as a percentage of the heart-count measured on the same occasion. This method eliminated the need for calculating biological or radioactive decay. With a Pitman Ratemeter as used in this study, the radioactivity at each point on the leg could be expressed as a percentage of the heart count by simple use of a control which adjusted the precordial counts to a figure of 100%. This obviated calculations and greatly simplified the measurement. The count rate at each one point on the limb, expressed as a percentage of the heart rate measured on the same occasion, was compared with the rate at the same point on the previous day and was also compared with the adjacent points on the same limb to the corresponding points on the opposite limb. A rise of 20% using the Pitman Ratemeter indicated the presence of the venous thrombosis, provided

that the rise in activity persisted and increased on the succeeding day.

3. DOPPLER ULTRASOUND

The apparatus used was a Sonicaid D.205M which consisted of a portable box which contained a transmitter, receiver, audio-amplifier, a loudspeaker and a writeout. The transmission frequency was 2 megaHertz. The patients were examined sitting in bed in the ward with the hip flexed to 45°. The lower limbs were straight and the ankles were supported to allow good passive filling of the calf veins. A transducer was applied to the skin overlying the veins to be examined, using a suitable coupling medium such as olive oil. The transducer was sited over the common femoral vein and popliteal vein. To produce the augmentation or "A wave", the leg was squeezed by the hand over the mid thigh and mid calf. Visual recordings of the sounds heard were made by attaching the Sonicaid D205M to an electro-cardiograph machine. If this squeeze was applied to the leg distal to the side of the transducer an acceleration of venous flow velocity occurred and a roar was heard from the loudspeaker. This augmentation or "A wave", indicated the presence of a deep venous flow between the site of the squeezing and the transducer. The presence of moving blood was therefore indicated by a sound from the loudspeaker while in venous obstruction there was silence. For this study it was accepted that either a sound was present which indicated vein patency or the sound was absent indicating venous obstruction.

Patency in the inferior vena cava and iliac veins were assessed by applying a Doppler probe over the common femoral vein during hyperventilation. Absence of obstruction was indicated by a wave-like roar corresponding to the respiratory excursion.

4. VENOGRAPHY (PHLEBOGRAPHY)

Venography was carried out routinely in the first 32 patients of the control group who were suspected of having deep vein thrombosis either Clinically, on Radio-active fibrinogen studies or Doppler Ultrasound. The procedure is carried out in the Radiology Department of Groote Schuur Hospital. Each leg was examined separately. Patients lay supine on the table and a tourniquet was applied around the ankle to distend the foot veins. A disposable needle was introduced percutaneously into a vein of the dorsum of the foot. The needle was directed towards the toes i.e. in an up-stream direction. A second tourniquet was applied above the knee to trap the contrast medium in the calf veins. The table was tilted 20° downwards and the legs internally rotated to separate the images of the tibia and fibula. The syringe containing 50 ml of the contrast medium, Meglumine Iothalamate 60%, was connected to the needle by a polythene tube and a hand injection was begun under television control. Two exposures were made, one below the knee and one including the knee in the postero-anterior projection. The third exposure was made with the leg externally rotated so that the calf muscle sinusoids were not obscured by the tibia and fibula. The upper tourniquet was removed and further exposures were taken from the popliteal vein to the inferior vena cava. Good filling of the upper femoral and iliac veins was obtained by the injector applying firm pressure in an upward direction to the calf. This procedure occasionally outlined the lower part of the vena cava. If difficulty was encountered a percutaneous transfemoral injection of the contrast medium on the non-obstructive side was carried out.

No pertrochanteric injections were used. Standard bilateral examination demonstrating the venous system from ankle to inferior vena cava required 200 to 400 ml of contrast medium. After the phlebographic examination was complete the contrast medium was cleared from the venous system with normal saline and active movement of the foot. Complete clearing of veins was checked by television screening.

5. DIAGNOSIS OF PULMONARY EMBOLISM

In all suspected cases of pulmonary embolism a full clinical examination was carried out. Routine electrocardiogram plain chest x-ray and lung scan using I^{131} - labelled macro-aggregates of human serum albumin and blood gases were measured. Pulmonary angiography and haemodynamic studies were not done.

SECTION B

1. INCIDENCE

2. PREVENTION

1. INCIDENCE

1. CONTROL GROUP IN GENERAL SURGERY

OBSERVATION

A. FACTORS

a. Analysis of Factors

b. Discussion

c. Conclusion

B. DIAGNOSIS OF POSTOPERATIVE DEEP VEIN THROMBOSIS

a. Analysis of Techniques

b. Discussion

c. Conclusion

2. NEUROSURGERY

a. Results

b. Discussion

c. Conclusion

3. OPHTHALMOLOGY, OTORHINOLARYNGOLOGY

a. Results

b. Discussion

c. Conclusion

4. POST-RENAL TRANSPLANTATION

a. Results

b. Discussion

c. Conclusion

2. PREVENTION

1. HEPARIN

a. Results

b. Discussion

c. Conclusion

2. SODIUM PENTOSAN POLYSULPHATE

a. Results

b. Discussion

c. Conclusion

INCIDENCE IN CONTROL GROUP IN GENERAL SURGERY

OBSERVATION

One hundred and thirty cases in the General Surgical Wards at Groote Schuur Hospital, Cape Town, were investigated for Postoperative Deep Vein Thrombosis as a Control Group. Diagnosis was made Clinically, using Radioactive Fibrinogen, Doppler Ultrasound and Venography.

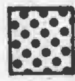
THE INCIDENCE WAS 51%

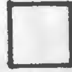
See Figure 6.

Because of this unexpectedly high incidence, an analysis of high risk factors was made.

In addition, the diagnostic techniques were evaluated for accuracy.

FIGURE 6. INCIDENCE OF POSTOPERATIVE DEEP VEIN THROMBOSIS IN THE GENERAL SURGERY WARDS AT GROOTE SCHUUR HOSPITAL IN 130 CASES. (1972 - 1973)


Positive


Negative

100
90
80
70
%
60
50
40
30
20
10

INCIDENCE IN CONTROL GROUP IN GENERAL SURGERY

A. FACTORS

a. Analysis of factors.

b. Discussion.

c. Conclusion.

B. THE DIAGNOSIS OF POSTOPERATIVE DEEP VEIN THROMBOSIS

a. Analysis of techniques

b. Discussion

c. Conclusion

A. FACTORS IN CONTROL GROUP

In the discussion of these patients the word "Positive" will be used for those who developed postoperative deep vein thrombosis and "Negative" for those who did not.

a. ANALYSIS OF FACTORS

I. The Patient

1. Age
2. Sex
3. Race
4. Obesity
5. Blood Group

II. Past History

1. Myocardial Infarction
2. Deep Vein Thrombosis
3. Pulmonary Embolus
4. Long Bone Fracture in Lower Limb

III. Present Admission

1. Chronic Obstructive Airways Disease
2. Contraceptive Pill (Oestrogen and/or Progesterone)
3. Varicose Veins
4. Varicose Ulcer or Healed Varicose Ulcer
5. Days in Hospital Preoperative

IV. Operation

1. Duration
2. Type
3. Pathology
4. Blood Loss

V. Postoperative

1. Complications
2. Days in Hospital Postoperative
3. Deaths

a. ANALYSIS OF FACTORS

I. The Patient

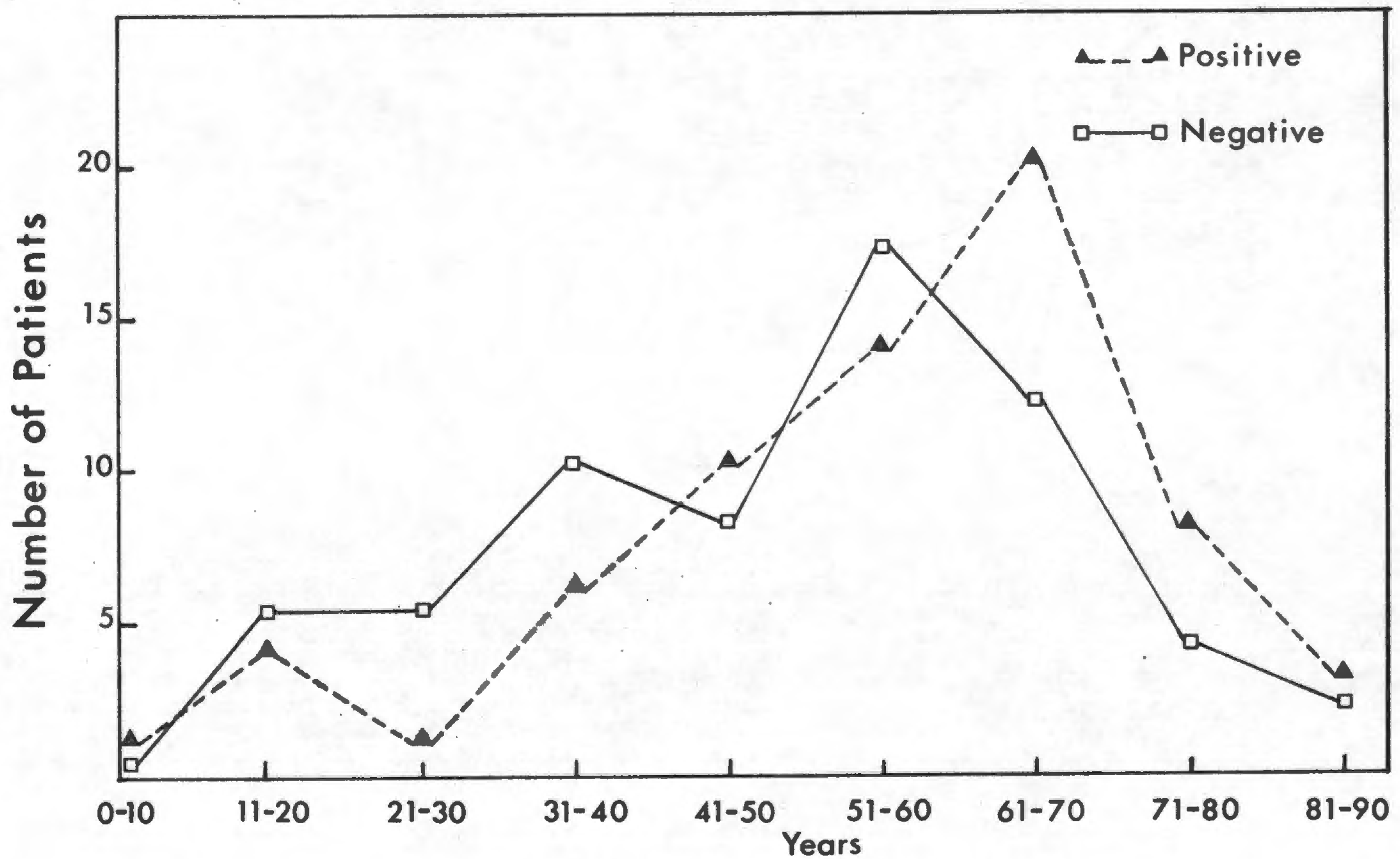
1. Age

The age distribution of the patients in the control group is shown in Figure 7, who developed deep vein thrombosis.

From the graph it would appear that the 60 to 70 year old age group was more prone to develop postoperative deep vein thrombosis, but this was not confirmed statistically ($0.50 < P < 0.75$) as the numbers were too few.

However, in dividing the below 40 year and above 40 year old age group, there was a statistically significant difference, with all patients over 40 years being more prone to develop postoperative deep vein thrombosis. ($0.05 < P < 0.25$)

FIGURE 7. AGE DISTRIBUTION OF POSTOPERATIVE DEEP VEIN THROMBOSIS IN THE GENERAL SURGERY WARDS IN 130 CASES.


Positive
Negative
Number of Patients
20
15
10
5
0-10
11-20
21-30
31-40
41-50
51-60
61-70
71-80
81-90
Years

2. Sex Distribution

Of the control group 55% were FEMALES and 45% were MALES. Postoperative deep vein thrombosis occured in

54% of the Females and in

46% of the Males.

This difference is not statistically significant ($0.25 < P < 0.50$). See Figure 8.

3. Racial Distribution

In the control group 62% were European and 38% were Non-European. Of these 56% of the Non-Europeans developed deep vein thrombosis as compared to only 47.5% of the European group. This difference is not statistically significant ($0.25 < P < 0.50$), although the incidence appears higher in the Non-European group.

The composition of the control group is shown in Table VII. in which the majority of the Non-European patients were Cape Coloured (70%), 19% were Bantu and 11% Indian.

The mean incidence of deep vein thrombosis in these three groups was 56%, with

54% in the Cape Coloured,

50% in the Bantu and

67% in the Indian patients.

The small numbers did not allow statistical analysis.

The sex distribution in the Non European patients in the three groups is also shown in Table VII and Figure 9.

FIGURE 8. SEX DISTRIBUTION OF POSTOPERATIVE DEEP VEIN THROMBOSIS IN THE GENERAL SURGERY WARDS IN 130 CASES

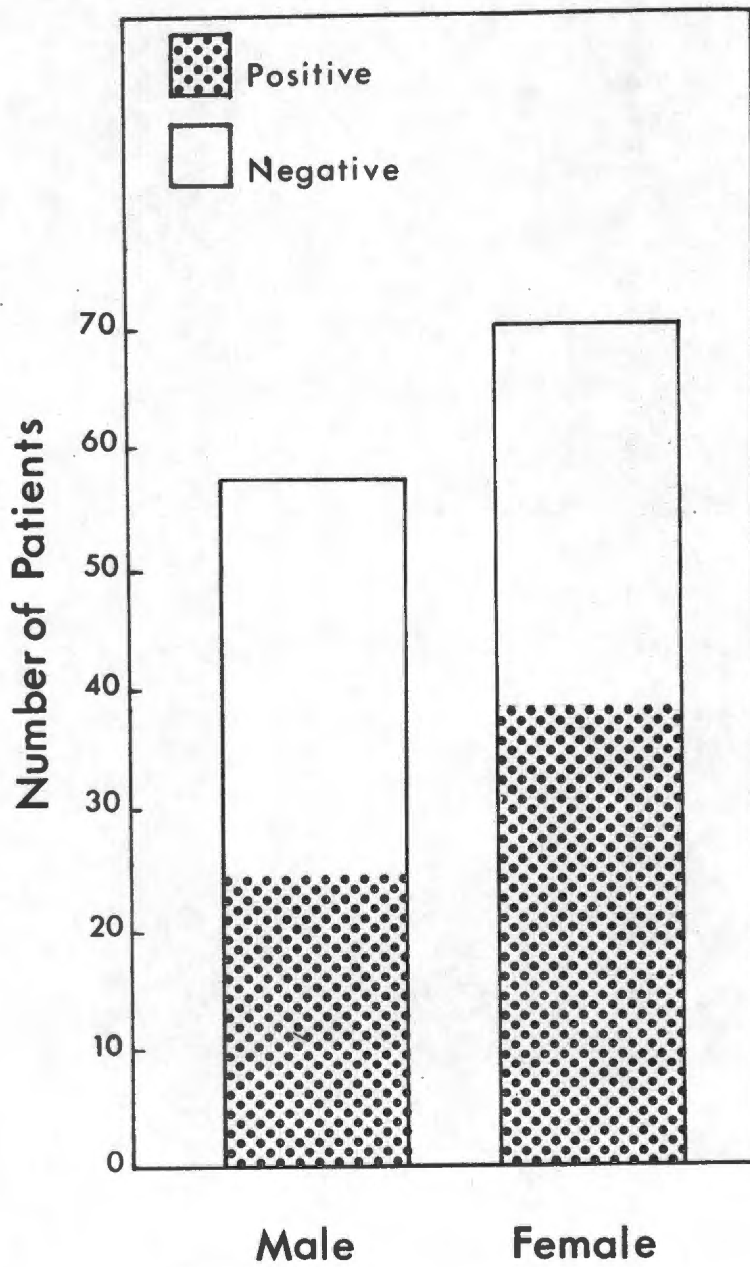

Positive
Negative
Number of Patients
70
60
50
40
30
20
10
0
Male
Female

FIGURE 9 RACIAL DISTRIBUTION OF POSTOPERATIVE DEEP VEIN THROMBOSIS

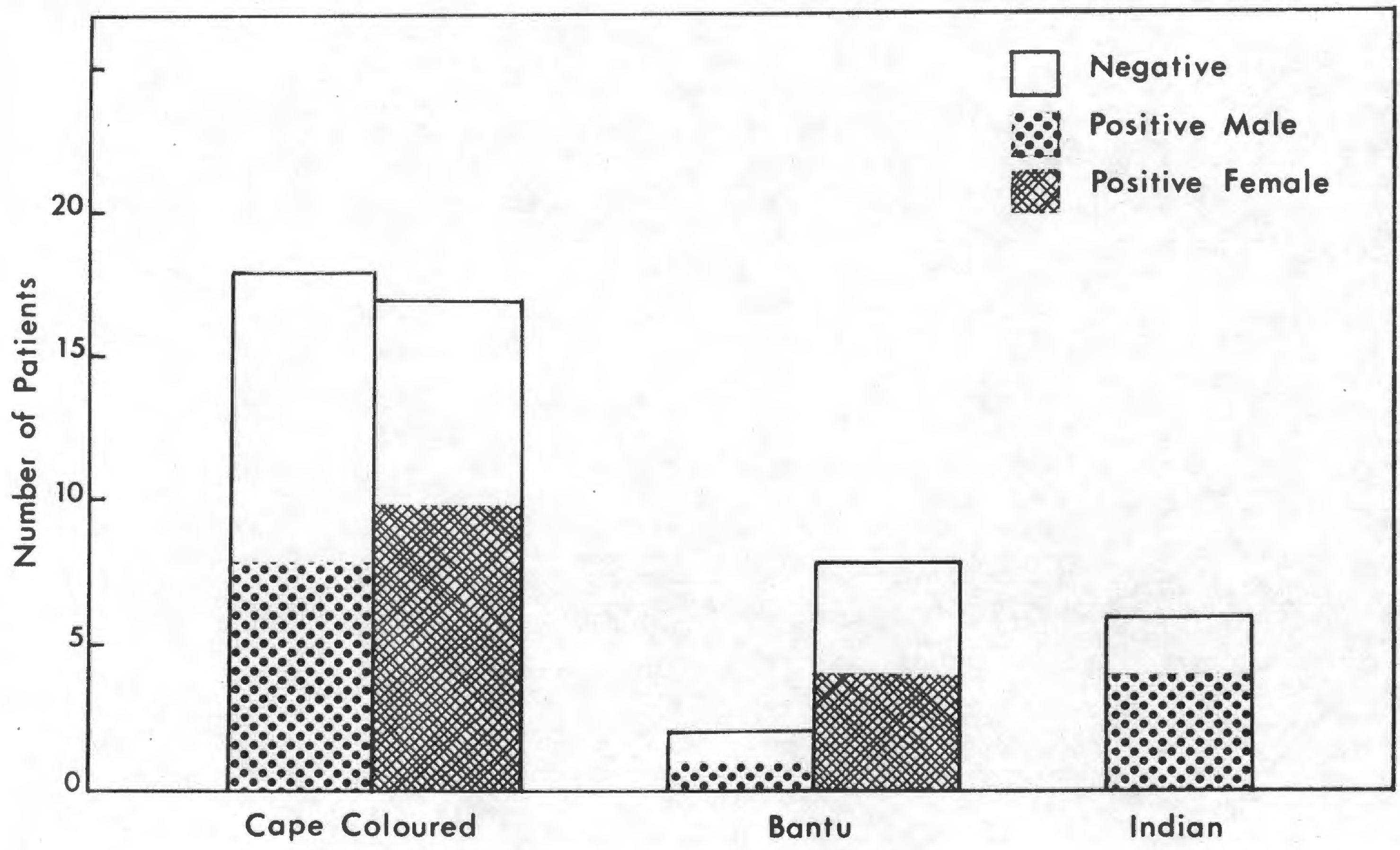

Negative
Positive Male
Positive Female
20
15
10
5
0
Number of Patients
Cape Coloured
Bantu
Indian

TABLE VII RACIAL DISTRIBUTION OF CONTROL GROUP OF 130 PATIENTS IN GENERAL SURGERY WARDS.

	TOTAL	POSITIVE	PERCENTAGE
European	79	38	47.5
Non European	51	28	56
Coloured	35	19	54
Males	18	9	
Females	17	10	
Bantu	10	5	50
Males	2	1	
Females	8	4	
Indian	6	4	67
Males	6	4	
Females	0	0	

4. Obesity

Obesity in relationship to height, to weight for each age group.

Three groups were analysed -

normal
mildly obese, and
severely obese,

as classified by the Metropolitan Life Insurance Company Statistical Bulletin (166) and the Society of Actuaries (167). Of all the patients, 67% were normal, 14% were mildly obese and 19% were severely obese.

It is noted in figure 10 that 68% of the severely obese patients developed deep vein thrombosis as compared to 45% of the mildly obese and 47% of the normal patients.

As these differences are significant severe obesity is a predisposing factor to development of deep vein thrombosis. ($P < .05$).

5. Blood Group

Distribution of patients into blood groups ABO and Rh is shown in Figure 11. It would appear that Rh negative is more protected than Rh positive. The two patients in blood group AB developed venous thrombosis but the numbers are too small to draw any conclusions.

FIGURE 10. OBESITY AND POSTOPERATIVE DEEP VEIN THROMBOSIS.
(From Tables based on Height to Weight and Age (166, 167)

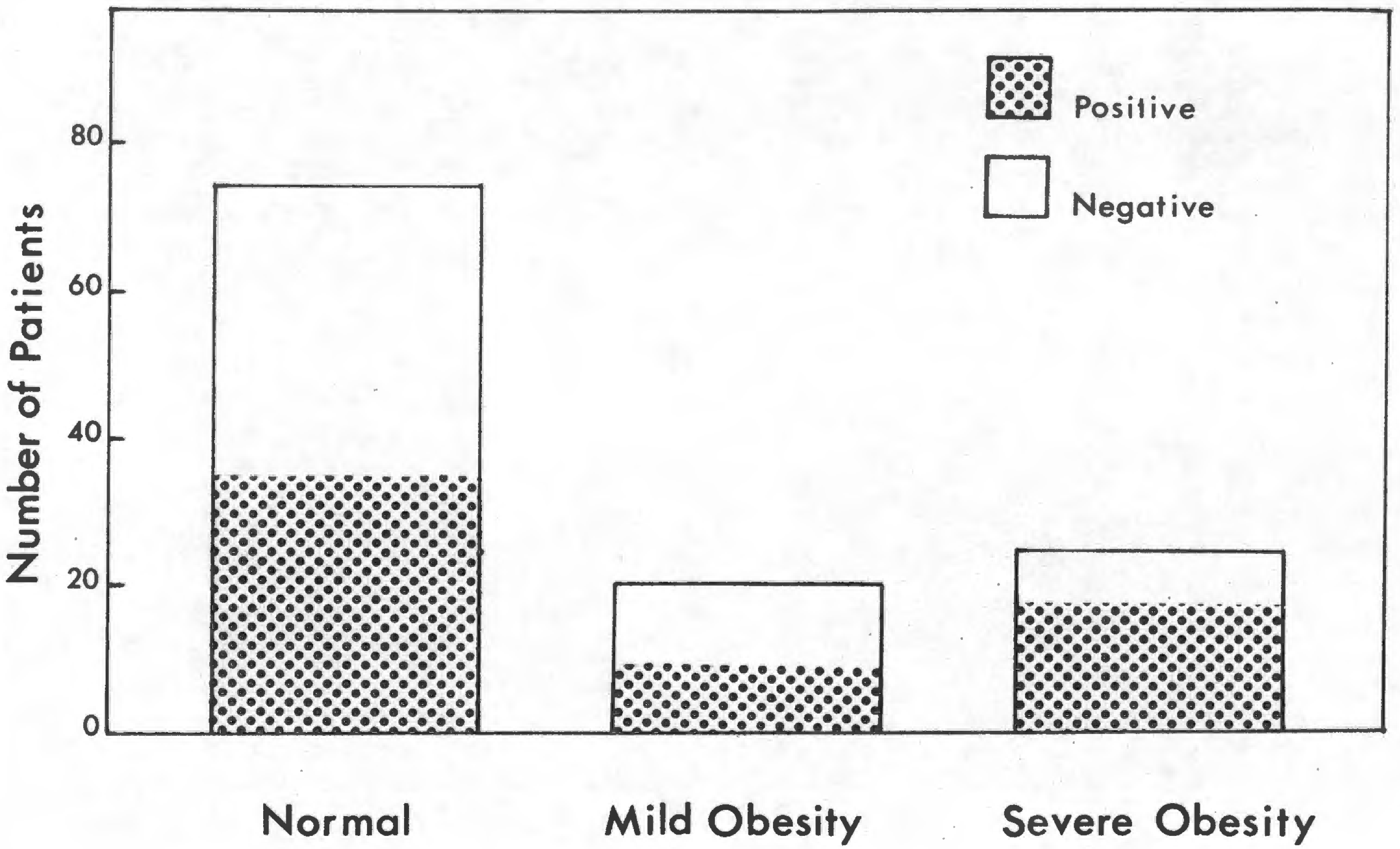
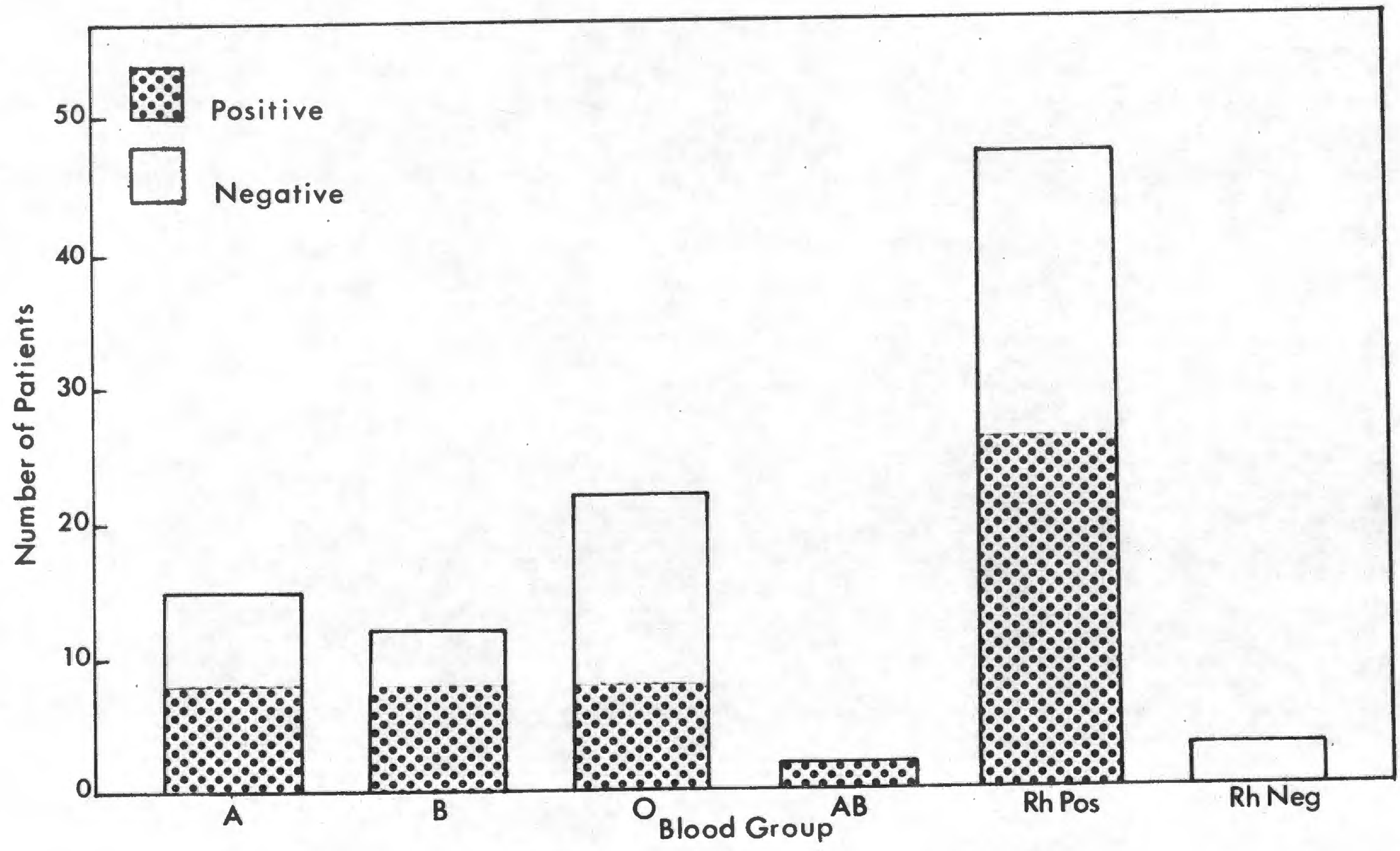

Positive
Negative
Number of Patients
80
60
40
20
0
Normal
Mild Obesity
Severe Obesity

FIGURE 11. BLOOD GROUP AND POSTOPERATIVE DEEP VEIN THROMBOSIS.


Positive
Negative
Number of Patients
50
40
30
20
10
0
A
B
O
AB
Rh Pos
Rh Neg
Blood Group

II. Past History

1. Myocardial Infarction (diagnosed by Electrocardiograph)
2. Deep Vein Thrombosis
3. Pulmonary Embolus (Chest Pain with or without Haemoptysis)
4. Long Bone Fracture in Lower Limb

From Table VIII it will be noted that one patient had a fracture of the tibia and fibula on the left side 9 years before and developed a deep vein thrombosis on the same side.
One patient had a previous deep vein thrombosis diagnosed clinically, but remained negative.

TABLE VIII PAST HISTORY OF CONTROL GROUP AND POSTOPERATIVE DEEP VEIN THROMBOSIS

	Negative	Positive	Total
1. Myocardial Infarction	1	1	2
2. Deep Vein Thrombosis			
Right	1	0	1
Left	0	0	0
3. Pulmonary Embolus	0	0	0
4. Long bone fracture in lower limb			
Right	0	0	0
Left	0	1	1

III. Present Admission

1. Chronic Obstructive Airways Disease

Of 8 patients with this complication, 6 developed postoperative deep vein thrombosis.

2. Oral Contraceptive Pill

Only 2 patients were on the pill and both were negative.

3. Varicose Veins

Of the 10 patients with varicose veins, 9 developed deep vein thrombosis. Six patients had varicose veins on the right side and 5 developed deep vein thrombosis, 4 patients had varicose veins on the left side and all 4 developed deep vein thrombosis. This finding is significant in that patients with varicose veins have a very high risk of developing postoperative deep vein thrombosis. ($0.01 < P < 0.02$). See Table IX.

4. Varicose Ulcer and Healed Varicose Ulcer

There were no patients with varicose ulcers, but there were 3 with healed varicose ulcers on the right side of whom 2 developed a deep vein thrombosis on the same side.
The presence of healed varicose ulcers usually implies previous deep vein thrombosis and thus perhaps a greater susceptibility to the development of future postoperative deep vein thrombosis.

TABLE IX PRESENT ADMISSION IN CONTROL GROUP

	Negative	Positive	Total
Chronic Obstructive Airways Disease	2	6	8
Contraceptive Pill	2	0	2
Varicose Veins			
Right	1	5	6
Left	0	4	4
Varicose Ulcer	0	0	0
Right	0	0	0.
Left	0	0	0
Healed Varicose Ulcer			
Right	1	2	3
Left	0	0	0

5. Days in hospital preoperatively

Up to the 10th day in hospital preoperatively there was no significant difference between the positive and negative group, but of the 14 patients who were in hospital 10 to 20 days before operation, 9 were positive.

It seems that patients who required hospitalisation for more than 10 days had a greater risk of developing postoperative deep vein thrombosis shown in Figure 12.

IV. Operation

1. Duration of Operation

An operation lasting less than half an hour, or half to one hour there was no difference between the two groups (Figure 13). In the series of 63 patients who had operations lasting one to 2 hours, 35 were positive i.e. 55%. For operations lasting two to four hours there was no difference between the 2 groups. (Figure 13).

It appears that a patient undergoing an operation of any duration was liable to develop deep vein thrombosis, but was at a greater risk if the operations lasted one to two hours.

2. Type of Operation

The patients were grouped according to operative site as head and neck, breast, vascular, exploratory abdominal laparotomy, oesophagus, stomach and duodenum, small bowel and appendix,

large bowel, spleen, gall bladder and liver, anus and rectum, hernia and other.

From Table X, it will be seen that any patient undergoing any type of operation was prone to develop deep vein thrombosis postoperatively. Those undergoing operations on the stomach and duodenum were at a slightly greater risk. Again small numbersrender correlation difficult.

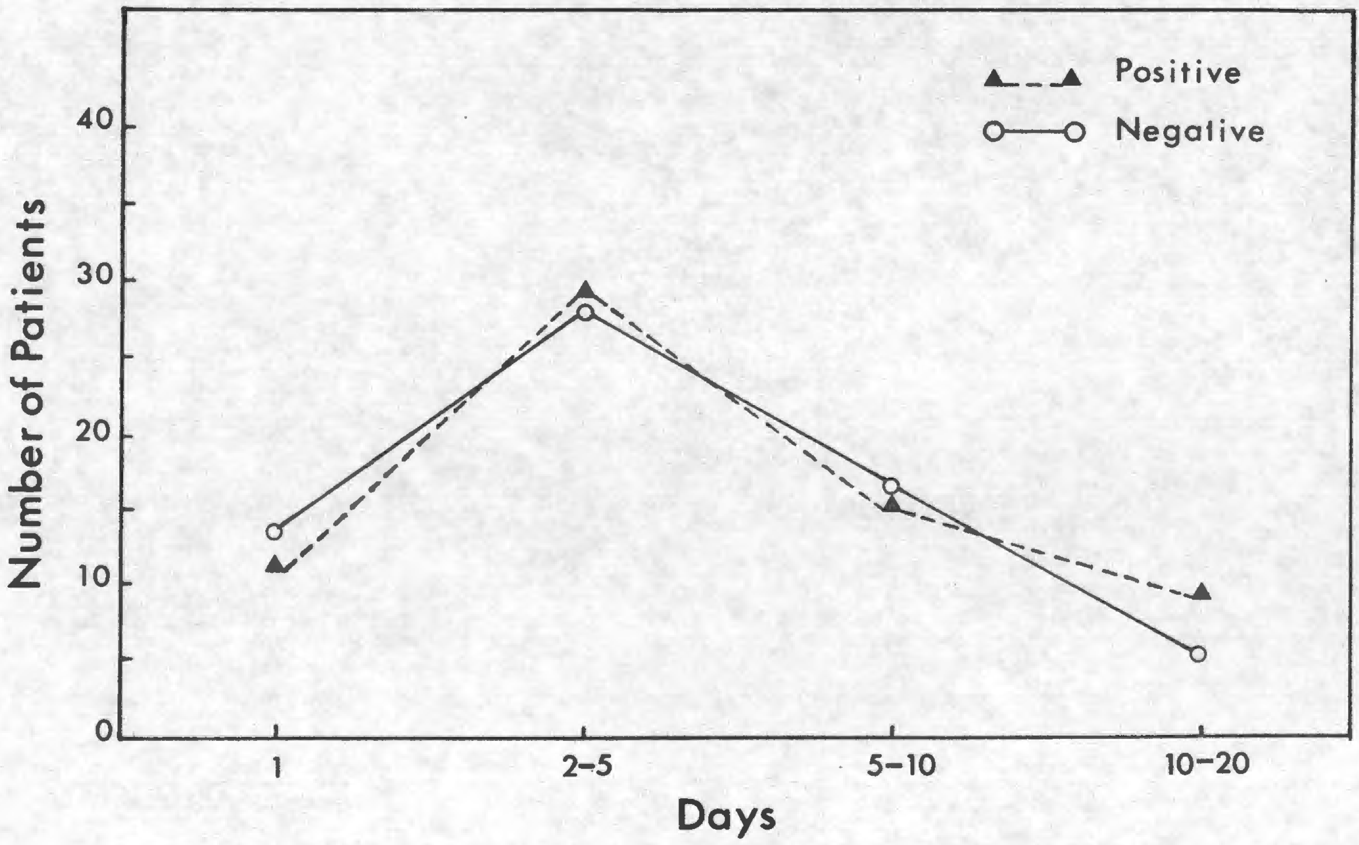
3. Pathology

Patients were grouped as shown in Table XI.
Irresectable carcinoma was associated with a higher risk as compared to resectable carcinoma, 65% and 33% respectively developed deep vein thrombosis.

4. Operative Blood Loss

In 13 patients, more than 3 pints of blood was given during operation and of these 7 were positive and 6 were negative. No conclusion can be drawn.

FIGURE 12 DAYS IN HOSPITAL PREOPERATIVELY AND POSTOPERATIVE DEEP VEIN THROMBOSIS



Positive
Negative
Number of Patients
0
10
20
30
40
1
2–5
5–10
10–20
Days

FIGURE 13. DURATION OF OPERATION AND INCIDENCE OF POSTOPERATIVE DEEP VEIN THROMBOSIS

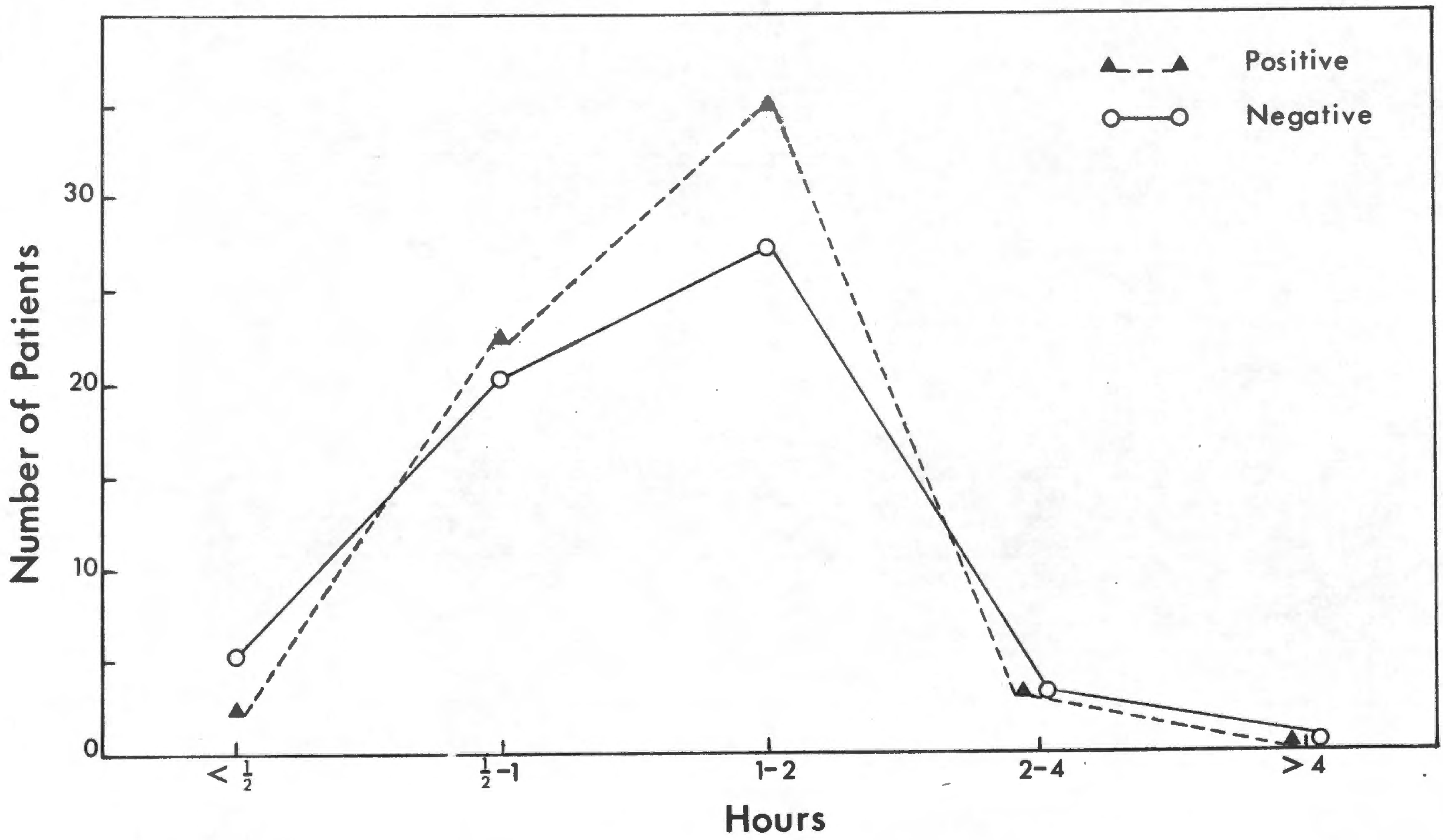

Positive
Negative
Number of Patients
30
20
10
0
< ½
½–1
1–2
2–4
> 4
Hours

TABLE X. SITE OF OPERATION

	Negative	Positive	Total
Head and Neck	4	3	7
Breast	1	1	2
Vascular	3	2	5
Exploratory Laparotomy	20	23	43
Oesophagus	0	0	0
Stomach and Duodenum	8	15	23
Small Bowel and Appendix	4	4	8
Large Bowel	3	3	6
Spleen	4	6	10
Gallbladder and Liver	8	10	18
Anus and Rectum	3	2	5
Hernia	8	9	17
Other	2	4	6

TABLE XI OPERATIVE PATHOLOGY

	Negative	Positive	Total
Congenital	0	1	1
Traumatic	11	15	26
Inflammatory	21	21	42
Carcinoma	20	21	41
Resectable	12	6 (33%)	18
Irresectable	8	15 (65%)	23
Miscellaneous	11	8	19

V. Postoperative

1. Complications

The range of postoperative complications is shown in Table XII. No correlation is noted with any specific complication.

2. Postoperative days in hospital

From Figure 14,
it is apparent that patients staying more than 21 days in hospital were at a much higher risk than patients staying less than 21 days. Of the 17 patients in hospital for more than 21 days, 14 developed deep vein thrombosis, (an incidence of 80%). In this group over 75% of the venous thromboses developed within the first 72 hours..
The patients either had severe gross pathology preoperatively or underwent major surgery necessitating prolonged postoperative care. These factors may have precipitated the early development of deep vein thrombosis.

3. Postoperative Deaths

From Figure 15 it would appear that patients dying after the 21st postoperative day were more likely to develop deep vein thrombosis than any other group. Three out of the 4 patients who died after the 21st day developed deep vein thrombosis which was detected early postoperatively. The aetiological factor for the increased incidence of deep vein thrombosis in these patients dying is probably the same as above viz. major pathology and surgery including postoperative morbidity.

TABLE XII POSTOPERATIVE COMPLICATIONS

	Negative	Positive	Total
Pulmonary	12	15	37
Urinary	7	6	13
Wound Infection	3	4	7
Wound Dehiscence	0	1	1
Miscellaneous	4	3	7

FIGURE 14. POSTOPERATIVE DAYS IN HOSPITAL TILL DISCHARGE AND INCIDENCE OF POSTOPERATIVE DEEP VEIN THROMBOSIS

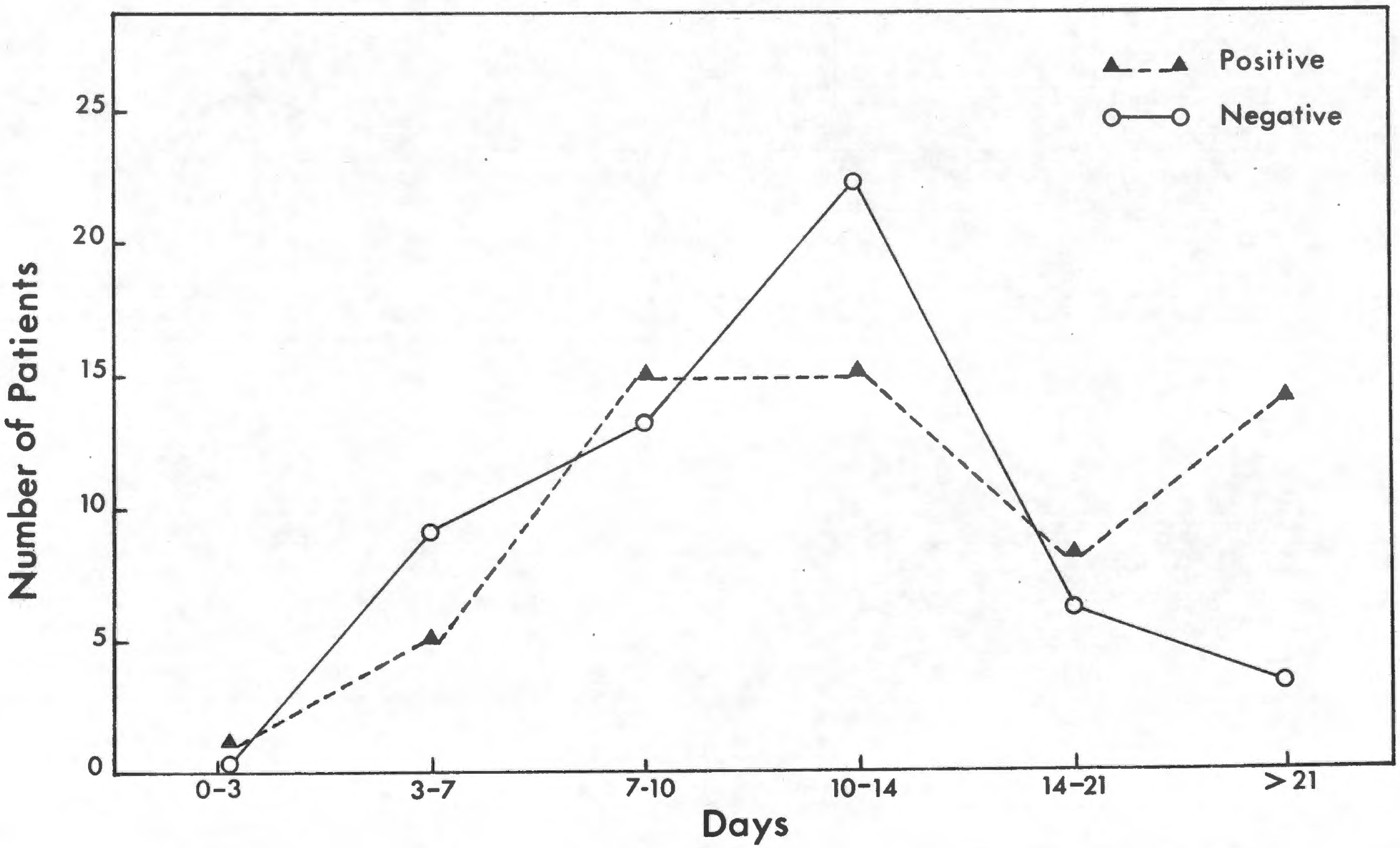
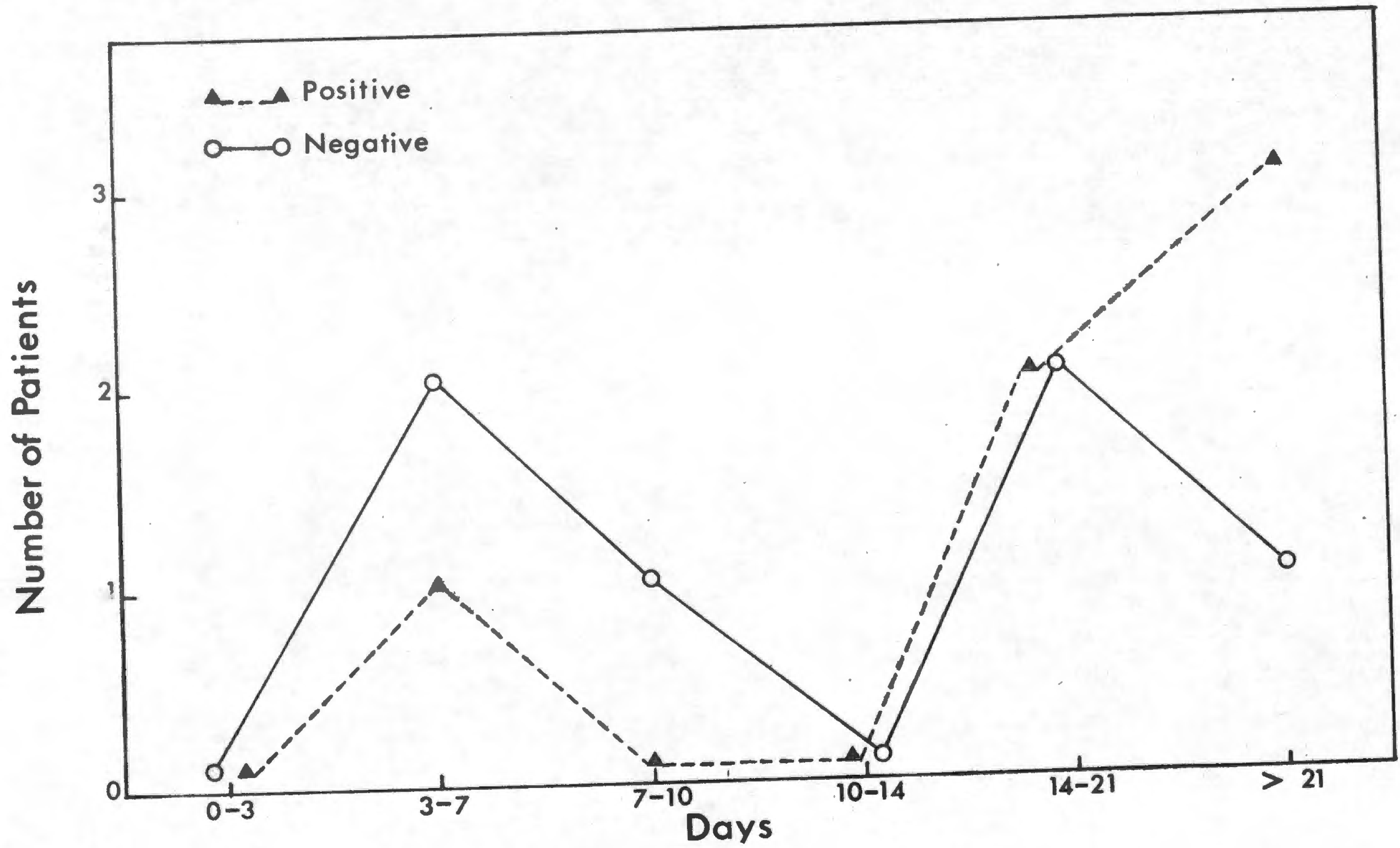

Positive
Negative
Number of Patients
25
20
15
10
5
0
0-3
3-7
7-10
10-14
14-21
>21
Days

FIGURE 15. POSTOPERATIVE DEATHS IN CONTROL GROUP



Positive
Negative
Number of Patients
0
1
2
3
0–3
3–7
7–10
10–14
14–21
> 21
Days

b. DISCUSSION

Recent studies have shown that there is a High Risk Group of patients liable to develop postoperative deep vein thrombosis (1, 4, 7, 23, 26, 168).

The factors which appear to be important are patients over the age of 40 years (23) or elderly (28), undergoing a major surgical operation (168), who have had a past history of deep vein thrombosis or pulmonary embolism (28, 168), have varicose veins (168) and found to have carcinoma at operation (28, 168, 170).

Browse (26) considers patients undergoing a splenectomy or with certain blood disorders as polycythaemia predispose to venous thrombosis. For purposes of this discussion, orthopaedic cases which comprise a high risk group, have been excluded (23, 152).
Preoperative and postoperative assessment of the high risk patients is important, for it is this very group who should be screened with radioactive fibrinogen and Doppler ultrasound and be treated by suitable PROPHYLACTIC means to prevent the deep vein thrombosis.

In an analysis of High Risk Factors, in this study, several facts have emerged. Patients in the a) age group of over 40 years, especially if b) severely obese were at high risk.
c) Those showing evidence of varicose veins and healed varicose ulcer seemed susceptible. d) Patients admitted for investigations preoperatively or transferred from the medical wards where they had been investigated for more than 10 days were at an increased risk. e) Any operation requiring a general anaesthetic lasting longer than one to two hours especially if the patient had f) an irresectable carcinoma,was also of importance.

c. CONCLUSION

A number of conditions in the patient, his history, the operation or the postoperative course may influence the development of deep vein thrombosis.

An awareness of these should lead to prophylaxis and earlier treatment.

B. THE DIAGNOSIS OF POSTOPERATIVE DEEP VEIN THROMBOSIS

1. ONSET OF POSTOPERATIVE DEEP VEIN THROMBOSIS

2. RADIOACTIVE FIBRINOGEN TECHNIQUE

3. DOPPLER ULTRASOUND TECHNIQUE

4. VENOGRAPHY

5. CLINICAL

6. CONCLUSION

1. ONSET OF POSTOPERATIVE DEEP VEIN THROMBOSIS

a. Introduction

b. Results

c. Discussion and Conclusion

a. Introduction

Recent studies by Kakkar (26) and Negus (8) suggest that deep vein thrombosis occurs much earlier than is suggested by standard texts.
In fact, that the thrombi start to form while the patient is on the operating table or within the next 48 to 72 hours.
The 130 cases under review were studied for the time of onset of the deep vein thrombosis.

b. Results

The incidence of postoperative deep vein thrombosis in the General Surgical Wards at Groote Schuur Hospital in 130 cases was 51%.

The diagnosis was made by a combination of clinical assessment, the radioactive fibrinogen technique, Doppler ultrasound technique and venography.

From Figure 16 it will be seen that 50% of the cases developed deep vein thrombosis within the first day postoperatively and a further 26% developed deep vein thrombosis between the second and third day postoperatively. Therefore, 76% of the postoperative deep vein thromboses occurred within the first 48 to 72 hours postoperatively. Only 6.5% developed deep vein thrombosis on the 7th - 10th day postoperatively and there were no cases recorded after the 10th postoperative day.

All cases were screened with radioactive fibrinogen, preoperatively and counting was continued daily postoperatively. In a large percentage of cases (75%) there were increased counts at points over the lower limb which were not as yet diagnostic of a deep vein thrombosis i.e. had not yet increased by 20%, but over the subsequent days the level of radioactivity increased at those sites to diagnostic levels as defined by Negus (8), Kakkar (26) and Browse (28).

In 40 cases who were screened within 1 to 2 hours postoperatively i.e. immediately on returning to the ward from theatre, it was found that 10% of these cases had evidence of deep vein thrombosis in the calf as detected by the radioactive fibrinogen technique.

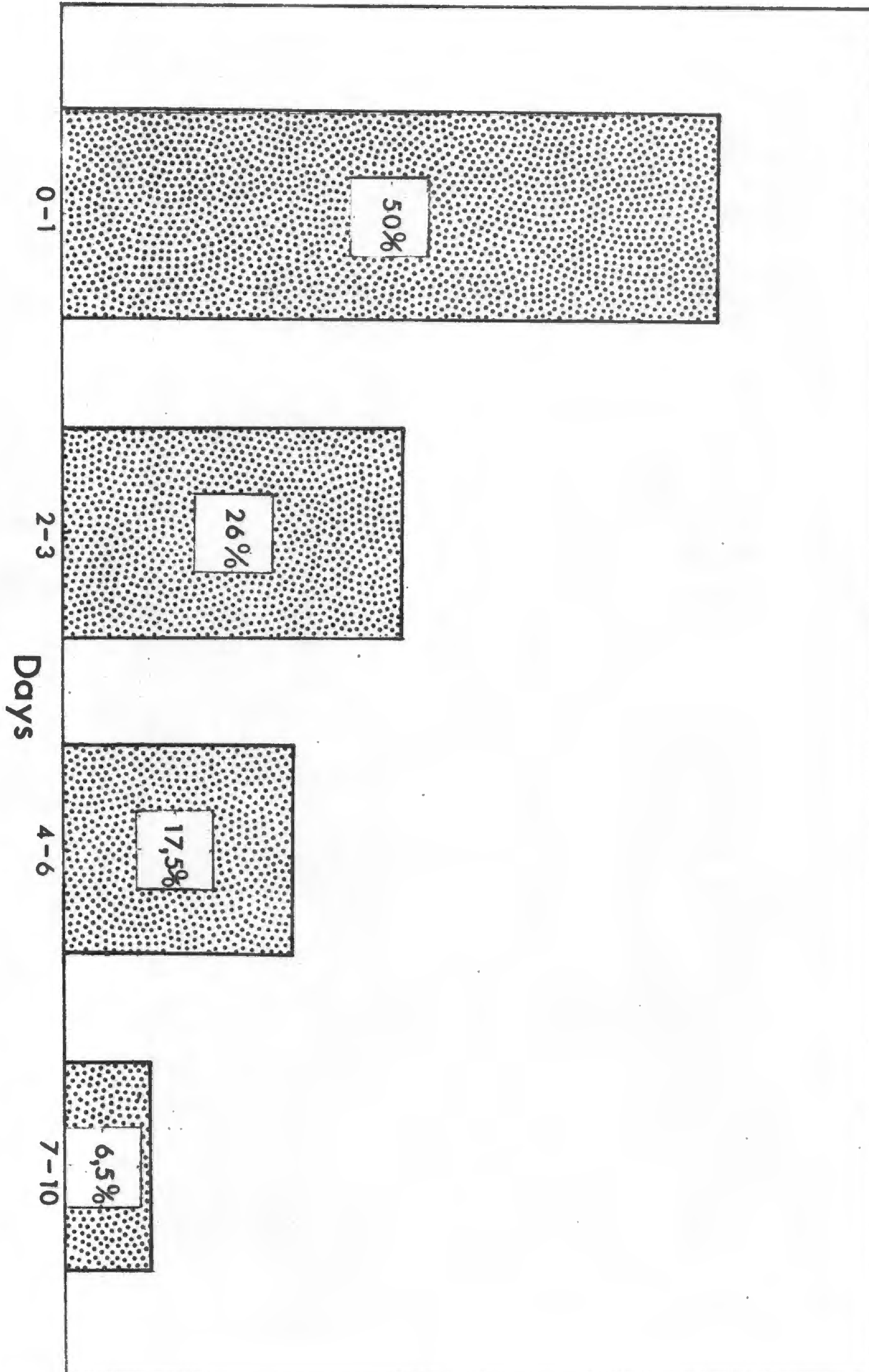
c. Discussion and Conclusion

The early onset of deep vein thrombosis is of the utmost importance in its prevention as measures must begin interoperatively and even preoperatively and must continue postoperatively.

Our results confirm that venous thrombosis begins on the operating table or within the first 48 to 72 hours postoperatively as was shown in 76% of the cases.

FIGURE 16. ONSET OF POSTOPERATIVE DEEP VEIN THROMBOSIS IN GENERAL SURGERY IN 130 CASES

Patients



2. RADIOACTIVE FIBRINOGEN TECHNIQUE

a. Introduction
b. Results
Incidence
Onset
Side
Site
Duration
c. Discussion
d. Conclusion

a. Introduction

I^{125} fibrinogen was used to screen patients for deep vein thrombosis, recognizing that its accuracy was probably limited to calf and lower thigh.

b. Results

Incidence

Sixty-Six of 130 control cases were positive giving an incidence of 51%.

Onset

The onset of the deep vein thrombosis occurred in 50% of the cases within the first postoperative day and in a further 26% of cases between the second and third postoperative day. (See Figure 16)

Side

Out of 66 patients, 42 developed bilateral deep vein thrombosis (64%) Deep vein thrombosis occurred twice as commonly on the right side as on the left side. (See Table XIII).

Site

The different sites were analysed at which the deep vein thrombosis occurred. The sites were subdivided into 1) calf, 2) popliteal, 3) thigh, 4) calf and popliteal, 5) calf, popliteal and thigh, 6) popliteal and thigh and 7) calf and thigh. (See Table XIV) Deep vein thrombosis in the calf alone, occurred in 43% of cases. In the popliteal vein or popliteal and calf veins, deep vein thrombosis occurred in 33% and in the thigh alone or in combination in 24%. Thus in the Ilio-Femoro-Popliteal veins the incidence of deep vein thrombosis was 57%.

Duration

Duration of radioactive fibrinogen counting (Fig. 17). It is noted that at 7 to 10 days, 44% of cases with positive readings were still registering counts as compared with 27% of the negative cases. From 10 days onwards both counts dropped precipitously.

TABLE XIII

SIDE OF DEEP VEIN THROMBOSIS IN 66 GENERAL SURGERY CASES DIAGNOSED BY I^{125} FIBRINOGEN TEST

Bilateral in 42 cases	-	64%
Unilateral in 24 cases	-	36%
Right 16		24%
Left 8		12%

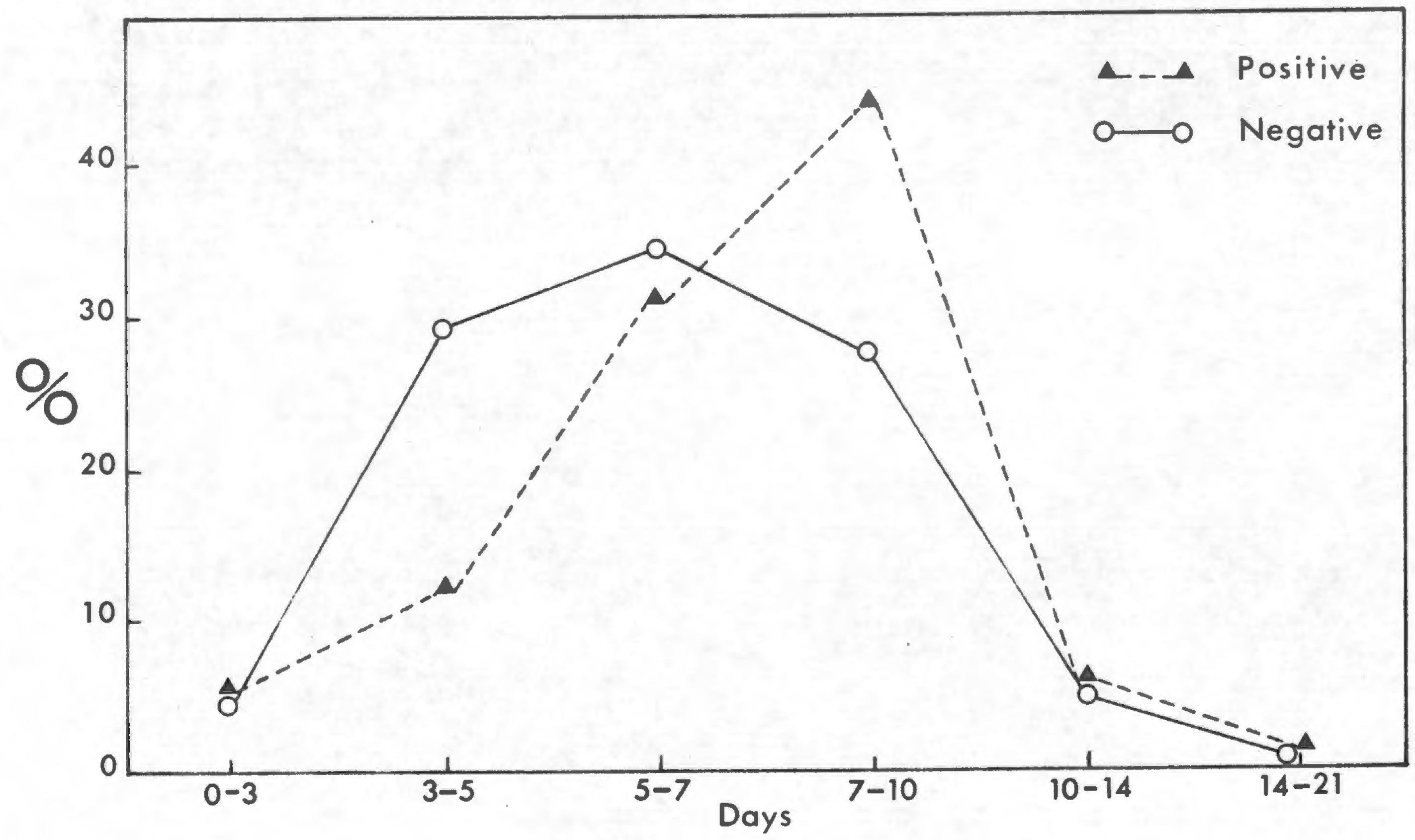
TABLE XIV

SITE OF DEEP VEIN THROMBOSIS IN 66 GENERAL CASES (AS A PERCENTAGE)

DIAGNOSED BY I^{125} FIBRINOGEN TEST

	% Right	% Left	% Total
1. Calf	46	40	43
2. Popliteal	14	8	11
3. Thigh	2	2	2
4. Calf and Popliteal	19	23	21
5. Calf and Popliteal and Thigh	12	17	14.5
6. Popliteal and Thigh	3.5	2	3%
7. Calf and Thigh	3.5	8	6%

FIGURE 17. DURATION OF RADIOACTIVE FIBRINOGEN COUNTING IN 130 GENERAL SURGERY CASES


Positive
Negative
%
40
30
20
10
0
0-3
3-5
5-7
7-10
10-14
14-21
Days

c. Discussion

Deep vein thrombosis may be considered to occur in

1. The peripheral or calf or lower segment, and

2. The thigh or ilio-femoral or upper segment including popliteal veins.

1. Calf deep vein thrombosis accounts for the majority (80 to 90%) as reported by Negus (8) and Kakkar (26). One third occur on the left side, one third occur on the right side, and one third bilaterally (26).

In this series, only 43% of the postoperative deep vein thrombosis occurred in the calf alone. Sixty-four percent were bilateral and the right side was twice as commonly involved as the left. As shown by the duration of the radioactive fibrinogen counting in the fig. 17 the thrombi persisted in the veins for up to three weeks and did not undergo spontaneous thrombolysis within several days as has been reported (171). The fall- off of radioactive fibrinogen counting must be seen as predominantly due to the short half-like of the radioactive I^{125} and the degradation of the fibrinogen by the body. This therefore does not necessarily mean that the clot underwent spontaneous thrombolysis. In fact, the thrombus could have remained in situ for weeks to months during which period it could have extended and embolised.

The natural history of the deep vein thrombosis is in the majority of cases to undergo spontaneous thrombolysis. Small percentage will undergo recanalisation with resulting incompetent perforator veins and the long term morbidity of venous hypertension (174). Approximately 10% to 25% (172, 173) extend into the popliteal and ilio-femoral veins. In this group of extension, 50% to 70% will have pulmonary emboli which are usually small and not very serious, but may be multiple and large resulting in considerable morbidity and mortality. (172, 173, 175).

2. Ilio-Femoral Venous Thrombosis

occurs in the minority of cases. Kakkar (26) reported an incidence of 10.5% diagnosed by radioactive fibrinogen technique. The thrombosis may be localised to the iliac, femoral or popliteal vein or can be extensive, it may be occlusive or non-occlusive, unilateral or bilateral, consecutive or non-consecutive and multifocal (50, 173).

It has been stated that the left common iliac vein is more commonly involved than the right side in proportion of 3 : 1, but if pulmonary emboli are present, the right side is more often involved than the left side (173). Mavor in his series of 260 cases found that pulmonary emboli occurred in 50% of the patients and that pulmonary emboli were the presenting symptom in 50% of these cases (173). Ilio-femoral venous thrombosis carries a mortality of 30% due to pulmonary emboli (176, 177) and a concomitant severe morbidity due both to the local thrombosis and due to recurrent pulmonary embolism. The morbidity must be assessed in the acute phase and in the chronic long term results (173). From the results presented it is important to note that the popliteal vein was involved either alone or in combination in 33% of

cases and the femoral vein was involved alone or in combination in 24% of cases making a total of 57% involvement of the femoro-popliteal venous system. This is a much higher figure than has been recorded previously (26).
It must also be observed from the results that the veins can be involved in a multi-focal distribution e.g. the calf on one side, and the thigh on the opposite side, or calf and thigh on one side and popliteal on opposite side ie. various combinations of venous involvement (Table XIV)

d. Conclusion

A much higher incidence of involvement of the femoro-popliteal venous system has been found on screening with radioactive fibrinogen than has been previously recorded. Two fifths of the deep vein thromboses occurred in the calf whereas three fifths occurred in the femoro-popliteal region.
The popliteal vein belongs to the high or ilio-femoral deep vein thrombosis group in regard to morbidity and mortality.
The clots can be local or extensive, consecutive or non-consecutive, bilateral in two thirds of the patients and unilateral in one third with the right side being more commonly involved than the left side and the clots can occur in a multi-focal distribution. The radioactive fibrinogen technique is however not reliable in the upper one third of the thigh due to the increased blood flow in this area and therefore a combination of ultrasound, radioactive fibrinogen and venography has been used for the diagnosis of venous thrombosis in this area.

3. DOPPLER ULTRASOUND TECHNIQUE

a. Introduction

b. Results

c. Discussion and Conclusion

a. Introduction

Doppler ultrasound was used for the diagnosis of popliteal and ilio-femoral venous thrombosis. The investigation was carried out preoperatively and performed daily postoperatively and "all or none" principle was used in that either a sound was present which indicated a patent vein or a sound was absent on either calf or thigh compression which indicated venous obstruction.
The probe was placed over the femoral vein and compression was applied firstly to the calf and then to the thigh. The probe was then moved to the popliteal fossa and calf compression was applied. With the probe over the femoral veins, the patient was requested to perform a Valsalva manoeuvre and an augmentation sound was listened for indicating patency of the iliac veins and inferior vena cava.

b. Results

Seventy-five patients were screened using Doppler ultrasound and radioactive fibrinogen. Thirty-nine cases were positive by Doppler ultrasound testing giving postoperative incidence of deep vein thrombosis of 52%. There were no cases of false positive results. However, 6 of 39 cases gave false negative results. All these cases had thrombosis of the calf with

no extension into the popliteal vein. In 39 positive cases, 24 were bilateral (62%) and 20% occurred on the right side with 18% on the left.

c. Discussion and Conclusion

Doppler ultrasound has a place in the screening of postoperative deep vein thrombosis for the detection of thrombi in the popliteal and ilio-femoral veins. It is unreliable for the detection of small thrombi in calf muscles (34, 37).
In the partially occluded vein where there is still blood flow through the lumen, it is theoretically unreliable (36).
However, in this series there were no false negative results, in this regard. In long standing cases of venous thrombosis with the development of adequate collateral circulation Doppler ultrasound is only reliable in 80% of cases (36).
It is thus of limited value in the isolated single screening of a patient thought to have a silent "pulmonary embolus".
In the patient who present with a swollen leg or other evidence of deep vein thrombosis, if the Doppler ultrasound is positive indicating obstruction of the major veins, it is extremely reliable (35). However, if negative, indicating flow beneath the probe, this could mean a partial occlusion of the veins or a long standing occlusion with development of adequate collateral venous circulation. In order to make a definitive diagnosis venography is indicated.

Doppler ultrasound has a useful place in the screening of patients to detect development of deep vein thrombosis provided that a baseline is obtained preoperatively and that the patient is screened daily postoperatively in search of an alteration in venous blood flow. As an isolated investigation, if positive,

it may be diagnostic but if negative it does not exclude deep vein thrombosis.

The disadvantages of the procedure relate especially to the high false negative results, if the calf veins alone are involved and the inability to detect thrombi in the pelvic veins. There may be difficulty in interpreting results of Valsalva manoeuvre for patency of the inferior vena cava and iliac veins because patients may be unable to sit up and perform the Valsalva manoeuvre adequately immediately after abdominal operation.

Overall, the ultrasound procedure is very suitable for mass application screening and surveillance provided its limitations are borne in mind (31), and for routine use in a General Hospital (38). The advantages of the procedure include safety, simplicity and economy acceptable to both physician and patient. Examination can be performed on a traumatised extremity, takes only a few minutes and there is no delay between examination and results.

4. VENOGRAPHY

a. Introduction
b. Results
c. Discussion
d. Conclusion

a. Introduction

Venography was not performed routinely, but was employed to confirm the screening methods and then later used only in selected patients for specific reasons. The evaluation of a screening surveillance procedure is best expressed

in terms of sensitivity and specificity compared to more definite definitive final outcome (36).

Sensitivity is defined as the number of positive extremities obtained divided by the actual number of extremities proved to have venous occlusion by venography or anatomical confirmation. Specificity is defined as the number of negative extremities observed, divided by the number of extremities proven to be non-occluded. Both sensitivity and specificity are expressed as percentages (36, 178).

b) Results.

A total of 32 patients in the control group underwent peripheral venography of the lower limb. The technique used was a percutaneous injection of contrast medium into the veins of the feet using the standard method described by Lea Thomas (50-54). A total of 60 lower extremities were examined. The sensitivity which is defined as above was 106% by venography. See Table XV .

TABLE XV SENSITIVITY OF RADIOACTIVE FIBRINOGEN IN DETECTING DEEP VEIN OCCLUSION

Number of extremities found occluded by venography	48
Number of extremities identified by radioactive fibrinogen	51
Sensitivity	106%

The specificity defined as above was 92%. See Table XVI.

TABLE XVI. SPECIFICITY OF RADIOACTIVE FIBRINOGEN IN DETECTING DEEP VEIN THROMBOSIS

Number of extremities found non-occluded by venography	12
Number of extremities identified as non-occluded by radioactive-fibrinogen	11
	- 92%

c. Discussion

When the investigation into the incidence of postoperative deep vein thrombosis was begun, radioactive fibrinogen and Doppler ultrasound were used for screening. If a deep vein thrombosis was shown, venography was performed to confirm the diagnosis. However, after 32 patients had been examined by venography and the correlation of venography versus the screening procedures was found to be accurate, it was felt not justifiable to submit every positive patient with a deep vein thrombosis to venography. Thereafter venography was performed in patients who had failed to respond to anticoagulant therapy or in those in whom surgery was contemplated or if there was any other specific indication, e.g. unable to carry out screening procedures. Venography was thus not used merely to confirm the diagnosis, but was carried out only in selected patients. In three patients deep vein thrombosis was demonstrated by radioactive fibrinogen but not by venography, probably due to the presence of small thrombi in the calf muscle venous plexus which could not be adequately demonstrated by venography. Thus radioactive fibrinogen is probably a more sensitive method of demonstrating small thrombi in the soleal plexus of veins than venography.

Interpretation

Interpretation of venograms depends on identification of a thrombus as a cylindrical or round translucency in an opacified vein. A completely occluded vein may be totally blocked or bypassed by collaterals. Common causes for artefacts were underfilling, dilution or streamlining of the dye. (50)

Advantages

Venography can demonstrate the veins from the ankle to the inferior vena cava. It gives an indication of the size and extent of the thrombus, and the fixity or loose adherence to the vein wall. In one case a loose thrombus was blocked in by a more proximal adherent thrombus and was therefore unable to embolise. The main limitation of venography is that some clinical indication for its use is necessary and only too often thrombosis occurs without physical signs. Thus it had value in the diagnosis of a suspected case, but was of no use as a screening or a research tool. The procedure took an average of 30 minutes to perform bilateral lower limb venography. In no cases was it found necessary to perform a percutaneous transfemoral venogram nor a pertrochanteric injection. With improved expertise the iliac veins were demonstrated in most cases and with adequate patient co-operation in seven cases the inferior vena cava was demonstrated.

Complications

It has been reported by Lea Thomas (50-54) that peripheral venography can be carried out without significant complication, but several possibilities exist and some were encountered in this series.

1. Thrombosis due to the contrast medium

After the use of the contrast medium Conray 280 (Meglumine Iothalamate 60%) followed at the end of the procedure by the veins being thoroughly cleared with normal saline. There were no thromboses in this series as a result of contrast used.

2. Local sepsis

This may occur at the site of puncture and therefore careful aseptic precautions are necessary. It is especially important to avoid sepsis in those patients with impaired vascular supply to the lower limb. This complication occurred in four of the 60 lower limbs examined in this series (an incidence of 15%). Streptococci were grown in two cases and the other two cases were thought to be local allergic response to the extravasation of dye into the subcutaneous tissues. One occurred in a patient with severe peripheral vascular disease and the resultant necrotic ulcer took three months to heal. It was thus felt that venography should not be performed in any patients showing severe peripheral vascular disease unless there was an absolute indication. Under these conditions a transfemoral percutaneous venogram should preferably be performed. Intraosseous pertrochanteric venography carries a risk of osteomyelitis, and no such procedure was undertaken in this series.

3. Precipitation of pulmonary embolism

The use of Valsalva maneouvre and the use of calf pressure has been criticised as likely to precipitate pulmonary embolism. This complication has not been reported (50) and no obvious cases of pulmonary embolism developed in this series.

4. Pain

Lea Thomas (50) states that the contrast medium (Meglumine Iothalamate) injection is painless when administered and produces little discomfort to the patient apart from a bursting sensation in an obstructed venous system.

However, on special interrogation over 50% of our patients complained of an unpleasant burning sensation associated with pain on injection of the contrast medium. Premedication such as Omnopon and Valium was thus routinely prescribed before the procedure.

5. Drug allergy and hypersensitivity.

The relatively large quantity of contrast medium which may be necessary (up to 400 ml) to show the veins of both legs and pelvis has not resulted in any complications and appears to be entirely safe. This is confirmed by others (50).

6. Gangrene

Lea Thomas (52) reports two out of 400 patients who developed gangrene of the foot following peripheral venography. In these patients there was evidence of malformation or thrombosis of the deep venous system which prevented the contrast medium from escaping readily from the site of injection. This suggests that if deep venous filling does not occur, examination should be abandoned and may be later repeated by an intraosseous injection of contrast medium into the medial malleolus.

d. Conclusion

Thirty-two patients have undergone venography and a total of 60 lower limbs have been examined. The advantages are the demonstration of veins from the ankle to inferior vena cava and confirmation of the diagnosis of venous thrombosis in all cases in which it was carried out. Investigation is not however reliable for demonstrating small thrombi in the calf muscle veins.

It seems that the investigation does have complications and therefore must not be carried out as a routine in all patients suspected of or found to have deep vein thrombosis on screening with radioactive fibrinogen and Doppler ulatrasound. Venography should be reserved for those patients in whom thrombolytic therapy or surgical treatment such as thrombectomy and venous ligation are being contemplated.

5. CLINICAL ASSESSMENT IN THE DIAGNOSIS OF POSTOPERATIVE DEEP VEIN THROMBOSIS

a. Introduction
b. Results and Discussion
c. Conclusion

a. Introduction

Until the development of the aforementioned techniques, clinical assessment was the only method of diagnosis of postoperative deep vein thrombosis.

With the advent of the new techniques the inaccuracy of clinical signs has become evident.

b. Results and Discussion

1. Signs
2. Symptoms

1. Signs

The classical signs of deep vein thrombosis were looked for in all cases. In only 6 cases was deep vein thrombosis clinically detected.

Signs found :-

1. Swelling of calf in 5. Severe in 2 and minimal in 3.
2. Oedema of calf in 4.
3. Tenderness over popliteal and femoral vein in one.
4. Homan's sign in 0.

Five out of the six clinically detected deep vein thromboses were found to have positive radioactive fibrinogen and Doppler ultrasound findings. One patient who had a clinical deep vein thrombosis on the right side, which was not confirmed on fibrinogen, had an asymptomatic venous thrombosis on the left side. The overall incidence of clinically detected and confirmed deep vein thrombosis was 7.5%.

2. Symptoms

Thirty-eight patients were questioned about the development of pain in the calf. This was carried out retrospectively once the deep vein thrombosis had been diagnosed by the screening methods. Ten out of the 38 cases mentioned that they had experienced pain in the calf postoperatively but in the majority it was not severe enough to report to the medical attendant. Furthermore the pain had developed in the calf after the first 5 days postoperatively.

Discussion:

"Silent" pulmonary emboli repeatedly showed the inadequacy of physical signs and symptoms in the diagnosis of lower limb deep vein thrombosis. Not only is deep vein thrombosis often overlooked, but it is also frequently diagnosed where none is present (10). Lambie (7) studied a group of 111 surgical patients at high risk and found that two thirds of those developing deep vein thrombosis were never suspected clinically, despite careful assessment.

In those in whom a clinical diagnosis of thigh and leg venous thrombosis was made, this diagnosis was falsely positive in one quarter. It thus appears that close and repeated clinical evaluation is highly unreliable and little importance should be set by it. It is better to be conscious of the large number of patients who have thigh and leg venous thrombosis despite the apparent normality of their legs.

Lambie et al (7) results showed that

> Calf tenderness was present in 6/61 legs with thrombosis and 5/161 legs without thrombosis.
> Homan's sign was positive in 14/61 legs with thrombosis and 2/161 legs without thrombosis.
> Ankle oedema was present in 18/61 limbs with thrombosis and in 3/161 limbs without thrombosis.
> Fever was noted in 14/49 patients with thrombosis and 30/62 patients without thrombosis.

From the results at Groote Schuur Hospital only 7.5% patients with deep vein thrombosis had classical signs of deep vein thrombosis and in one patient there was a false positive result. However, the symptom of pain in the calf was present in 26% of the patients found to have venous thrombosis.

It was then decided to investigate the sign of tenderness over the popliteal and femoral vein in patients clinically suspected of having deep vein thrombosis as seen in consultation with other wards.

Results showed that in 9 patients with ilio-femoral-popliteal venous thrombosis confirmed by Doppler ultrasound and venography, all had tenderness in one or more sites over the femoral and popliteal veins, which could be detected by careful digital palpation.

c. Conclusion

Classical clinical signs of deep vein thrombosis were present in less than 10% of patients found to have venous thrombosis. However, local tenderness over the popliteal or femoral vein if present, appears to be an extremely reliable physical sign of an underlying venous thrombosis. The symptom of pain in the calf must be carefully sought daily and should it be present, an underlying venous thrombosis must be suspected despite the absence of signs. The symptom of pain therefore warrants further investigation rather than the signs of venous thrombosis.

6. CONCLUSION ON ASSESSMENT OF TECHNIQUES FOR THE DIAGNOSIS OF POSTOPERATIVE DEEP VEIN THROMBOSIS

Conclusion

1. Clinical detection

   a. Signs - 7.5%

   b. Symptoms - 26%

2. Radioactive fibrinogen - 66/66 = 100%

3. Ultrasound - 33/39 = 85%

4. Venography - 48/51 = 94%

It has been shown that a combination of daily postoperative screening of patients with radioactive fibrinogen and Doppler ultrasound gave a highly reliable method of the detection of postoperative deep vein thrombosis. Venography was reserved for selected cases only. The clinical detection of deep vein thrombosis by physical signs was extremely unreliable but the symptoms of pain was found to warrant further investigation in unscreened patients.

INCIDENCE in NEUROSURGERY
OPHTHALMOLOGY AND OTORHINOLARYNGOLOGY
POST RENAL TRANSPLANTATION

Introduction

A survey was conducted into the incidence of deep vein thrombosis in patients undergoing different forms of operation.

Neurosurgery because of no previous reports in the literature, procedures with minimal operative tissue trauma as in ophthalmology and otorhinolaryngology and post renal transplantation as a result of late thromboembolic disease which was fatal in two patients at Groote Schuur Hospital.

INCIDENCE

2. NEUROSURGICAL CASES

a. Results

b. Discussion

c. Conclusion.

a. Results

Twenty three patients were screened for postoperative deep vein thrombosis using radioactive fibrinogen and Doppler ultrasound. See Table XVII.

Assessment of

i. Age distribution

The patients undergoing spinal operations who were positive, were predominantly in the lower age group.

ii. Sex Distribution

This was evenly distributed in the craniotomy but there was a male preponderance in patients positive after spinal operations.

iii. Obesity

Two of the 6 positive spinal cases were severely obese and the one patient had bilateral varicose veins with a past history of deep vein thrombosis.

iv. Days in hospital preoperatively

There appeared to be no difference in the two groups, but there were too few patients for an adequate comparison.

TABLE XVII. INCIDENCE OF POSTOPERATIVE DEEP VEIN THROMBOSIS IN NEUROSURGERY

Total	23 patients - 10 positive	= 43%
Spinal	10 patients - 6 positive	= 60%
Cranial	13 patients - 4 positive	= 39%

v. Race

Eleven of the patients were European and 12 Non-European. Sixty-six percent of the Europeans developed deep vein thrombosis whereas only 25% of the Non-Europeans developed postoperative deep vein thrombosis which is significant ($0.05 < P < 0.1$). The ratio of European to Non-European developing postoperative deep vein thrombosis in those undergoing craniotomy was 3 : 1 and those undergoing spinal operation 2 : 1 respectively.

vi. Type of Operation (See Table XVII and Figure 18)

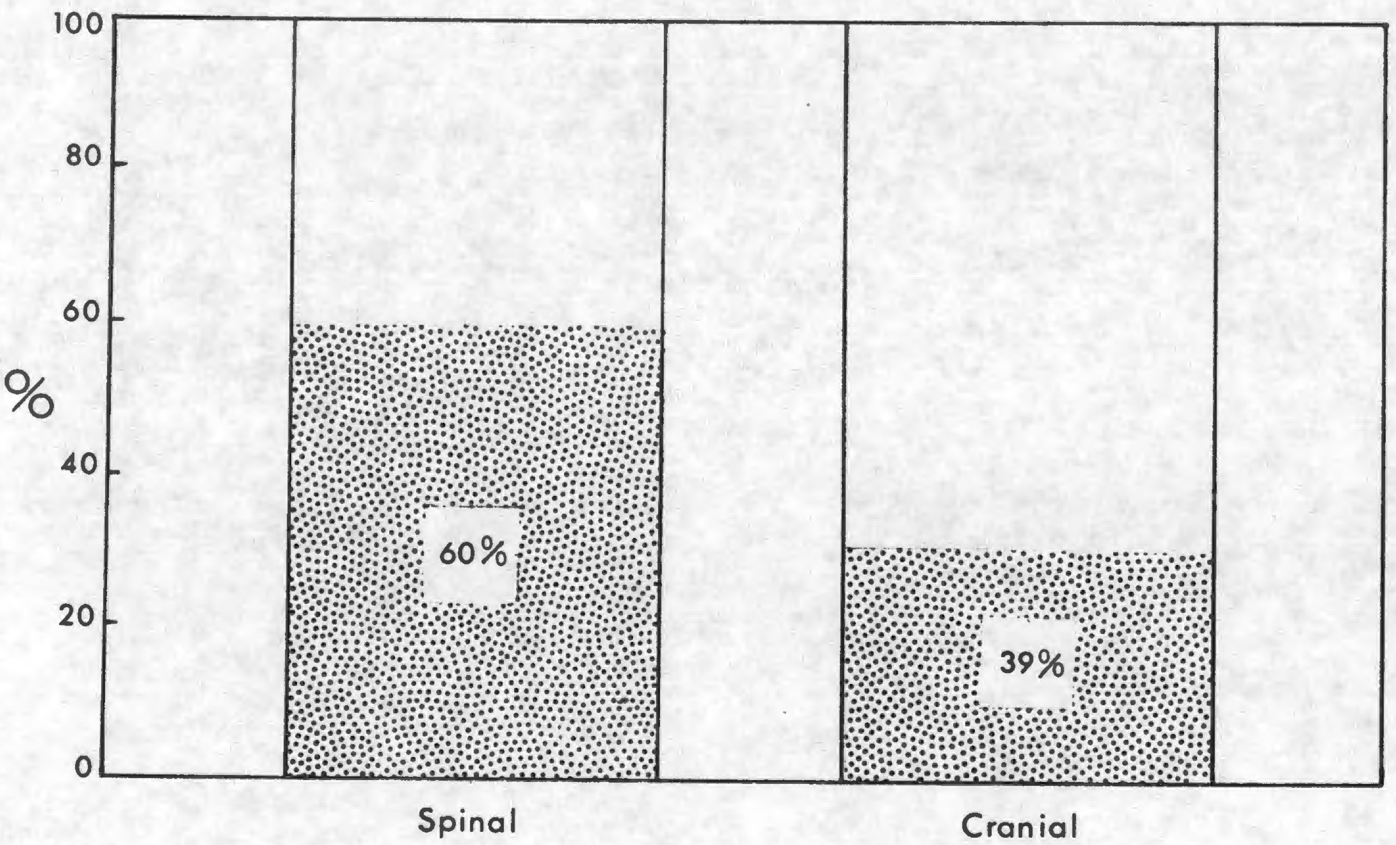
The operations were subdivided into spinal in which 60% were positive and craniotomy in which 39% were positive ($0.1 < P < 0.2$)

b. Discussion

The literature contains little information about the postoperative incidence of deep vein thrombosis in neurosurgical patients. The overall incidence is presumed to be low because of the early movement and mobilisation of these patients. However, in acute paraplegia following spinal injury a major cause of death is pulmonary embolism. Walsh and Tribe (179) in 1965 found that of 500 cases of traumatic spinal injury admitted at the Stoke Mandeville Hospital, 15 died of pulmonary emboli. Chesire (180) in a group of 315 admissions had two deaths from pulmonary emboli. Watson (181), in 1968 found that amongst 413 similar admissions over a 10 year period, there were 7 deaths from pulmonary emboli and a further 15 patients were diagnosed clinically as having this condition although they recovered.

Silver and Moulton found 6 pulmonary emboli in 42 patients with acute traumatic paraplegia with 2 being fatal. Clinical deep vein thrombosis was present in 6, half of which developed pulmonary emboli (182).

FIGURE 18 POSTOPERATIVE INCIDENCE OF DEEP VEIN THROMBOSIS IN NEUROSURGERY


100
80
60
40
20
0
%
60%
39%
Spinal
Cranial

Warlow (183) studied 30 patients with recent cerebro-vascular accident resulting in a stroke, for evidence of deep vein thrombosis using radioactive labelled fibrinogen technique. Sixty percent developed deep vein thrombosis in their paralysed leg and 7% in addition had a thrombus in the non paralysed leg. Four of their patients developed pulmonary embolism and two died of this complication at a stage when improvement in the disability of the stroke itself could not have been expected. The clinical signs of deep vein thrombosis could be detected in 60% of their cases with a positive fibrinogen count.

In the results presented only one patient had obvious clinical evidence of a deep vein thrombosis. The one patient who had a laminotomy did not develop a deep vein thrombosis. It would appear therefore that patients undergoing spinal operation such as laminectomy which necessitates prolonged bed rest despite being turned at two hourly intervals are more likely to develop postoperative deep vein thrombosis.

c. Conclusion

It has been demonstrated that postoperative deep vein thrombosis in the neurosurgical wards is a real problem and has an overall incidence of 43%. Those patients undergoing spinal operations were nearly twice as likely to develop this complication as those patients undergoing craniotomy. There was one postoperative death, but no postmortem was performed.

Deep vein thrombosis and pulmonary emboli have been found to result in considerable morbidity and mortality in the traumatic paraplegic patient and in those patients following cerebro-vascular accident. Thus it must be presumed that such a situation exists in the postoperative neurosurgical patients.

3. INCIDENCE OF POSTOPERATIVE DEEP VEIN THROMBOSIS IN OPHTHALMOLOGY AND OTORHINOLARYNGOLOGY PATIENTS

a. Results

b. Discussion

c. Conclusion

a) Results

Twenty two cases from the ophthalmology unit undergoing lens extraction under general anaesthetic for cataracts were screened using the radioactive fibrinogen and Doppler ultrasound.
Only one out of 22 patients developed postoperative deep vein thrombosis in both calves on the 8th postoperative day. i.e. an incidence of 4.5%. This patient fell into the high risk group in that she was 76 years old and very obese. Clinically there was no evidence of a deep vein thrombosis.

Nine patients from the otolaryngology wards were screened for postoperative deep vein thrombosis. They all underwent an operative procedure under general anaesthetic lasting more than 30 minutes. Only one of the patients was positive and she developed bilateral calf deep vein thrombosis on the first postoperative day. She was a very obese Non-European female, aged 53 years who underwent a Caldwell-Luc operation for a pathological diagnosis of a plasmacytoma of the upper alveolus. Clinically, there was no evidence of a deep vein thrombosis.

b. Discussion

Because of the high incidence of deep vein thrombosis in the general surgery wards, it was felt necessary to investigate the

incidence occurring in those patients undergoing relatively minor operative trauma e.g. lens extraction, but requiring a general anaesthetic, a procedure lasting $\frac{1}{2}$ to 1 hour and postoperative inpatient hospital stay of more than 3 days.
Those patients undergoing ophthalmological and otolaryngological procedures appeared to be the ideal patients to study.
Our results of 4.5% and 11% respectively with an overall incidence of 6% in these 31 patients studied illustrated that postoperative deep vein thrombosis and its sequelae were not of considerable importance in these circumstances. It would however appear that the very obese patients were the most likely to be at risk and therefore a lens extraction might be performed under local anaesthetic in the high risk patient.

Patients in both units were actively mobilised early postoperatively and underwent minimal operative tissue damage. These two factors alone might be important in the aetiology of deep vein thrombosis.

c. Conclusion

A very low incidence of postoperative deep vein thrombosis was found in the ophthalmology and otolaryngology wards.

4. INCIDENCE OF POSTOPERATIVE DEEP VEIN THROMBOSIS AFTER RENAL TRANSPLANTATION

a. Results

b. Discussion

c. Conclusion

a. Results

Seven patients who underwent renal transplantation were screened with radioactive fibrinogen and Doppler ultrasound. Four of these developed postoperative deep vein thrombosis (57%). One patient showed obvious clinical evidence of deep vein thrombosis and a second patient had equivocal clinical signs. Five patients were European, 2 were Non-European, 4 were Male and 3 Female, and only one patient was severely obese. All patients were admitted within 24 hours preoperatively and duration of the operation was from 2 to 4 hours. Venography was performed in only one patient and this showed patency of the major deep venous system bilaterally. One patient developed clinical and radiological lung changes compatible with a pulmonary embolus and was treated with anticoagulants.

The onset of the postoperative deep vein thrombosis was on the 9, 11, 12 and 14th postoperative days. The duration of counting in two cases was two weeks and for 5 cases continued beyond the 21st day following a single injection of 100 microcuries I^{125} radioactive fibrinogen.

Of the 4 patients who developed postoperative deep vein thrombosis, two had their transplanted kidneys on the right side and two on the left side. However, in two cases the deep vein thrombosis developed bilaterally with extension into popliteal and femoral veins. One unilateral positive was on the same side as the transplanted kidney.

Two further patients underwent nephrectomy, one bilateral in a girl of 14, who did not develop a deep vein thrombosis and the other for graft rejection who developed a calf venous thrombosis.

b. Discussion

Postoperative deep vein thrombosis occurred in patients undergoing renal transplantation but appeared to be unrelated to the side upon which the transplanted kidney was inserted. The venous thrombosis developed only in the second to third postoperative week. In an analysis of reasons for the late development, the most obvious cause was that following renal transplantation the patients usually had renal dialysis every second day. The machine was primed with heparin as the anticoagulant. This probably acted as an effective prophylactic measure in the early postoperative period. Once the patient began passing urine spontaneously and haemodialysis was discontinued the deep vein thrombosis developed late.

A further interesting finding was the period of time that the radioactive labelled fibrinogen stayed in circulation and could be measured. There is no known explanation for this at present. In regard to the negative venogram in the one patient, it must be presumed that the venous thrombosis occurred either in the superficial veins or the small venous plexuses in the muscles of both the calf and the thigh which were not demonstrated by venography.

Starzl (184) in 1964 reported that 9 out of 42 patients following renal transplantation developed thrombophlebitis and five probably had pulmonary emboli. The conditions which predisposed to this high incidence of deep vein thrombosis, and also the lengthy manipulations of veins within the pelvis, could also be expected to predispose to thrombosis of the transplanted renal vein, yet there are few references to renal vein thrombosis as a complication of transplantation.

Clarke (185) reports one case in which the renal vein graft was occluded by thrombus ascending from the venous thrombosis of the leg.

A retrospective analysis was made at Groote Schuur Hospital over a five year period (1967 to 1972) in which 47 renal transplants were performed in 43 patients. Of the 15 patients who died, there were at least two deaths due to pulmonary emboli. However it was not noted what percentage had deep vein thrombosis.

c. Conclusion

Deep vein thrombosis and its sequelae following renal transplantation carries severe morbidity and possible mortality in an already ill patient. Such patients usually have a combination of severe postoperative complications following transplantation. They often require multiple operations and they can ill afford to have the added problems of thrombo-embolic disease.

2. PREVENTION

1. HEPARIN

a. Introduction

b. Results

c. Discussion

d. Conclusion

2. SODIUM PENTOSAN POLYSULPHATE - "TAVAN-SP 54."

a. Results

b. Discussion

c. Conclusion

PREVENTION

INTRODUCTION

Due to the high incidence of deep vein thrombosis reported in Section B of this study under Incidence, methods of Prevention were investigated.

1. HEPARIN

a. INTRODUCTION

Prevention of the postoperative deep vein thrombosis was thought to play as important a role as the diagnosis by special means. The final outcome of treatment, cannot always be predicted. Fifty four patients undergoing a major elective surgical procedure were given prophylactic low dose subcutaneous heparin in an attempt to prevent or decrease the incidence postoperative venous thrombosis.

The patients were allocated to a treated or control group on the basis of a computerised random allocation. Patients in the treatment group received subcutaneous heparin, 5000 units 2 hours preoperatively and 8 hourly after this for the first 6 postoperative days i.e. a total of 7 days treatment. If, at the end of the 6th postoperative day, the patient was still confined to bed due to any condition, heparin was continued in the same dosage until the patient was fully mobile. The injection was given, using a 26 gauge needle into the subcutaneous tissue of the anterior abdominal wall. A fold of skin was raised and the needle inserted at right angles to the skin. After injection, the needle was withdrawn at the same angle. Other sites such as arms and thighs were not used for injection. One sheet of the proforma was provided on which administration of the calcium heparin by the nursing staff could be recorded. This was of vital importance to the trial as evidence that the drug had been given.

b. RESULTS

1. Introduction
2. Results
3. Factors
4. Clinical Diagnosis
5. Diagnosis with radioactive fibrinogen and Dopper ultrasound
6. Treatment
7. Complications

1. Introduction

Using radioactive fibrinogen and Doppler ultrasound for screening and venography in selected cases to confirm the diagnosis the results have shown that deep vein thrombosis is more common than previously suspected. Thrombosis appears to occur more commonly in the elderly patient, in the obese, in those undergoing major operations, in patients with varicose veins or malignancy, and especially in those with a previous history of venous thrombosis and pulmonary embolism. Many thrombi start to form while the patients are on the operating table and most of the remainder develop within the next 48 hours to 72 hours. Patients particularly at risk require protection throughout this danger period. That is as long as their activities are restricted. Method which attempts to provide this, must be simple and capable of being used on a large scale.

2. Results of Low Dose Heparin Trial

Five patients out of 54 who received low dose calcium heparin developed deep vein thrombosis postoperatively diagnosed on screening with radioactive fibrinogen and Doppler ultrasound.

The incidence of postoperative deep vein thrombosis in the prophylactically treated group was 9% as compared to the incidence in the control group of 51%.

This reduction is statistically significant ($P < 0.0005$).

A further 7 patients had equivocal results and were excluded. Of these 7 patients

- 3 were positive at 1 point in the calf for 1 day only.
- 2 patients were positive preoperatively and over the subsequent 2 days became negative.
- 1 patient stopped heparin on the 3rd day because of an allergic reaction and
- 1 patient stopped heparin following excessive bleeding post-splenectomy for myelofibrosis. Within two days she developed a deep vein thrombosis with multiple pulmonary emboli, was then fully heparinised with no further episodes of pulmonary emboli and no further bleeding diatheses.

3. Factors Possibly predisposing deep vein thrombosis.
   - The Patient
   - Past History
   - Present History
   - Operation

3. Factors

I. The Patient

1. Age distribution of patients developing postoperative deep vein thrombosis in the heparin prophylactically treated group was in;

Age group 51-60 years	1 out of 13 positive
Age group 61-70 years	2 out of 12 positive
Age group 71-80 years	1 out of 6 positive
Age group 81-90 years	1 out of 3 positive

Comparison of age distribution as a percentage of positive control and heparin treated group is shown in Figure 19 In all age groups there was a significant reduction in the incidence.

2. Sex

Of the 5 positives,

3/28 were males

and 2/26 were females

3. Obesity

a. Severely obese	1 of 5 positive
Mildly obese	1 of 4
Normal	3 of 45

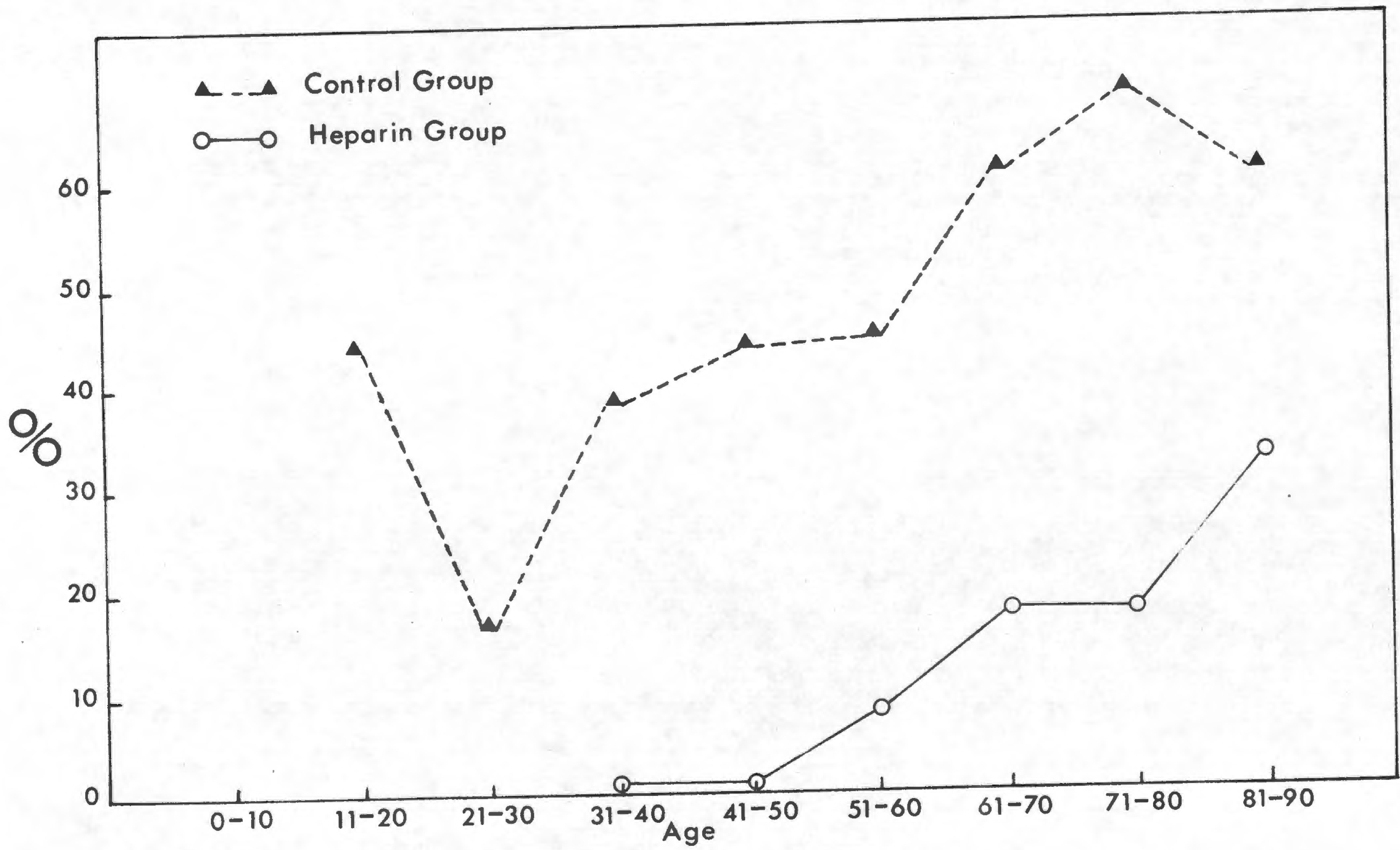
Obesity did not therefore appear to be an increased risk in the treated group but numbers are small.

4. Blood Group

Patients developing postoperative deep vein thrombosis in

Blood group A	2/16 positive
Blood group B	0/4 positive

FIGURE 19 AGE DISTRIBUTION OF PATIENTS DEVELOPING POSTOPERATIVE DEEP VEIN THROMBOSIS IN CONTROL AND HEPARIN PROPHYLACTICALLY TREATED GROUP. EXPRESSED AS A PERCENTAGE OF POSITIVES.


Control Group
Heparin Group
%
60
50
40
30
20
10
0
0-10
11-20
21-30
31-40
41-50
51-60
61-70
71-80
81-90
Age

Blood Group 0	3/20 positive
Blood Group AB	0/2 positive
Blood Group Rh positive	5/37 positive
Blood Group Rh negative	0/3 positive

Rh Positive appears to be at an increased risk.

II. Past History

1. Previous Myocardial Infarction

One positive out of a total of 3 patients who had a previous myocardial infarction.

2. Previous Deep Vein Thrombosis

No patients positive out of 2.

3. Previous Pulmonary Emboli

One positive out of a total of 4 patients.

4. Previous Fracture of long bone of lower limb

No patients were positive out of a total of 3.

III. Present History

1. Chronic Bronchitis

One patient positive out of 10.

2. The Pill

No patients positive out of 2.

3. Varicose Veins

One patient with bilateral varicose veins was positive out of a total of 5.

4. Varicose Ulcer

In one patient who was negative.

5. Healed Varicose Ulcer

One patient out of 2 was positive. This was the same patient who had the bilateral varicose veins.

6. Days in Hospital Preoperatively

Did not have any influence on the incidence. Two positive patients were in hospital one day preoperatively, two patients for 2 to 5 days and one patient for 10 to 20 days respectively.

IV Operation

1. Duration of the Operation

Two positive had operations lasting $\frac{1}{2}$ to one hour. Three positive had operations lasting one to two hours i.e. 2/18 were positive and 3/27 were positive respectively. Therefore duration of operation did not seem to have any importance.

2. Type of Operation

All 5 who were positive had abdominal operations, 2 were cholecystectomies, 2 were colonic resections for carcinoma and one was a gastrostomy for acute gastric erosions. Thus 5 cases out of the total of 46 abdominal operations were positive.

3. Operative Blood Loss

In 9 patients in whom it was greater than 3 pints, none were positive.

4. Operative Pathology

Inflammation - 3/21 patients were positive.
Operable carcinoma - 2/6 patients positive.
Inoperable carcinoma - 0/7 patients were positive.

It would thus appear that the inoperable carcinoma group which showed a high control incidence of postoperative deep vein thrombosis were adequately protected by prophylactic heparin.

5. Postoperative Complications

Only one patient developed a urinary tract infection (1/5 positive).

Mr H.H. a European male aged 63 years developed a postoperative deep vein thrombosis on the first day. On the second postoperative day he had an acute myocardial infarction,

developed congestive cardiac failure and then a cerebral embolic episode with diplopia. This resolved over the next 48 hours. On the 7th postoperative day he had a further episode of chest pain with extension of his myocardial infarction shown on electrocardiography. He developed ventricular fibrillation and despite all resuscitation died. Unfortunately, postmortem was refused.

4. Clinical diagnosis of deep vein thrombosis

In none of the 5 patients were there any signs of deep vein thrombosis, but one patient developed pain in the right calf which was the site of the venous thrombosis shown by radioactive fibrinogen.

5. Diagnosis by Radioactive Fibrinogen and Doppler Ultrasound

All 5 patients developed calf venous thrombosis.
The onset in three was within the first 24 to 72 hours postoperatively. Two cases had bilateral venous thrombosis, the remaining three cases were unilateral on the right side.
In no case was there extension to the popliteal fossa nor was there ilio-femoral venous thrombosis.
No cases developed pulmonary emboli on clinical or radiological examination.

6. Treatment

In all five cases the deep vein thrombosis was treated symptomatically consisting of elevation of the foot of the bed and elastic stockings.

7. Complications In this prophylactically treated series:

a. Bleeding

There was no increased objective evidence of interoperative bleeding in the treated group. In one patient following a splenectomy for myelofibrosis, with a thrombocytopaenia there was postoperative bleeding from the splenic bed on the third postoperative day. Subcutaneous heparin was discontinued and the patient then developed a deep vein thrombosis with multiple pulmonary emboli. She was anticoagulated with a full dose heparin schedule with no further bleeding problems nor further pulmonary emboli.

b. Wound Haematoma

In the treated group no patients developed wound haematoma.

c. Haematoma at Heparin Injection Site

This occurred in one patient and was found to be due to an incorrectly administered injection using a thick needle into the biceps muscle.

d. Allergy

This occurred in one patient and was probably due to the alcohol swab to which the patient was shown to be allergic.

e. Pain and Discomfort

Provided the injection was correctly administered as according to the instruction sheet, no patients complained of pain or discomfort.

In 20 patients in whom random clotting times were done, it was found that these were not prolonged.

c. DISCUSSION

Prevention

Most prophylactic measures are designed to antagonise the more likely causes of thrombosis included in Virchow's Triad of stasis in the deep veins, injury to the intima and changes in blood coaguability (113). The physical methods such as leg exercises, active compression of the calf by pneumatic leggings and electrical stimulation of the calf during operation have not provided sufficiently clear benefit to lead to their general use (6, 120, 123, 128).

Drugs

Many attempts have been made to prevent venous thrombosis by drugs. Anticoagulants have been used with variable success and are moderately effective in preventing pulmonary embolism if given under strict laboratory control. Anticoagulation before surgery increases the risk of bleeding at operation (11, 186). Although infusion of dextran, reduces the incidence of thrombosis it seems not to affect that of pulmonary embolism. Moreover, dextran has a number of disadvantages (23, 106, 187).
Aspirin and dipyridamole have been tried because they reduce platelet adhesiveness and aggregation. Both have, however, been shown to be ineffective (162, 186).
Hydroxychloroquine sulphate also reduces platelet aggregation and has been reported to prevent thrombosis, however it requires further trials (159).

Low Dose Subcutaneous Heparin in the Prevention of Postoperative Deep Vein Thrombosis

1. Historical

Sharnoff and his associates began this work 10 years ago, and they claimed in 1970 that low dose subcutaneous heparin prevented fatal thromboembolism (140).

2. Mechanism of action

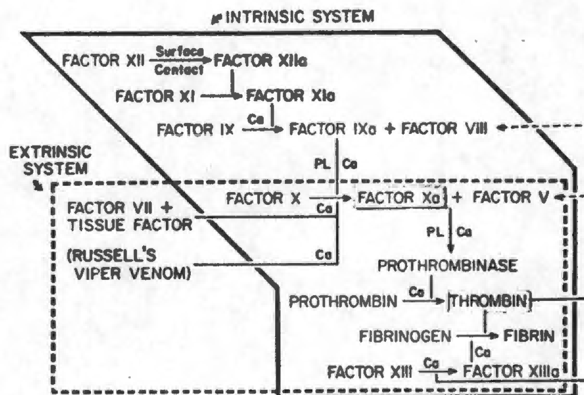
Heparin impedes normal blood coagulation by potentiating the action of natural inhibitors to activate factor-X (anti-factor Xa) and thrombin (anti-thrombin 111). (135, 141).
Cascade mechanism for blood coagulation is shown in Figure 20 (188).

Very low levels of heparin affect these inhibitors and high levels render blood incoagulable probably by completely blocking the autocatalytic action of factor Xa and the thrombin which it generates. A low plasma level of heparin greatly augments the effect of antifactor Xa. In the presence of 0.1 units of heparin/ml. plasma, antifactor Xa is increased to 190% of the amount present in normal plasma (137).
In investigating the plasma levels of heparin when administered intravenously and subcutaneously, it was found that subcutaneous heparin maintained a low but effective and constant level of plasma heparin when compared with the wide fluctuation obtained by 6 hourly intravenous administration of 10,000 units. The steady low level of heparin in plasma resulted from the slow release of heparin from 5,000 and 10,000 units given subcutaneously.

FIGURE 20. A MODIFIED CASCADE MECHANISM FOR BLOOD COAGULATION
After Williams (188)

PL = Phospholipid

Ca = Calcium


INTRINSIC SYSTEM
FACTOR XII
Surface Contact
FACTOR XIIa
FACTOR XI
FACTOR XIa
FACTOR IX
Ca
FACTOR IXa + FACTOR VIII
EXTRINSIC SYSTEM
PL
Ca
FACTOR VII + TISSUE FACTOR
FACTOR X
FACTOR Xa + FACTOR V
(RUSSELL'S VIPER VENOM)
PROTHROMBINASE
PROTHROMBIN
THROMBIN
FIBRINOGEN
FIBRIN
FACTOR XIII
FACTOR XIIIa

When giving intravenously, heparin disappeared from the plasma in 4 to 6 hours as judged by the calcium thrombin clotting-time although it was likely that there remained some potentiating effect of antifactor Xa (137). The high heparin level which followed intravenous injection could lead to serious haemostatic problems if surgery were carried out immediately.
It was found that the dose regime of 5,000 units of subcutaneous heparin given 1 hour before operation is used by Kakkar (131) and Gordon-Smith (3) produced, during surgery levels similar to those resulting from 10,000 units given subcutaneously 8 to 10 hours before the operation as used by Sharnoff (140).
In summary the mechanism of action of low dose subcutaneous heparin is to increase the quantity of two naturally occurring inhibitors of coagulation i.e. antifactor Xa and antithrombin 111 (135, 141) and to reduce platelet adhesiveness (136).

3. Clinical Studies of low dose subcutaneous heparin in prevention of deep vein thrombosis

The ability of subcutaneous low dose heparin to prevent postoperative deep vein thrombosis has been assessed in a number of controlled trials in which radioactive I^{125} fibrinogen test was used to detect the thrombosis. (1, 3, 5, 131, 133). Labelled fibrinogen was given intravenously and subsequent persistent concentration of the isotope in the tissues of the calf or lower thigh correlated well with the demonstration of deep vein thrombosis by phlebography. Table V shows the results of 5 recent trials in patients who underwent surgery. In all the incidence of positive tests indicating deep vein thrombosis was much lower than in the controls. In the trial of Williams (5) the difference was somewhat obscured by the high incidence of positive tests after prostatectomy in both treated and control groups.

However in the trial by Gordon-Smith (3), no evidence of thrombosis was detected in the 6 treated patients who had a retropubic prostetectomy.

In addition the total incidence of positive tests in patients treated for only one day after operation did not differ significantly from that in patients treated for 5 days (3). However, in the patients who had malignant disease, the incidence of positive tests was reduced only by the longer period of treatment (3).

The largest and most recently published trial by Nicolaides (133) has provided the first clear link between the incidence of positive fibrinogen tests and that of thrombi extending dangerously into the proximal veins. Such a thrombus was found in 9 patients in the control group and none in the heparin treated group, a highly significant difference. None of the patients in the trial developed signs of pulmonary embolism, perhaps because the 9 patients with extending thrombi were promptly treated with anticoagulants.

In another series (1) relatively few positive tests of deep vein thrombosis were found in a series of 133 patients considered to be at high risk for postoperative thrombosis, all of whom received low dose heparin. This was similar whether the patients had benign or malignant disease. However, positive tests were seen in 40% of 50 patients having operations for fractured neck of femur (1). The failure of low dose heparin to protect patients with such fractures or with cardiac infarction is explained by the fact that activation of the factor Xa follows tissue damage and once this has occurred, higher doses of

heparin are required to neutralise it (141).

4. Reported Complications

No side effects were reported in two of these studies by Kakkar (13) and Williams (5). Wound haematomas developed in 4 per cent of treated patients in Gordon-Smith's study (3) but in a largest trial so far by Nicolaides, they occurred with equal frequency in the control and treated patients (133). Troublesome bleeding was reported in two trials, the incidence being 4 out of 345 patients (1, 131). In all 4 patients there were other factors which may have been partly responsible. Bruising at the injection site did not give rise to many complaints, even when doses of 7,500 units were given 12 hourly (142). In some trials (1, 131) calcium heparin was used because it was supposed to cause less local bleeding, but in other trials (3, 131) sodium heparin caused haematomas at the injection sites in only 6 out of 222 patients, and in 4 of these the injection was given incorrectly.

This treatment is safe, cheap and simple to administer and the basic National Health Service cost of 5 ml bottle containing 5000 international units of heparin per ml is less than 25 pence. A 7 day perioperative course would thus cost 75 to 90 pence i.e. less than R2.00.

c. CONCLUSION

Prophylactic subcutaneous heparin has reduced the incidence of postoperative deep vein thrombosis in patients undergoing major elective general surgical procedures

from 51% in the control group, to 9% in the treated group

at Groote Schuur Hospital ($P < 0.0005$)

Furthermore, in those patients who did develop postoperative deep vein thrombosis, this was localised to the calf and did not extend proximally. There were no cases of popliteal or ilio-femoral venous thrombosis or pulmonary emboli.

Low dose subcutaneous heparin is therefore an effective, safe simple to administer and low cost method of preventing postoperative deep vein thrombosis with its associate morbidity both in the acute and chronic phase and its mortality.

2. PREVENTION

2. SODIUM PENTOSAN POLYSULPHATE - "TAVAN-SP54"

a. Results
b. Discussion
c. Conclusion

a. RESULTS

1. HIGH DOSE TAVAN - SP 54

Twelve patients were included in the trial using high dose Tavan SP-54. One hundred mg. was given two hours preoperatively followed by 100 mg 6 hourly. Of the 12 patients, 6 were positive and 6 were negative. Of the 6 patients who developed deep vein thrombosis, 3 developed the complication of bleeding which resulted in wound haematoma, and of the 6 negative patients, 4 developed bleeding. Bleeding was thus a complication in 7 of the 12 cases. Three patients were returned to theatre for evacuation of wound haematomas. It was felt unethical to continue and the trial was stopped.

2. LOW DOSE TAVAN SP-54

Sixty one patients were included in the low dose trial. However 13 cases were either discharged before the third postoperative day or the fibrinogen count had disappeared, and were thus excluded from the trial.

Of the 48 remaining patients, 7 were positive according to the criteria and thus were diagnosed as having developed postoperative deep vein thrombosis whilst on treatment giving an incidence of 15% ($P < .005$). One patient died due to septicaemia and at postmortem it was confirmed that there was venous thrombosis in the right femoral vein, the posterior tibial vein with the presence of small pulmonary emboli.
Forty one patients (85%) were negative and did not develop a deep vein thrombosis postoperatively whilst on Tavan SP-54. However, 12 of the 41 negative patients had an isolated count in the calf which lasted for one day only (25%). By Kakkar's criteria (26) these cases were regarded as not having developed postoperative deep vein thrombosis.

The onset of the deep vein thrombosis was within the first postoperative day in 4 patients and within the second post operative day in 3.
In only one of the 7 patients was there extension of the thrombosis over the next three days and it subsequently underwent spontaneous thrombolysis.

On clinical and special investigations there was no evidence of pulmonary emboli except in the one fatal case previously referred to.

Complications

Bleeding resulting in wound haematomas occurred in two patients, one from each group.

b. DISCUSSION

1. Chemistry

Sodium Pentosan Polysulphate is the generic chemical name for a polysaccharide ester which is semi-synthetically prepared and is a sulphated polyanion. The basic units are pentoses in a polymer chain. (196).

2. Spectrum of Action

Shown experimentally and clinically

There have been numerous publications of the action of Tavan SP-54 (157, 189, 190, 191, 194) It appears to activate the fibrinolytic system (189) and cause thrombolysis (190). It accelerates intrvascular lipolysis (157) with release of clearing factors and mobilisation of lipoid deposits in the tissue (191, 192). It has an anti-sludge effect with the correction of rouleaux formation in the micro-circulation (193). It inhibits hyaluronidase activity (194) and appears to have anti-inflammatory and anti-oedema effects (195).

3. Indications

The manfacturers claim that the drug can be used in degenerative arterial disease, thrombosis and embolism and hyperlipidaemia (196).

4. Postoperative Prevention of Deep Vein Thrombosis

Kraft (158) reported the use of Tavan SP 54 in the prevention of postoperative deep vein thrombosis. The drug was given to 3,522 cases, the majority undergoing abdominal operations. Results of these cases showed that only 3 patients ($< 0.1\%$) died of pulmonary embolism. (Table XVIII). There were no side effects nor contraindications to its use, that the drug had no anticoagulant action and probably activated the fibrinolytic system.

Although the results show a significant reduction in the postoperative complications (See Table XVIII), the criticism of this trial is that the diagnosis of deep vein thrombosis was made purely on clinical grounds which would approximate the local incidence diagnosed clinically. No mention was made either of the method of diagnosis of pulmonary embolism and whether the patients reported having died of pulmonary emboli had confirmatory post mortem or not.

TABLE XVIII INCIDENCE OF POSTOPERATIVE DEEP VEIN THROMBOSIS, PULMONARY EMBOLI AND DEATHS IN CONTROL AND TAVAN SP-54 TREATED PATIENTS. After Kraft (158)

	No Prophylaxis 1950-1957	Prophylaxis 1958-1962
	13,600	3,522 cases
1. Postoperative deep vein thrombosis	3.15 ± 0.58%	< 1%
2. Pulmonary emboli	1.5 ± 2.9%	< 0.2%
3. Death due to pulmonary emboli	0.53 ± .15%	0.08%

haemotological investigations for its control of dosage.

Tavan SP 54 in the low dose of 50 mgm 2 hours preoperatively and then 50 mgm 12 hourly by injection caused significant reduction in the incidence of postoperative deep vein thrombosis from

51% in the control to

15% in the treated group ($P < .005$)

As this was the only clinically reported work on Tavan SP-54 in the prevention of deep vein thrombosis, it was decided to undertake a controlled trial to test its efficacy.

This study shows a reduction in the incidence of postoperative deep vein thrombosis from 51% in the control group to 15% in the in the treated group using low dose Tavan SP-54. In one case deep vein thrombosis and multiple pulmonary emboli were shown which were not the cause of death. In only one case was there extension of the thrombosis and all the remaining cases underwent thrombolysis. The only complication recorded was in two cases who developed wound haematoma which spontaneously resolved over a subsequent week. High dose Tavan SP 54 however did not prevent postoperative deep vein thrombosis and caused bleeding. Why there should be this difference in the results with the two doses cannot be explained.

c. CONCLUSION

The pharmacological action of Tavan SP-54 has not been adequately elucidated in the literature. Past reports on its effects in the postoperative prevention in deep vein thrombosis are outdated (158) due to the modern methods of screening and diagnosis.
It has been shown that there is a place for Tavan SP 54 in the prevention of postoperative deep vein thrombosis. However, Tavan SP-54 used in the high dose of 100 mgs 2 hours preoperatively and 100 mgs 6 hourly postoperatively carried considerable morbidity due to bleeding and did not prevent deep vein thrombosis.
If this drug is to be used in the treatment of postoperative deep vein thrombosis it must obviously not be used too early postoperatively in higher doses or must be used in a reduced dosage. The reason for this is that there are no reliable

SECTION C

FINAL CONCLUSION AND POSSIBLE FUTURE RESEARCH

The INCIDENCE of deep vein thrombosis occurring postoperatively in the General Surgery wards at Groote Schuur Hospital in an analysis of 130 cases was 51%. The diagnosis of deep vein thrombosis was made by Clinical examination, Radioactive fibrinogen scanning, Doppler ultrasound and Venography in selected cases.

In the ANALYSIS OF FACTORS which may have contributed to this high incidence, it was shown that deep vein thrombosis occurs at all age groups, but there was a significant increase in the over 40 year age group. There was no sex difference and the complication occurred equally in European and Non-European patients. The Non-European patients were predominantly Cape Coloured, however in a few cases of Bantu and Indian patients studied. the incidence was approximately the same. Obesity appeared to play a significant role - the severely obese patients as defined by height and weight for age, had a much higher incidence of deep vein thrombosis. Blood group did not appear to play any significant role but numbers too small. Past history of myocardial infarction, fractures of the long bones of the lower limb, pulmonary embolus or deep vein thrombosis did not play a significant role. However, there were too few patients who had a previous pulmonary embolus or deep vein thrombosis diagnosed clinically. No further comment could be made in this regard.

Patients with varicose veins were more prone to the development of deep vein thrombosis on the side of the varicose veins as well as those patients demonstrating a varicose ulcer. This was presumably related to the past deep vein thrombosis underlying the aetiology of the varicose ulcer.

Duration of stay in hospital preoperatively did not appear to be a significant factor, although it seemed likely that the longer the operation the more prone the patient should be to the development of deep vein thrombosis but our figures did not confirm this.

In the type of operation performed there was an equal distribution among all types of operations grouped into head and neck, breast, vascular, exploratory laparotomy and hernia. A slight increase was shown in those patients undergoing stomach, duodenal and extrahepatic biliary operations, however, this was shown to be not statistically significant.

Incidence, according to operative blood loss exceeding more than 3 pints did not play a role. The operative pathology was evenly distributed amongst the sub-groups of congenital, traumatic, inflammatory, however the irresectable carcinoma in which a palliative procedure was performed, showed a significant increased risk.

Postoperative complications as well as postoperative days in hospital were not related to an increased risk.

In conclusion the only high risk cases found in this study have been patients in the age group of over 40 years, who were

severely obese, with varicose veins and healed varicose ulcer with an irresectable carcinoma undergoing an elective major operation under a general anaesthetic.

Factors which were not of significance were race, duration of preoperative stay, type of operation, length of operation, postoperative hospitalisation, operative bloodloss and postoperative complications. One could not , however exclude the patients who had had a past deep vein thrombosis as not being at increased risk as well as patients who had sustained fractures of their lower limbs as the series did not include a sufficient number of these patients.

TECHNIQUES OF DIAGNOSIS

The results showed that the classical clinical signs for the diagnosis of deep vein thrombosis were absent in the majority of cases,and only 7.5% of the total number of patients who developed a postoperative deep vein thrombosis would have been diagnosed on clinical grounds alone. Furthermore clinical diagnosis was erroneous in one patient. The symptom of pain in the calf, often only obtained by careful questioning, was far more reliable than the clinical signs and accounted for 26% of the cases diagnosed clinically. Radioactive fibrinogen technique was found to be a safe reliable method of diagnosis, but required trained technical staff and the duration of the investigation was 15 to 20 minutes per patient per day. It was reliable in 100% of our cases, and its sensitivity was superior to that of venography in that small thrombi in the calf muscles were demonstrated by fibrinogen but were not shown up by venography.

In the duration of radioactive fibrinogen counting there were initial problems at the beginning of the trial due to the poor quality of fibrinogen. However, in the latter part of the trial, counts were being obtained up to two to three weeks postoperatively.

If the patient presented with a deep vein thrombosis which was labelled by radioactive fibrinogen, and over the subsequent few days the counts disappeared, it was possible that the patients' thrombus had embolised to the lung. However, in no patients was there a correlation found between the disappearance of the thrombus and the development of the pulmonary embolus shown clinically radiologically, electro-graphically or by enzyme increases. The loss of radioactive counting was thought due either to the metabolism of the fibrinogen or to loss of radioactivity. The only complications encountered by the radioactive fibrinogen procedure was an iodine allergic reaction in one patient. The serum came from a select group of donors, Australian antigen negative, and although the follow up was too short there have been no cases with serum hepatitis attributable to the radioactive fibrinogen. In all cases the thyroid was blocked by sodium iodide. It must be pointed out, however, that in 5 patients not in this series who presented with pleuritic chest pain, no clinical signs, normal ECG and x-ray chest, only on lung scan was there a wedge shaped infarct compatible with a pulmonary embolus. Therefore, in the future to assess the true incidence of postoperative pulmonary emboli, routine lung scans should be performed in addition to ECG and radiological investigations.

Radioactive fibrinogen test was found to be an extremely useful screening test for the diagnosis of calf and lower thigh

venous thromboses i.e. from 10 cms below the inguinal ligament to the ankle joint, but was unreliable for the upper thigh.

Doppler ultrasound used as a screening procedure in combination with radioactive fibrinogen was found to be a reliable test for the diagnosis of popliteal, femoral and iliac venous thromboses. It was unreliable for the diagnosis of small calf venous thrombosis where there was no disturbance of venous flow. In the patients who were thought to have a pulmonary embolus with no clinical evidence of lower limb deep vein thrombosis, used as an isolated test, the findings at Groote Schuur Hospital in 22 of these patients who were not included in the trial, it was not very reliable.
The Doppler ultrasound was reliable in 80% of patients shown on venography to have venous occlusion, and in 20% of patients there was a false negative result. This was due to either a non-occlusive venous thrombosis or the development of adequate collateral circulation. Furthermore, using the Doppler ultrasound on the principle of "all or none" in regard to a sound being present or absent, non-occlusive venous thrombosis can be missed.

Doppler ultrasound therefore was found to be a useful screening method provided it was used with radioactive fibrinogen and provided the screening was carried out preoperatively for a baseline and daily or every second day to detect a change in the recording.

Venography was used as a definitive diagnostic method. It carried a small risk of complications and thus should not be used as a routine method in the diagnosis of deep vein thrombosis postoperatively. It is usually only carried out once and was thus useless as a screening procedure.

Furthermore, the venous thrombosis could occur several days or weeks after the venography was performed and therefore be missed. Indications for its use should be reserved for those patients who present as diagnostic problems, those undergoing thrombectomy or thrombolytic therapy using streptokinase or urokinase.

ONSET OF VENOUS THROMBOSIS

Results show that the deep vein thrombosis began to form while the patient was still on the operating table and over 75% were present within the first 48 to 72 hours. This fact is of the utmost importance in using measures to prevent venous thrombosis.

Deep vein thrombosis was bilateral in two thirds of the patients and unilateral in one third, the right side being twice as commonly involved as the left side. The site of the venous thrombosis in two fifths of the patients was localised to the calf and in three fifths the popiteal and ilio-femoral veins were involved. The popliteal vein was involved in 33% and the thigh alone or in combination in 24%.
This presents a considerably greater incidence of involvement of the popliteal and ilio-femoral venous segments than previously reported in clinical studies using radioactive fibrinogen alone (26), but confirms the pathological findings at post-mortem (88.89).

Calf venous thrombosis in the acute phase is only important if it extends into the popliteal and ilio-femoral veins, when

50% of patients may have pulmonary emboli, which is the presenting symptom in 50%, and 30% may die as a direct result of their pulmonary emboli (173). It is thus important to have a daily screening programme to detect the calf venous thromboses which extend and to watch the natural progression of the calf vein thrombosis as well as to diagnose early on the popliteal and ilio-femoral venous thrombosis so that treatment can be urgently carried out.

THE NATURAL HISTORY

The natural history of venous thrombosis is said to be to undergo spontaneous thrombolysis in the majority of cases. A small percentage recanalise and give rise to incompetent perforators and the post-phlebitic syndrome. A long term follow up of the cases in this series have not been carried out. It appeared to be of the utmost importance to follow these patients up long term and to try and define the natural history of postoperative deep vein thrombosis. The questions to be answered are whether these patients were more liable to further attacks of venous thrombosis both spontaneously or following trauma or operation. Furthermore, what percentage would develop the post-phlebitic syndrome. Dodd and Cockett (12) state that over 75% would develop the post-phlebitic syndrome. If this is so, the length of time required for the development of venous ulcers should be determined and what prevention could be used in the early and the late stage. At present at Groote Schuur Hospital heparin is the only anticoagulant used initially, if the venous thrombosis extended into the popliteal vein or involved the ilio-femoral vein. However, the question arises whether perhaps anticoagulants should be given to patients with

thrombi in the calf veins to prevent the thrombotic extension and thus prevent the early complication of pulmonary emboli and the late sequelae of the post-phlebitic limb.

The results also show that a number of the venous thromboses were bilateral, extensive, non-consecutive, multifocal and non-occlusive. A full assessment of the venous system of both lower limbs should always be made.

NEUROSURGICAL

In the neurosurgical unit an incidence of 43% of postoperative venous thrombosis was detected. Those undergoing spinal operations showed nearly twice the incidence of those undergoing cranial operations. In both groups the only possible differences were that the patient undergoing spinal operations were turned passively two hourly by attending nursing staff. Stasis might therefore have played a very important role in this group. It would appear in this group the role of prophylaxis should be extensively investigated.

In the OPHTHALMOLOGY AND OTOLARYNGOLOGY wards the combined incidence was less than 10%. This group of patients underwent an operation under general anaesthetic, lasting more than half an hour. Age distribution was compatible with the control group and the major difference was the minimal interoperative tissue trauma especially in the ophthalmology patients undergoing lens extraction. It was interesting to note that both the patients who developed deep vein thrombosis were obese, elderly and one had bilateral varicose veins.

Interoperative tissue trauma might thus play an important role in the production of the postoperative hypercoaguable state. In the ophthalmology patients, a study should be carried out to determine the incidence of patients developing deep vein thrombosis following a lens extraction under local anaesthetic. If the incidence is lower than the present incidence, all cases at high risk should undergo their operations under local anaesthetic.

PROPHYLAXIS

In the prevention of deep vein thrombosis mention has been made that all factors contributing to Virchow's triad should be taken into consideration i.e. stasis, intimal damage of veins and hypercoaguability.

The results, using low dose heparin show a decline in incidence of postoperative deep vein thrombosis from 51% to 9% which is statistically significant. As only 5 patients developed postoperative deep vein thrombosis on heparin, it was difficult to reach any definite conclusion concerning possible high risk factors in these patients.

Tavan SP-54 also reduced the postoperative incidence of deep vein thrombosis from 51% to 15% but there was the associated complication of bleeding. The development of deep vein thrombosis in the high dose trial has not been adequately explained.

In the routine prophylaxis of postoperative deep vein thrombosis low dose heparin would appear to be the drug of choice.

The general surgical unit at Groote Schuur Hospital where surgery on more than 350 patients is performed under general anaesthetic per month, it would be a costly procedure to screen every patient daily preoperatively and then postoperatively with radioactive fibrinogen and Doppler ultrasound. Two fulltime technicians using two sets of instruments would be required. The monthly cost of salaries and equipment would be approximately R1000 per month with an initial outlay of R5000 for the equipment.

To reach a compromise it would appear better to screen those high risk patients liable to develop deep vein thrombosis postoperatively such as the very obese patients with varicose veins or a varicose ulcer, past history of deep vein thrombosis or pulmonary emboli and with possible operative pathology of carcinoma.

Perhaps an even more practical approach to the problem would be that every patient undergoing a general anaesthetic procedure lasting more than half an hour should be routinely given low dose heparin - 5000 units two hours preoperatively or with the premedication and then 8 hourly postoperatively until the patient was fully mobilised.

It would appear that an effective low cost, practical method of the prevention of postoperative deep vein thrombosis has been found in heparin. It would thus be more logical that if such a method is available, it is far easier and more practical to prevent the deep vein thrombosis than to try and diagnose and then have to treat more than half of the patients with full anticoagulation.

The possible complications of deep vein thrombosis, pulmonary emboli and anticoagulation would be prevented.

REFERENCES:

1. Kakkar, V.V., Corrigan , T., Spindler, J., Fossard, D.P., Flute, P.T., Crellin, R.Q., Wessler, S., Yin, E.T., (1972).

   Efficacy of low doses of heparin in prevention of deep vein thrombosis after major surgery.

   Lancet, 2, 101-106.

2. Nicolaides, A.N., Kakkar, V.V., Field, E.S., Renney, J.T.G., (1971).

   The origin of deep vein thrombosis : a venographic study.

   Brit. J. Radiol., 44, 653-663.

3. Gordon-Smith, I.C., Grundy, D.J., Le Quesne, L.P., Newcombe, J.F., Bramble, F.J., (1972).

   Controlled trial of two regimens of subcutaneous heparin in prevention of postoperative deep vein thrombosis.

   Lancet, 1, 1133-1135.

4. Kemble, J.V.H., (1971).

   Incidence of deep vein thrombosis.

   Brit. Jnl. Hosp. Med., 6, 721-726.

5. Williams, H.T., (1971).

   Prevention of postoperative deep vein thrombosis with perioperative subcutaneous heparin.

   Lancet, 2, 950-952.

6. Browse, N.L., Negus, D.,
(1970).

Prevention of postoperative leg vein thrombosis by electrical muscle stimulation. An evaluation with ^{125}I-labelled fibrinogen.

Brit. Med. J., 3, 615-618.

7. Lambie, J.M., Mahaffy, R.G., Barber, D.C., Karmody, A.M., Scott, M.M., Matheson, N.A.,
(1970).

Diagnostic accuracy in venous thrombosis.

Brit. Med. J., 2, 142-143.

8. Negus, D., Pinto, D.J., Le Quesne, L.P., Brown, N., Chapman, M.,
(1968).

^{125}I-Labelled fibrinogen in the diagnosis of deep vein thrombosis and its correlation with phlebography.

Brit. J. Surg., 55, 835-839.

9. Editorial,
(1971).

Pharmacological fibrinolysis after surgical operations.

Lancet, 1, 789-790.

10. Evans, D.S., Negus, D.,
(1971).

Diagnosis of deep vein thrombosis.

Brit. J. Hosp. Med., 6, 729-734.

11. Sevitt, S., Gallagher, N.G.,
(1959).

Prevention of venous thrombosis and pulmonary embolism in injured patients.

Lancet, 2, 981-989.

12. Dodd, H., Cockett, F.B.,
(1956).

THE PATHOLOGY AND SURGERY OF VEINS OF LOWER LIMB.

1st Ed., Edin. and Lond., Livingstone, 297,312.

13. Popkin, R.J.,
(1962).

THE POSTTHROMBOPHLEBITIS SYNDROME.

1st Ed.,
Springfield, Illinois,
Charles, C. Thomas, 85.

14. Haller, J.A.,
(1967).

DEEP THROMBOPHLEBITIS. PATHOPHYSIOLOGY AND TREATMENT.
1st Ed.
Philadelphia and London,
W.B. Saunders Co.,
Vol. V1 - Major problems in Clinical Surgery.,
Edit. J. Englebert Dunphy, 14-21.

15. Faris, I.B., Rosengarten, D.S., Dudley, H.A.F.
(1972).

Temperature - chart analysis in the diagnosis of postoperative deep vein thrombosis.

2, 775-776.

16. Hobbs, J.T., Davies, J.W.,
(1960).

Detection of venous thrombosis with ^{131}I - labelled fibrinogen in the rabbit.

Lancet, 2, 134-135.

17. Atkins, P., Hawkins, L.A., (1965).

Detection of venous thrombosis in the legs.

Lancet, 2, 1217-1219.

18. Nanson, E.M., Palko, P.D., Dick, A.A., Fedoruk, S., (1965).

Early detection of deep vein thrombosis of the legs using ^{131}I - tagged human fibrinogen. A clinical study.

Ann. Surg. 162, 438-444.

19. Flanc, C., Kakkar, V.V., Clarke, M.B., (1968).

The detection of venous thrombosis of the legs using ^{125}I - labelled fibrinogen.

Brit. J. Surg., 55, 742-747.

20. Rosengarten, D.S., Laird, J., Jeyasingh, K., Martin, P. (1970).

The failure of compression stockings (Tubigrip) to prevent deep venous thrombosis after operation.

Brit. J. Surg., 57, 296-299.

21. Calnan, J.S., Pflug, J.J., Mills, C.J., (1970).

Pneumatic intermittent-compression legging simulating calf-muscle pump.

Lancet, 2, 502-503.

22. Sabri, S., Roberts, V.C., Cotton, L.T., (1971).

Prevention of early postoperative deep vein thrombosis by passive exercise of leg during surgery.

Brit. Med. J., 3, 82-83.

23. Lambie, J.M., Barber, D.C., Dhall, D.P., Matheson, N.A., (1970).

Dextran 70 in prophylaxis of postoperative venous thrombosis. A controlled trial.

Brit. Med. J., 2, 144-145.

24. Kakkar, V.V., Flanc, C., Howe, C.T., O'Shea, M., Flute, P.T., (1969).

Treatment of deep vein thrombosis. A trial of heparin, streptokinase and Arvin.

Brit. Med. J., 1, 806-810.

25. Browse, N.L., Clapham, W.F., Croft, D., Jones, D.J., Lea Thomas, M., Williams, J.O., (1971).

The diagnosis of established deep vein thrombosis using the ^{125}I - fibrinogen uptake test.

Brit. Med. J., 4, 325-329.

26. Kakkar, V.V., (1972).

The diagnosis of deep vein thrombosis using the I^{125} fibrinogen test.

Arch. Surg., 104, 152-159.

27. Kakkar, V.V., Nicolaides, A.N., Renney, J.T.G., (1970).

^{125}I - Labelled fibrinogen test adapted for routine screening for deep vein thrombosis.

Lancet, 1, 540-542.

28. Browse, N.L.,
(1972).
The ^{125}I - Fibrinogen uptake test.
Arch. Surg., 104, 160-163.

29. Strandness, D.E., Schultz, R.D., Summer, D.S., Rushmer, R.F.,
(1967).
Ultrasonic flow detection. A useful technique in the evaluation of peripheral vascular disease.
Amer. J. Surg., 113, 311-320.

30. Sigel, B., Popky, G.L., Wagner, D.K., Boland, J.P., Mapp, E. Mc.D., Feigl, P.,
(1968).
Comparison of clinical and Doppler ultrasound evaluation of confirmed lower extremity venous disease.
Surgery, 64, 332-338.

31. Sigel, B., Popky, G.L., Wagner, D.K., Boland, J.P., Mapp, E., Feigl, P.,
(1968).
A Doppler ultrasound method for diagnosing lower extremity venous disease.
Surg. Gynec. Obstet., 127, 339-350.

32. Evans, D.S., Cockett, F.B.,
(1969).
Diagnosis of deep vein thrombosis with an ultrasonic Doppler technique.
Brit. Med. J., 2, 802-804.

33. Evans, D.S.,
(1970).
The early diagnosis of deep vein thrombosis by ultrasound.
Brit. J. Surg., 57, 726-728.

34. Strandness, D.E., Summer, D.S., (1972).

Ultrasonic velocity detector in the diagnosis of thrombophlebitis.

Arch. Surg. 104, 180-183.

35. Yao, S.T., Gourmos, C., Hobbs, J.T., (1972).

Detection of proximal vein thrombosis by Doppler ultrasound flow detection method.

Lancet, 1, 1-6.

36. Sigel, B., Felix, R., Popky, G.L., Ipsen, J., (1972).

Diagnosis of lower limb venous thrombosis by Doppler ultrasound technique.

Arch. Surg., 104, 174-179.

37. Evans, D.S., (1971).

The early diagnosis of thromboembolism by ultrasound.

Ann. Roy. Coll. Surg. Eng., 49, 225-248.

38. Mc Ilroy, R.F., (1972).

The routine use of ultrasound for the diagnosis of postoperative deep vein thrombosis in a district general hospital.

Brit. J. Surg., 59, 133-135.

39. Berberich, J., Hirsch, S., (1923).

Die rontgenologische Darstellung der Arterien und Venem im lebenden Menschen.

Klin. Wschr., 49, 2226-2228.

40. Rabinov, K., Paulin, S.,
(1972).
Roentgen diagnosis of venous thrombosis in the leg.
Arch. Surg., 104, 134-144.

41. Bauer, G.,
(1940).
Venographic study of thrombo-embolic problems.
Acta. Chir. Scand., 84. (Supp. 61), 61-75.

42. Dougherty, J., Homans, J.,
(1940).
Venography a clinical study.
Surg. Gynec. Obstet., 71, 697-702.

43. Lesser, A., Danelius, G.,
(1944).
Venography: Its value in the diagnosis and management of venous disturbances of the lower extremities.
Ann. Surg., 119, 903-921.

44. Greitz, T.,
(1954).
The technique of ascending phlebography of the lower extremity.
Acta. Radiol., 42, 421-441.

45. Almen, T., Nylander, G.,
(1964).
False signs of thrombosis in lower leg phlebography.
Acta. Radiol., 2, 345-352.

46. Scott, H.W., Roach, J.F.,
(1951).
Phlebography of the leg in the erect position.
Ann. Surg., 134, 104-109.

47. Bergvall, U.,
(1971).

Phlebography in acute venous thrombosis of the lower extremity. A comparison between centripetial ascending and descending phlebography.

Acta.Radiol., 11, 148-166.

48. Browse, N.L., Lea Thomas, M., Solan, M.J.,
(1967).

Management of the source of pulmonary emboli : the value of phlebography.

Brit. Med. J., 4, 596-597.

49. Browse, N.L., Thomas, M.L., Solan, M.J.,
(1969).

Prevention of recurrent pulmonary embolism.

Brit. Med. J., 3, 382-386.

50. Lea Thomas, M.,
(1971).

Radiology of deep vein thrombosis.

Brit. J. Hosp. Med., 6, 735-740.

51. Lea Thomas, M., Mc Allister, V.,
(1971).

The radiological progression of deep venous thrombosis.

Radiology, 99, 37-40.

52. Lea Thomas, M.,
(1970).

Gangrene following peripheral phlebography of the legs.

Brit. J. Radiol., 42, 528-530.

53. Lea Thomas, M., Andress, M.R., Browse, N.L., Fletcher, E.W.L., Phillips, J.D., Mc Allister, V., (1970).

Phlebography in the prevention of recurrent pulmonary embolism - techniques and value.

Amer. J. Roentgenol. Radium Ther. Med., 110, 725-733.

54. Lea Thomas, M., (1969).

An improved intraosseous phlebography cannula.

Brit. J. Radiol., 42, 395-396.

55. Galloway, J.M.D., Karmody, A.M., Mavor, G.E., (1969).

Thrombophlebitis of the long saphenous vein complicated by pulmonary embolism.

Brit. J. Surg., 56, 360-361.

56. Halliday, P., (1968).

Phlebography of the lower limb.

Brit. J. Surg., 55, 220-226.

57. Mahaffy, R.G., Mavor, G.E., Galloway, J.M.D., (1971).

Iliofemoral phlebography in pulmonary embolism.

Brit. J. Radiol., 44, 172-183.

58. Mavor, G.E., Galloway, J.M.D., Karmody, A.M., (1970).

The surgical aspects of deep vein thrombosis.

Proc. Roy. Soc. Med., 63, 126-131.

59. Mullick, S.C., Wheeler, H.B., Songster, G.F., (1970).

Diagnosis of deep vein thrombosis by measurement of electrical impedance.

Amer. J. Surg., 119, 417-422.

60. Wheeler, H.B., Pearson, D., O'Connell, D., Mullick, S.C., (1972).

Impedance phlebography technique, interpretation and results.

Arch. Surg., 104, 164-169.

61. Dmochowski, J.D., Adams, D.F., Couch, N.P., (1972).

Impedance measurement in the diagnosis of deep vein thrombosis.

Arch. Surg., 104, 170-173.

62. Steer, M.L., Spotnitz, A.J., Cohen, S.I., Paulin, S., Salzman, E.W., (1973).

Limitations of Impedance Phlebography for the diagnosis of venous thrombosis.

Arch. Surg., 106, 44-48.

63. Deuvaert, F.E., Dmochowski, J.R., Couch, N.P., (1973).

Positional factors in venous impedance plethysmography.

Arch. Surg., 106, 53-55.

64. Lane, W.Z., (1967).

Thermography in diagnosis of lower limb thrombophlebitis.

Hosp. Pract., 2, 36-39.

65. Bygdeman, S., Eliasson, R., Johnson, S.R., (1966).

Relationship between postoperative changes in adenosine - diphosphate induced platelet adhesiveness and venous thrombosis.

Lancet, 1, 1301-1302.

66. Fletcher, A.P., Alkjaersig, N., O'Brien, J., Tulevski, V.G., (1970).

Blood hypercoagulability and thrombosis.

Trans. Assoc. Amer. Physicians., 83, 159-167.

67. Negus, D., Pinto, D.J., Brown, N., (1969).

Platelet adhesiveness in postoperative deep vein thrombosis.

Lancet, 1, 220-224.

68. Ruckley, C.V., Das, P.C., Leitch, A.G., Donaldson, A.A., Copland, W.A., Redpath, A.T., Scott, P., Cash, J.D., (1970).

Serum fibrin/fibrinogen degradation products associated with postoperative pulmonary embolus and venous thrombosis.

Brit. Med. J., 4, 395-398.

69. Wood, E.H., Prentice, C.R.M., Mc Nicol, G.P., (1972).

Association of fibrinogen - fibrin related antigen (F.R. - Antigen) with postoperative deep vein thrombosis and systemic complications.

Lancet, 1, 166-169.

70. Mansfield, A.O.,
(1972).

Alteration in fibrinolysis associated with surgery and venous thrombosis.

Brit. J. Surgery., 59, 754-757.

71. Fletcher, A.P., Alkjaersig, N., O'Brien, J.,
(1972).

THROMBOEMBOLISM : DIAGNOSIS AND TREATMENT.

Proceedings of a symposium held at King's College Hospital, London.

Edit. V.V. Kakkar, A.J. Jouhar.

Fibrinogen - Fibrin Degeneration Products and Venous Thromboembolism.
1st Ed. Edin. & London. Churchhill, Livingstone, 25-38.

72. Flute, P.T., Kakkar, V.V., Renney, J.T.G., Nicolaides, A.N.,
(1972).

THROMBOEMBOLISM : DIAGNOSIS AND TREATMENT.

Proceedings of a symposium held at King's College Hospital, London.

Edit. V.V. Kakkar, A.J. Jouhar.

The Blood and Venous Thromboembolism.

1st Ed. Edin. & London.
Churchhill, Livingstone. 2-12.

73. Registrar General.

STATISTICAL REVIEW OF ENGLAND AND WALES FOR THE YEAR 1970, (1972).

Part 1, London. H.M.S.O.

74. Smith, G.T., Dammin, G.J., Dexter, L., (1964).
Post-mortem arteriographic studies of the human lung in pulmonary embolization.
J.A.M.A., 188,143-151.

75. REGISTRAR-GENERAL'S STATISTICAL REVIEW OF ENGLAND AND WALES (1941 to 1967),
Part 1, London. H.M.S.O.

76. Hume, M., Sevitt, S., Thomas, D.P., (1970).
VENOUS THROMBOSIS AND PULMONARY EMBOLISM.
Harvard University Press, Cambridge, Mass.
Publ. Harvard College, 3,

77. Coon, W.W., Willis, P.W., (1959).
Deep vein thrombosis and pulmonary embolism : prediction, prevention and treatment.
Amer. J. Cardiol., 4, 611-621.

78. Sevitt, S., Gallagher, N.G., (1961).
Venous thrombosis and pulmonary embolism : A clinicopathological study in injured and burned subjects.
Brit. J. Surg., 48, 475-489.

79. Bruzelius, S., (1945).
Dicoumarin in clinical use : Studies on its prophylactic and therapeutic value in the treatment of thromboembolism.
Acta. Chir. Scand., 92, Suppl. 100.

80. Bauer, G.,
(1944).
Thrombosis following leg injuries.
Acta. Chir. Scand., 90, 229-248.

81. Aurin, F.B., Herrmann, L.G.,
(1948).
Management of venous thrombosis and pulmonary embolism following injury to the extremities.
Amer. J. Surg., 76, 586-590.

82. Barker, N., Nygaard, K., Walters, W., Priestly, J.T.,
(1941).
Statistical study of postoperative venous thrombosis and pulmonary embolism; time of occurrence during postoperative period.
Proc. Mayo Clinic., 16, 17-21.

83. Rössle, R.,
(1937).
"Über die Bedeutung und Entstehung der Wadenvenen-thrombosen."
Virchows Arch. Path. Anat., 300, 180.

84. Neumann, R.,
(1938).
Ursprungszentren und Entwickelungsformen der Bein - Thrombosen.
Virchows Arch. Path. Anat., 301, 708-735.

85. Putzer, R.,
(1939).
Die Waden venenthrombose in ihrer Beziehung zur Architektur der Wade.
Arch. Gynäk, 169, 444-452.

86. Hunter, W.C., Krygier, J.J., Kennedy, J.C., Sneeden, V.D., (1965).

Etiology and prevention of thrombosis of the deep leg veins; study of 400 cases.

Surgery, 17, 178-190.

87. Greenstein, J., (1945).

Thrombosis and pulmonary embolism.

S. Afri. Med. J., 19, 350.

88. Mc Lachlin, J., Richards, T., Paterson, J.C., (1962.

An evaluation of clinical signs., the diagnosis of venous thrombosis.

Arch. Surg., 85, 738-744.

89. Gibbs, N.M., (1957).

Venous thrombosis of the lower limbs with particular reference to bed rest.

Brit. J. Surg., 45, 209-236.

90. Roberts, G.H., (1963).

Venous thrombosis in hospital patients. A post-mortem study.

Scot. Med. J., 8, 11-15.

91. Brenner, O., (1935).

Pathology of the vessels of the pulmonary circulation.

Arch. Intern. Med., 56, 211,457,724.

92. Hampton, A.O., Castelman, N.,
(1941).
Correlation of postmortem chest teleroentenograms with special reference to pulmonary embolism and infarction.
J. Tech. Methods, 21, 5-11.

93. Cohn, R., Walsh, J.,
(1946).
Incidence and anatomical site of origin of pulmonary emboli.
Stanf. Med. Bull., 4, 27-31.

94. Pulvertaft, R.J.V.,
(1947).
Postoperative pulmonary embolism.
Ann. Roy. Coll. Surg. Eng., 1, 181-190.

95. Morell, M.T., Dunnill, M.S.,
(1968).
The postmortem incidence of pulmonary embolism in a hospital population.
Brit. J. Surg., 55, 347-352.

96. Coon, W.W., Coller, F.A.,
(1959).
Some epidemiological considerations of thromboembolism.
Surg. Gynec. Obstet., 109, 489-501.

97. Sandritter, W.,
(1962).
Die pathologische Anatomie der Thrombose und Lungenembolie.
Sonderuck ans Behringwerk - Mittelungen, 41, 37.

98. Morrell, M.T., Truelove, S.C., Barr, A., (1963).
Pulmonary embolism.
Brit. Med. J., 2, 830-835.

99. Braconier, J.H., (1967).
Venous thrombi and pulmonary emboli in an autopsy series.
(Personal communication of Hume - ref. 76.)

100. Freiman, D.G., Suyemoto, J., Wessler, S., (1965).
Frequency of thrombo-embolism in man.
New Engl. J. Med., 272, 1278-1280.

101. Welch, C.E., Faxon, H.H., (1941).
Thrombophlebitis and pulmonary embolism.
J.A.M.A., 117, 1502-1508.

102. Becker, J., Borgström, S., Saltzman, G.F., (1970).
Occurence and course of thrombosis following prostatectomy. A phlebographic investigation.
Acta.Radiol., 10, 513-533.

103. Hedlund, P.O., Plamlöv, A., Sjogren, S., (1971).
Trombosprofylax vid prostatektomi en dubbelblindstudie.
Nord. Med., 85, 187.

104. Rosengarten, D.S.,
(1971).

The natural history of postoperative deep vein thrombosis.

Aust, N.Z. J. Surg., 40, 285-289.

105. Tsapogas, M.J., Miller, R., Peabody, R.A.,
(1970).

Detection of postoperative venous thrombosis and effectiveness of prophylactic measures studied with the fibrinogen ^{125}I technique.

Arch. Surg., 101, 149-154.

106. Ahlberg, A., Nylander, G., Robertson, B., Cronberg, S., Nilsson, I.M.,
(1968).

Dextran in prophylaxis of thrombosis in fractures of the hip.

Acta. Chir. Scand., Suppl. 287, 83-85.

107. Borgström, S., Greitz, T., Linden, W. van der.,
(1965).

Anticoagulant prophylaxis of venous thrombosis in patients with fractured neck of femur ; a controlled clinical trial using venous phlebography.

Acta. Chir. Scand., 129, 500-508.

108. Hamilton, H.W., Crawford, J.S., Gardiner, J.H.,
(1970).

Venous thrombosis in patients with fracture of the upper end of the femur. A phlebographic study of the effect of prophylactic anticoagulants.

J. Bone Joint Surg., 52, 268-289.

109. Hjelmstedt, A., Bergvall, U.,
(1968).

Phlebographic study of the incidence of thrombosis in the injured and uninjured limb in 55 cases of tibial fracture.

Acta Chir. Scand., 134, 229-234.

110. Johnson, D.C., Reeve, T.S.,
(1968).

The effect and clinical significance of low molecular weight and clinical dextran on an experimental venous thrombosis in sheep.

Ann. Surg., 168, 123-127.

111. Myhre, H.O., Holen, A.,
(1969).

Tromboseprofylakse. Dextran eller warfarin-natrium ?

Nord. Med., 82, 1534-1538.

112. Stevens, J., Fardin, R., Freeark, R.J.,
(1968).

Lower extremity thrombophlebitis in patients with femoral neck fractures.
A venographic investigation and review of the early and late significance of the findings.

J. Trauma., 8, 527-534.

113. Virchow, R.,
(1854).

HANDBUCH DER SPECIELLEN PATHOLOGIE UND THERAPIE.

Bd 1: Enke, Erlangen, 156-182.

114. Virchow, R.,
(1856).

ABHANDLUNGEN ZUR WISSENSCHAFTLICHEN MEDICIN.

Meidinger, Sohn and Comp., Frankfurt., 221-232.

115. Jansen, H.,
(1972).

Postoperative Thromboembolism and its Prevention with 500 ml. Dextran given during Operation, with a special study of the venous flow pattern in the lower extremity.

Acta. Chir. Scand., Suppl. 427, 1-73.

116. Murley, R.S.,
(1950).

Postoperative venous thrombosis and pulmonary embolism with particular reference to current methods of treatment.

Ann. R. Coll. Surg., 6, 283-322.

117. Sharnoff, J.G., Rosenberg, M.,
(1964).

Effects of age and immobilisation on the incidence of postoperative thromboembolism.

Lancet, 1, 845-846.

118. Blodgett, J.B., Beattie, E.J.,
(1946).

Early postoperative rising; statistical study of hospital complications.

Surg. Gynec. Obstet., 82, 485-489.

119. Powers, J.H.,
(1949).

Prompt postoperative activity after hernioplasty; its influence on incidence of complications and rate of recurrence.

Arch. Surg., 59, 601-608.

120. Flanc, C., Kakkar, V.V., Clarke, M.B.,
(1969).

Postoperative deep vein thrombosis : Effect of intensive prophylaxis.

Lancet, 1, 477-478.

121. Sigel, B., Edelstein, A.L., Felix, W.R., Memhardt, C.R., (1973).
Compression of the deep venous system of the lower leg during inactive recumbency.
Arch. Surg., 106, 38-43.

122. Doran, F.S.A., Drury, M., Sivyer, A., (1964).
A simple way to combat the venous stasis which occurs in the lower limbs during surgical operations.
Brit. J. Surg., 51, 486-492.

123. Doran, F.S.A., White, H.M., (1967).
A demonstration that the risk of postoperative deep venous thrombosis is reduced by stimulating the calf muscles electrically during the operation.
Brit. J. Surg., 54, 686-689.

124. Nicolaides, A.N., Kakkar, V.V., Field, E.S., Fish, P., (1972).
Optimal electrical stimulus for prevention of deep vein thrombosis.
Brit. Med. J., 3, 756-758.

125. Moloney, G.E., Morrell, M.T., Fell, R.H., (1972).
The effect of electrical stimulation of the legs on postoperative thrombosis.
Brit. J. Surg., 59, 65-68.

126. Dejode, L.R., Khurshid, M., Walther, W.W.,
(1973).

The influence of electrical stimulation of the leg during surgical operations on the subsequent development of deep vein thrombosis.

Brit. J. Surg., 60, 31-32.

127. Roberts, V.C., Sabri, S., Pietroni, M.C., Gurewich, V., Cotton, L.T.,
(1971).

Passive flexion and femoral vein flow : A study using a motorized foot mover.

Brit. Med. J., 3, 78-81.

128. Hills, N.H., Plug, J.J., Jeyasingh, K., Boardman, L., Calnan, J.S.,
(1972).

Prevention of deep vein thrombosis by intermittent pneumatic compression of calf.

Brit. Med. J., 1, 131-135.

129. Sabri, S., Roberts, V.C., Cotton, L.T.,
(1971).

Prevention of early postoperative deep vein thrombosis by intermittent compression of the leg during surgery.

Brit. Med. J., 4, 394-396.

130. Pinto, D.J.,
(1970).

Controlled trial of an anticoagulant (Warfarin Sodium) in the prevention of venous thrombosis following hip surgery.

Brit. J. Surg., 57, 349-352.

131. Kakkar, V.V., Field, E.S., Nicolaides, A.N., Flute, P.T., Wessler, S., Yin, E.T.,
(1971).

Low doses of heparin in prevention of deep vein thrombosis.

Lancet, 2, 669-671.

132. Charnley, J.,
(1972).

Prophylaxis of postoperative thromboembolism. (Letters).

Lancet, 2, 134.

133. Nicolaides, A.N., Dupont, P.A., Desai, S., Lewis, J.D., Douglas, J.N., Dodsworth, H., Fourides, G., Luck, R.J., Jamieson, C.W.,
(1972).

Small doses of subcutaneous sodium heparin in preventing deep venous thrombosis after major surgery.

Lancet, 2, 890-893.

134. Sharnoff, J.G., Rosen, R.L., Sadler, A.H., Cea, R.J., Palazzo, P.J.,
(1972).

Prophylaxis of postoperative embolism. (Letters).

Lancet, 2, 488.

135. Biggs, R., Denson, K.W.E., Akman, N., Borrett, R., Hadden, M.,
(1970).

Antithrombin III, antifactor XA and heparin.

Brit. Jnl. Haem., 19, 282-305.

136. Negus, D., Pinto, D.J., Slack, W.W., (1971).
Effect of small doses of heparin on platelet adhesiveness and Lipoprotein Lipase activity before and after surgery.
Lancet, 1, 1202-1204.

137. Bonnar, J., Denson, K.W.E., Biggs, R., (1972).
Subcutaneous heparin and prevention of thrombosis. Letters to Editor.
Lancet, 2, 539-540.

138. Lisse, K., (1965).
Die postoperative Blutung nach Antikoagulantien - Behandlung.
Zbl. Gynaek., 87, 1758-1762.

139. Jorpes, J.E., (1964).
Heparin zur Einleitung der Dauer behandlung mit Antikoagulantien.
Thromb. Diath. Haemorrh. Suppl. 12, 7-9.

140. Sharnoff, J.G., De Blasio, G., (1970).
Prevention of fatal postoperative thromboembolism by heparin prophylaxis.
Lancet, 2, 1006-1007.

141. Yin, E.T., Wessler, S., Stoll, P.J., (1971).

Indentity of plasma-activated factor X inhibitor with antithrombin 3 and heparin factor.

J. Biol. Chem., 246, 3712-3719.

142. Handley, A.J., (1972).

Low dose heparin after myocardial infarction.

Lancet, 2, 623-624.

143. Ingelman, B., Grönwall, A., Gelin, L.E., Eliasson, R., (1969).

Properties and applications of dextrans.

Acta. Acad. Reg. Scient. Ups., 12, 1-90.

144. Bygdeman, S., Eliasson, R., (1967).

Effect of dextrans on platelet adhesiveness and aggregation.

Scan. J. Clin. Lab. Invest., 20, 17-23.

145. Silver, D., (1968).

An evaluation of dextran in the prevention and treatment of thrombosis.

Acta. Chir. Scand., Suppl. 387, 69-72.

146. Gelin, L.E., Ingelman, B., (1961).

Rheomacrodex - a new dextran solution for rheological treatment of impaired capillary flow.

Acta. Chir. Scand., 122, 294-302.

147. Kockenberg, L.J.L.,
(1962).
Experimental use of Macrodex as a prophylaxis against postoperative thromboembolism.
Bull. Soc. Int. Chir., 21, 501-512.

148. Sawyer, R.B.,
(1968).
Clinical experiences with dextran treatment.
Acta. Chir. Scand., Suppl. 387, 58-60.

149. Elsner-Mackey, P., Ledermair, O., Shostok, H., Vinazzer, H.,
(1969).
Zur wirkung von Macrodex auf die postoperative Thrombo-emboliefrekvenz.
Wien. Med. Wschr., 119, 149-153.

150. Hartshorn, J.W.S., Teale, S.N., Faiz, M.,
(1969).
Dextran 75 and postoperative phlebitis.
Arch. Surg., 98, 694-697.

151. London, D., Crosfill, M.L.,
(1969).
The effect of dextran 70 on postoperative deep venous thrombosis.
Brit. J. Clin. Pract., 23, 158-160.

152. Atik, M., Harkess, J.W., Wichman, H.,
(1970).
Prevention of fatal pulmonary embolism.
Surg. Gynec. Obstet., 130, 403-413.

153. Evarts, C.M., Feil, E.L.,
(1970).
The influences of low molecular - weight dextran on venous thrombosis following elective hip surgery.
Tenth Multidiscipline Research Forum of the American Medical Association.
J.A.M.A., 212, 872.

154. Lambie, J.M., Barber, D.C., Dhall, D.P., Matheson, N.A.,
(1970).
Dextran 70 in prophylaxis of postoperative venous thrombosis.
Brit. Med. J., 2, 144-145.

155. Stadil, F.,
(1970).
Prevention of venous thrombosis. (Letters.).
Lancet, 2, 50.

156. Rapport om läkemedsbiverkningar,
(1969).
Dextran och anafylaktoid reaktion.
Läkartidningen, 66, 1964-1965.

157. Frandoli, G., Spreafico, P.L.,
(1972).
Action on fibrinolysis and platelet aggregation of a synthetic heparin-like sulfated polyanion (SP 54). Given orally and parenterally, as related to lipidic fractions.
Arzneim-Forsch. (Drug Res.), 22, 759-763.

158. Kraft, E.,
(1962).

Treatment of phlebothrombosis and embolism by activating endogenous fibrinolysis.

Dtsch. med. Wschr., 45, 2299-2304.

159. Carter, A.E., Eban, R.,
(1971).

Prevention of postoperative deep venous thrombosis and pulmonary embolism.

Brit. Med. J., 1, 312-314.

160. Knisely, N.H., Strathman-Thomas, W.K., Eliot, T.S.,
(1941).

J.A.M.A., 116, 2430.

161. Madow, B.P.M.,
(1960).

Use of antimalarial drugs as "desludging" agents in vascular disease processes.

J.A.M.A., 172, 1630-1633.

161A. Browse, N.L., Hall, J.H.,
(1969).

Effect of dipyridamole on the incidence of clinically detectable deep vein thrombosis.

Lancet, 2, 718-720.

162. Report of the Steering Committee of a Trial sponsored by the Medical Research Council,
(1972).

Effect of Aspirin on postoperative venous thrombosis.

Lancet, 2, 441-444.

163. Chakrabarti, R., Hocking, E.D., Fearnley, G.R., (1969).

Reaction pattern to three stresses, electroplexy, surgery and myocardial infarction; of fibrinolysis and plasma fibrinogen.

J. Clin. Path., 22, 659-662.

164. Fearnley, G.R., Chakrabarti, R., (1968).

Effect of ethyloestrenol combined with phenformin or with metformin on platelet stickiness and serum-cholestrol in patients with occlusive vascular disease.

Lancet, 2, 1004-1007.

165. Brown, I.K., Downie, R.J., Haggart, B., Littler, J., Murray, G.H., Robb, P.M., Santer, G.H., (1971).

Pharmacological stimulation of fibrinolytic activity in the surgical patient.

Lancet, 1, 774-776.

166. Metropolitan Life Insurance Company Statistical Bulletin Nov . Dec. 1959.

40, and.

Dublin, L.I., Marks, H.H., (1958).

Life Insurance and Medicine.

Chapt. 24. Springfield I ll: Charles C. Thomas.

167. Society of Actuaries, (1959).

BUILD AND BLOOD PRESSURE STUDY.

Chicago, Vol. 1., 16.

168. Kakkar, V.V., Howe, C.T., Nicolaides, A.N., (1970).

Deep vein thrombosis of the leg : Is there a "high risk" group ?

Amer. J. Surg., 120, 527-530.

169. Friend, J.R., Kakkar, V.V., (1972).

THROMBOEMBOLISM : DIAGNOSIS AND TREATMENT.

The proceedings of a symposium held at King's College Hospital, London.

Editors V.V. Kakkar, A.J. Jouhar.

Deep vein thrombosis in obstetric and gynaecological patients.

1st Ed. Edin. & London. Churchhill, Livingstone., pg. 131-138.

170. Miller, G.A., Sutton, G.C., (1970).

Acute massive pulmonary embolism. Clinical and haemodynamic findings in 23 patients studied by cardiac catheterization and pulmonary arteriography.

Brit. Heart J., 32, 518-523.

171. Murray, J.G., (1971).

Chapt. 11. Management of deep vein thrombosis.

MODERN TRENDS IN SURGERY 3.

Edit. W.T. Irvine.

London, Butterworth, 198,

172. Kakkar, V.V., Howe, C.T., Flanc, C., Clarke, M.B., (1969).
Natural history of postoperative deep vein thrombosis.
Lancet, 2, 230-232.

173. Mavor, G.E., (1971).
Surgery of deep vein thrombosis.
Brit. J. Hosp. Med., 6, 755-764.

174. Mavor, G.E., Galloway, J.M.D., (1967).
Collaterals of the deep venous circulation of the lower limb.
Surgery, Gynec, Obstet., 125, 561-571.

175. Mavor, G.E., Galloway, J.M.D., (1969).
Iliofemoral venous thrombosis. Pathological considerations and surgical management.
Brit. J. Surg., 56, 45-59.

176. Barker, W.F., (1959).
The management of venous thrombosis and pulmonary embolism.
Surgery, 45, 198-203.

177. Donaldson, G.A., Linton, R.R., Rodkey, G.V., (1961).
A twenty-year survey of thromboembolism at the Massachusetts General Hospital, 1932-1959.
New Engl. J. Med., 265, 208-214.

178. Thorner, R.M., Remein, Q.R.,
(1961).

PUBLIC HEALTH SERVICE.

Publ. No. 846., Washington D.C.,
U.S. Government Printing Office.

179. Walsh, J.J., Tribe, C.R.,
(1965).

Phlebothrombosis and pulmonary embolism in paraplegia.

Paraplegia, 3, 209-213.

180. Cheschire, D.J.E.,
(1968).

The complete and centralized treatment of paraplegia :
A report on the spinal injuries centre for Victoria,
Australia.

Paraplegia, 6, 59-73.

181. Watson, N.,
(1968).

Venous thrombosis and pulmonary embolism in spinal cord
injury.

Paraplegia., 6, 113-121.

182. Silver, J.R., Moulton, A.,
(1970).

Prophylactic anticoagulant therapy against pulmonary emboli
in acute paraplegia.

Brit. Med. J., 2, 338-340.

183. Warlow, C., Ogston, D., Douglas, A.S.,
(1972).

Venous thrombosis following strokes.

Brit. Med. J., 1, 1305-1306.

184. Starzl, T.E.,
(1964).
EXPERIENCE IN RENAL TRANSPLANTATION.
1st Ed., Philadelphia, Saunders. 117 & 121.

185. Clarke, S.D., Kennedy, J.A., Hewitt, J.C., Mc Evoy, J., Mc Geown, M.G., Nelson, S.D.,
(1970).
Successful removal of thrombus from a renal vein after renal transplantation.
Brit. Med. J., 1, 154-156.

186. Salzman, E.W., Harris, W.H., de Sanctis, R.W.,
(1966).
Anticoagulation for prevention of thromboembolism following fractures of the hip.
New Engl. J. Med., 275, 122-130.

187. Brisman, R., Parks, L.C., Haller, J.A.,
(1971).
Dextran prophylaxis in surgery.
Ann. Surg., 174, 137-141.

188. Williams, W.J., Beutler, E., Erslev, A.J., Rundles, R.W.,
(1972).
HEMATOLOGY.
New York,
Mc Graw-Hill Book Co., 1st Ed., 1086,

189. Henk, W., Nebosis, G.,
(1968).
Untersuchung über den Einfluss eines Pentosanpolysulfoesters aus Blutgerinnung und Fibrondyse.
Wiener Klin. Wschr., 80, 191-194.

190. Fitzgerald, D.E., Szeto, I.L.F., Spero, J., Lewis, J.H., (1967).

Regression of preformed intravascular thrombi by SP 54 induced thrombolysis.

Thromb. Diath. Haem. 3/4, 418-422.

191. Schwartz, J., Bloch, R., Warter, J., (1962).

Trial of a new heparinoid.

Ann. Biol. Clin., 20, 1031-1035.

192. Brunaud, M., Segal, V., Ravold, J., Raveux, R., (1971).

Prog. Biochem. Pharmacol., 3, 393.

193. Bicher, H.I., (1970).

Anti-thrombotic effect of a heparin-like substance (SP 54) preventing red cell and platelet aggregation.

Arzneimittelforschung., 20, 379-381.

194. Mathies, H., Willms, D., (1965).

Vergleichende Untersuchungen der Einwirkung von Heparin und SP 54 auc das Farbstoff-Hyaluronidase-Spreading.

Med. Mschr. 19, 38-39.

195. Bohn, R., Kalbhen, D.A., (1971).

Der Einfluss von Pentosanpolysulfat auf die experimentell durch Kaolin ausgelöste E Entzündung in Rattenpfoten.

Arzneim - Forsch., 21, 1227-1230.

23 JUL 1973

196. Noristan Lab. (PTY) Ltd., Silverton, Pretoria, Manufacturers, South Africa.

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