SPECIAL ARTICLE

Deep Vein Thrombosis
Detection and Prevention

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VENOUS THROMBOSIS and pulmonary embolism are serious hazards after surgery and trauma, in childbirth, and in a variety of medical conditions, including cardiac failure and infarction. It has been estimated that approximately 21,000 patients die each year from this cause in the United Kingdom; the figures for the United States range between 47,000 and 142,000.1,2 Apart from the immediate risk to life, one must also consider the late sequelae of this disease — swelling of the legs, varicose veins, ulceration, and other trophic changes which represent an equally distressing condition.

Recently there has also been a greater awareness of the ubiquity of thromboembolic disease and of the possibility that we are experiencing an absolute as well as a relative increase in its occurrence. The deaths recorded in the Registrar General’s Report for England and Wales between 1943 and 1959 indicate that there has been an almost sixfold increase in mortality due to pulmonary embolism during this period.3 These findings clearly indicate that if this “epidemic” of deaths from pulmonary embolism is to be effectively controlled then the disease must be detected at an early stage when treatment may be effective or — an even better approach — a simple method of prophylaxis which is successful in the total elimination of this condition should be investigated. The recent developments that have taken place in the field of detection and prevention of venous thromboembolism are reviewed very briefly in this paper.

Detection of Deep Vein Thrombosis

In the past it has been difficult to diagnose this condition precisely because of the lack of a simple, accurate, and quick screening test which could be used to investigate large numbers of patients. It has been shown that clinical examination alone is not satisfactory for screening purposes since at best only 50% of thrombi are detected, and in up to 30% of patients with positive clinical diagnosis of deep vein thrombosis, the veins are in fact normal.4 During the last few years, a number of sensitive techniques have been developed for confirming the presence or absence of thrombosis. These include the radioactive fibrinogen test, the ultrasonic method, and electrical impedance plethysmography.

Radioactive Fibrinogen Test

The concept of using isotopes in the detection of venous thrombi was first introduced by Ambrus and others in 1959,5 when they produced radioactive thrombi in experimental animals by injecting 131I-labeled fibrinogen followed by thrombin into artificially-occluded vessel segments. Previously, McFarlane had shown that iodinated proteins are degraded at the same rate as corresponding unlabeled proteins.6 This led to the notion that fibrinogen labeled with radioactive iodine should behave in the same manner as the endogenous fibrinogen, with normal conversion to fibrin under the action of thrombin. This hypothesis was first tested by Hobbs and Davies7 in experimental animals, clearly demonstrating a preferential uptake of 131I-labeled fibrinogen by a forming thrombus and suggesting that this finding might form the basis of a valuable clinical test for the detection of early venous thrombi.

In 1964, Palko, Nanson, and Fedoruk confirmed the
early observations of Hobbs and Davies in experimental animals and in man. These workers extended their experience of the technique to 75 patients. However, they did not confirm their observations by venography and there were many defects in the test: the apparatus employed was heavy, cumbersome, and expensive and skilled staff were needed to obtain accurate results. Also, the isotope $^{131}$I used in their study had many disadvantages. In 1965, Atkins and Hawkins introduced the isotope $^{125}$I as an alternative to $^{131}$I for labeling fibrinogen because of its many advantages. This allowed considerable simplification of the test and portable equipment was subsequently developed which could be used at the patient’s bedside.

This test can be used in every type of patient: surgical, orthopedic, obstetric, and medical. The details of the technique have been described in a recent review. Its accuracy in detecting thrombi has now been confirmed by several workers. It is apparent that there is remarkably close agreement between the $^{125}$I-fibrinogen technique and phlebography. Similar findings have also been observed in postmortem studies. Of 1750 patients investigated by us, 42 have died during the postoperative period; the radioactive counts over the calf were increased in each of these patients. At postmortem examination, thrombi were found in the tibial and soleal veins and histology performed on the thrombi showed that they were all present before death. The radioactivity per gram of the thrombi was between five and fifty times that of an equivalent weight of blood taken from the patient. However, the test is of no value for detecting thrombi in the pelvic veins. Diagnosis by this method depends on a sufficient difference between the radioactivity in the thrombus and its surrounding background. In the pelvis, the proximity of the bladder containing radioactive urine or large arteries and other vascular structures give an increased background count which makes the test less reliable in these situations.

Some conditions produce high levels of leg radioactivity in the absence of deep venous thrombosis. These include superficial thrombophlebitis, hematomas, healing wounds and fractures, ulceration, cellulitis, arthritis, and gross edema. Care is required in the interpretation of radioactive counts in the presence of these conditions.

The introduction of this relatively simple test for the accurate detection of venous thrombi during life has provided a useful tool for objective assessment of the incidence of this disease. It has now become apparent that this condition occurs much more frequently (table 2) than realized previously. Postoperative deep venous thrombosis has been detected in between 17 and 66% of patients and it has been found that about 50% of thromboses detected begin during, or within a few hours of operation. Following fracture of the femoral neck, the incidence has been reported as 74% by Wood and his colleagues and 54% by Field and his coworkers. In contrast, the low figure of 3% has been obtained for puerperal women. Among medical patients the incidence following myocardial infarction has been found to lie between 19 and 37% (Bennett PN, Rawles JM, Warlow CP, Terry G, Kenmure ACF, Ogston W, and Douglas AS, unpublished observations, 1972). In the paralyzed leg of patients with a recent cerebrovascular accident, we have found an incidence of 60%.

The test has also been used to confirm diagnosis in patients who presented with clinical signs suggestive of deep vein thrombosis. A positive result is obtained only if a thrombus is still forming, however; once thrombi are fully established, the test may be negative. Although a negative result was obtained in one sixth of the limbs, the radioactive test was successful in diagnosing thrombosis in the majority of cases. In our studies, it proved to be a valuable diagnostic tool, particularly in those patients with minor clinical signs because it was in this group that

### Table 1

**Correlation of Venographic Findings with the $^{125}$I-Fibrinogen Test in Reported Series**

<table>
<thead>
<tr>
<th>Study</th>
<th>Detected by $^{125}$I-Fib. test</th>
<th>Confirmed by venography</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flanc, Kakkar and Clarke (1968)</td>
<td>18</td>
<td>17</td>
<td>94%</td>
</tr>
<tr>
<td>Negus and others (1968)</td>
<td>28</td>
<td>26</td>
<td>93%</td>
</tr>
<tr>
<td>Kakkar, Howe, Flanc and Clarke (1969)</td>
<td>40</td>
<td>39</td>
<td>97%</td>
</tr>
<tr>
<td>Lambie and others (1970)</td>
<td>44</td>
<td>40</td>
<td>89%</td>
</tr>
<tr>
<td>Pinto (1970)</td>
<td>22</td>
<td>20</td>
<td>90%</td>
</tr>
<tr>
<td>Kakkar (1972)</td>
<td>36</td>
<td>32</td>
<td>88%</td>
</tr>
<tr>
<td>Milne, Griffiths, Gunn and Buckley (1971)</td>
<td>18</td>
<td>18</td>
<td>100%</td>
</tr>
<tr>
<td>Bonnar and Walsh (1972)</td>
<td>15</td>
<td>15</td>
<td>100%</td>
</tr>
<tr>
<td>Hume and Gurewich (1972)</td>
<td>12</td>
<td>10</td>
<td>93%</td>
</tr>
</tbody>
</table>

_Circulation, Volume 51, January 1975_
Table 2
Incidence of Deep Venous Thrombosis (DVT) Detected by the 111I-Fibrinogen Test in Various Groups of Patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. studied</th>
<th>% Developed DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical patients (over 40 years)</td>
<td>1084</td>
<td>25</td>
</tr>
<tr>
<td>Urological (prostatectomy)</td>
<td>95</td>
<td>27</td>
</tr>
<tr>
<td>Gynecological (hysterectomy)</td>
<td>126</td>
<td>18</td>
</tr>
<tr>
<td>Orthopedic (fracture of femoral neck)</td>
<td>150</td>
<td>50</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>127</td>
<td>27</td>
</tr>
<tr>
<td>Geriatric (chronic medical illness)</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>Obstetric (postpartum)</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>1752</td>
<td></td>
</tr>
</tbody>
</table>

clinical diagnosis was most fallible. There is a further advantage of using this test in such patients: when the test is positive, it provides a simple method of assessing the effectiveness of treatment. By observing the change in radioactivity at the site of a thrombus, it is possible to tell whether the thrombus is extending, remaining stationary, or being lysed.

The test has also proved to be of great value in research since it is the only objective method for detecting early and forming thrombi, thus enabling accurate assessment to be made in studies of treatment and prophylaxis of this condition.

Ultrasonic Method

The development of the transcutaneous Doppler flowmeter by Rushmer and his colleagues provided a simple and noninvasive technique for assessing flow in the vessels. The flowmeter was based on the principle that when a beam of ultrasound is reflected from a moving object its frequency is altered according to the rate at which the object is moving, owing to the Doppler effect. In the bloodstream, the particles act as reflectors so that the frequency of an ultrasound beam, passing through a moving column of blood, is altered according to the rate of flow. This changed frequency can be either recorded on paper or amplified into an audible signal. Strandness et al. were the first to suggest the use of ultrasound for the diagnosis of venous disease.

In practice, a transducer composed of two ceramic crystals set adjacent and usually at a slight angle to each other is placed over the femoral vein. One crystal transmits the sound and the other receives back the scattered signal. Venous flow is indicated by sound while in obstruction there is silence. Sigel and his colleagues have shown that if a squeeze is applied to the leg distal to the transducer, along the line of the major vein, augmentation of venous flow occurs and a loud clear sound is heard. This they have termed as the augmented wave or "A" wave. The presence of an "A" wave indicates patency of the vein between the site of squeezing hard and that of the transducer, while its absence indicates occlusion. It is essential to squeeze the leg gently in order to avoid sudden detachment of fresh thrombi. In some patients gentle compression of the calf muscles may not be possible because of tenderness. Use of a calf squeezer has been advocated by Evans as an alternative to hand compression. A cuff is applied to the leg, with the proximal border at the level of the tibial tuberosity, and rapidly inflated to a known pressure. This has been claimed to produce less discomfort and helps to eliminate occasional false positive results.

The ultrasonic technique is the simplest of all the methods available but has many limitations. Although it is a quick and extremely simple way of detecting complete occlusion of the popliteal, femoral or iliac veins, the test may be negative in the presence of early thrombi which often propagate along these veins without producing any significant obstruction. Thrombi in the muscular veins of the calf and thigh may also not be detected because they do not alter the flow in major veins. In addition, flow in large collaterals or in a very large superficial vein will produce a sound similar to that produced by flow in a patent femoral vein.

The ultrasonic technique has been suggested by Evans and his colleagues as a method of choice for routine screening of patients confined to bed. However, in their survey of 121 patients who were supposed to have a positive diagnosis, only 31 were confirmed as having venous occlusion on reexamination. In the other 90, errors in technique and positioning of patients were found to account mainly for the difficulties in assessment. In a recent study of a fairly large number of patients in whom venography confirmed the presence of thrombi, there was positive correlation with the ultrasonic findings in only 65% of the cases.

Electrical Impedance Plethysmography

Plethysmography has been used quite extensively for investigating venous abnormalities. Wheeler and his colleagues were the first to use electrical impedance plethysmography to establish the diagnosis of deep vein thrombosis. They showed that sustained deep inspiration impeded venous return from the legs, probably by increasing intra-abdominal pressure and partially constricting the inferior vena cava. Blood was trapped in the calf and calf blood volume rose; with expiration, venous return from the limb was resumed, and consequently, blood volume in the limbs was diminished. These respiratory fluctuations in calf blood volume can easily be measured with an electrical impedance plethysmograph. Wheeler quan-
titated these impedance changes to detect venous thrombosis. He found that an impedance change of less than 0.2% in the first ten seconds after expiration was diagnostic of venous obstruction. The details of his technique have been published elsewhere.

Wheeler’s technique, however, has many shortcomings and often produces false negative results. Its main limitation is that it depends on the patient’s ability to sustain deep inspiration long enough to cause pooling of blood in the deep veins of the legs and produce measurable impedance changes. Several workers have now shown that about 30% of patients are unable to take a deep breath or sustain it long enough because of post-laparotomy pain, pleuritic chest pain, or apprehension, and consequently, volume measurements are impossible. Wheeler’s original technique has recently been modified to overcome this difficulty. An inflatable thigh pressure cuff is used to trap venous blood and allow measurement of the maximum rate of venous emptying. When the deep veins are patent, the calf volume rises quickly after thigh cuff inflation, and with deflation, the calf volume rapidly returns to baseline level. In the presence of deep vein thrombosis and obstruction to venous outflow, calf volume slowly returns to normal.

Even with these recent modifications, the technique still has certain limitations; results may be unreliable if the patient is unable to lie flat, is in severe congestive cardiac failure, or has peripheral arterial occlusion. Thrombi confined to the tibial or muscular veins of the calf are easily overlooked.

Comments

In considering the practical value of a method for detecting deep vein thrombosis, distinction must be made between its suitability as a routine screening procedure for asymptomatic occult thrombi, which have been shown to occur quite frequently, and its suitability for confirming the presence of established deep vein thrombosis. None of the methods available at present is perfect and each has its advantages and disadvantages.

There is no doubt that venography permits accurate localization of all thrombi of clinical importance. A number of improved venographic techniques have recently been described by several authors. Although each of these has been claimed by its exponents to be superior, they are in essence all based on a similar principle of watching almost continuously the filling of the deep veins of the legs with contrast medium, exposing films at the correct time, and thus allowing more precise diagnosis than ever before as to whether a thrombus is present or not.

Even with the recent modifications in technique, however, it is doubtful if venography will ever become widely used as a screening procedure to investigate large numbers of high risk patients. The techniques are cumbersome, time-consuming, involve a modest radiation, can at times cause considerable discomfort to the patient and require specially-trained personnel to produce good quality X-rays.

Despite these disadvantages, venography is the single most useful investigation available for confirming the diagnosis in a patient suspected of having this disease. It not only confirms the diagnosis, it also provides valuable information as to the exact site, extent, and nature of the thrombus, which can be of considerable help in deciding the best possible treatment. It also gives the only available baseline to use for validating other noninvasive diagnostic tools now being developed as screening tests.

Of all available tests, the radioactive fibrinogen test is the most suitable for screening a large number of patients at risk of developing deep vein thrombosis. It is accurate, quick, and simple; using this method of screening, it is possible to select those patients who need treatment and it can also be used to confirm diagnosis in a patient suspected of having the disease. It has, however, the disadvantage of a 6–24 hour delay before the counts are of diagnostic value. Occasionally the results may be equivocal and the test has certain disadvantages and limitations.

The failure of this test to detect iliac vein thrombosis is clearly a disadvantage but it is of little clinical significance since thrombi rarely start in this region and it is unusual for thrombosis to occur in the thigh or pelvis without concurrent lesions in the calf veins.

The second disadvantage is that this test carries a risk of serum hepatitis because of the administration of fibrinogen. This risk, however, can be minimized or eliminated by taking special precautions in the preparation of the fibrinogen. This should be obtained from a small pool of donors — usually less than five — who have donated blood for at least five previous transfusions without clinical evidence of viral hepatitis occurring in the recipients in the succeeding six months; also, each batch should be screened for the presence of Australian Antigen. In our present studies, this type of fibrinogen has been used in over 2,000 patients and not a single case of clinical serum hepatitis has occurred.

The only real disadvantage of the test concerns the manpower required to carry it out. Since in every hospital there are large numbers of patients at risk of developing deep vein thrombosis, it would seem impossible to screen each and every one by this method. If it is not possible to screen every patient, the test should at least be used in those who are at a greater risk of developing deep vein thrombosis — in other
words, the high risk group. The ultrasonic method and electrical impedance plethysmography are noninvasive, safe, and simple to perform. They are useful for establishing the diagnosis of thrombus in major veins. Of the two, the ultrasonic technique seems to be less reliable since it may easily fail to detect those dangerous, partially-occluding thrombi likely to produce major pulmonary embolism. To a large extent, this limitation can be overcome by using the modified form of impedance plethysmography which can readily detect nonocclusive thrombi in the iliac, femoral, or popliteal veins. Neither the ultrasonic method nor impedance plethysmography are a substitute for the proven value of the radioactive fibrinogen test for screening high risk patients or for venography for confirming the diagnosis of established thrombus.

Prophylaxis

As already mentioned, the radioactive fibrinogen test has clearly demonstrated that deep vein thrombosis occurs much more frequently than had been realized previously. These findings make it mandatory for a simple and effective method of prophylaxis to be developed.

In spite of the efforts of many workers over the past 90 years or so to develop an effective prophylaxis against venous thromboembolism, the methods employed today are empirical and not totally effective. This has been due to two main difficulties: first, the lack of essential knowledge concerning the nature of the "trigger" mechanism which initiates thrombosis in the legs; and second, the absence of sensitive and accurate techniques for measuring with precision the effects of prophylaxis. To some extent, this second difficulty has now been overcome; by using the I\textsuperscript{131}I-labeled fibrinogen test, it is possible to determine the true incidence of this disease and the effectiveness of a specific regime of prevention can be judged with greater accuracy. The main attempts to prevent deep vein thrombosis can be conveniently divided into two main groups: those directed toward elimination of stasis in the deep veins and those employed to counteract changes in blood coagulability.

Elimination of Stasis

Despite general agreement that stasis plays a significant role in the pathogenesis of venous thrombosis and despite increasing awareness of the hazards of bed-rest, there is conflicting evidence as to the efficacy of early ambulation in reducing the incidence of deep vein thrombosis. Flanc, Kakkar and Clarke\textsuperscript{a} showed that attempts directed at preventing stasis, including physiotherapy, would only marginally reduce the occurrence of thrombosis. In this trial, patients' legs were elevated before, during, and after operation; damage to the leg veins was avoided by using special sorob-rubber pads to prevent pressure on the calves; very strict supervision was exercised over postoperative physiotherapy and special care was taken to insure early ambulation. Despite all these precautions, there was still a 24% incidence of thrombosis in the test group.

More specific attempts have now been made to prevent stasis during surgery and several methods have recently been investigated for increasing venous return from the lower limbs. One of these is electrical stimulation of the calf muscles during operation: two electrodes are applied to the calf and a low voltage current is used to contract the muscles every 2–4 seconds. The beneficial results of this method of preventing stasis and thus reducing thrombosis, first reported by Doran, Drury and Sivyer in 1964,\textsuperscript{46} have now been investigated by several other workers, using the radioactive fibrinogen test for assessment.

Another method, pneumatic compression of the calves (Hill and others)\textsuperscript{46} involves encasing the legs in an envelope of plastic material and rhythmically altering the pressure to squeeze the calf muscles and increase venous return. In practice, an electric pump inflates each legging alternately so that compression at 40–45 mm Hg for 1 min is achieved, followed by relaxation for 1 min. The advantage of this method is that it can be used not only during surgery but also in the postoperative period.

The third method which has been investigated consists of passive plantar and dorsiflexion of the foot during operation by means of motor-driven pedals, again increasing blood flow.\textsuperscript{47} The results of some of the studies using these different methods are shown in table 3. In each study the radioactive fibrinogen test was used to detect the presence of deep vein thrombosis. There is little doubt that all these methods lessen stasis and lower the incidence of venous thrombosis, except in "high risk" patients undergoing operation for malignant disease. However, such physical methods present almost insuperable difficulties as a long-term solution: they must be applied to both legs; during certain types of operation — for example, fractured neck of femur and where the patient is in the lithotomy position — they are either impracticable or extremely inconvenient. These prophylactic measures must be applied not only during operation but at regular intervals for the first ten postoperative days and perhaps even longer. Some of the methods are uncomfortable for conscious patients, and above all, the logistical problem of applying such physical measures on a large scale would strain the resources of even the most lavishly-equipped hospital. Experience with less complicated regimens of inten-
DEEP VEIN THROMBOSIS

Table 3

Prophylaxis: Effect of Elimination of Stasis on the Incidence of Postoperative Deep Venous Thrombus (DVT) as Detected by the 11H-Fibrinogen Test

<table>
<thead>
<tr>
<th>Study</th>
<th>Control group</th>
<th>Treated group</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. studied</td>
<td>DVT</td>
<td>No. studied</td>
</tr>
<tr>
<td>Electrical stimulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of calf muscles</td>
<td>110 limbs</td>
<td>23 (20.9%)</td>
<td>110 limbs</td>
</tr>
<tr>
<td>(Browse and Negus, 1970)73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumatic compression</td>
<td>16 pts</td>
<td>8 (50%)</td>
<td>9 pts</td>
</tr>
<tr>
<td>of the calves</td>
<td>34 pts</td>
<td>7 (21%)†</td>
<td>41 pts</td>
</tr>
<tr>
<td>(Hills and others, 1972)66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive flexion of</td>
<td>47 limbs</td>
<td>13 (27.6%)</td>
<td>47 limbs</td>
</tr>
<tr>
<td>calf muscles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Sabri, Roberts and Cotton, 1971)47</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients with malignant disease.
†Patients without malignant disease.
‡Sequential analysis — the line of significance corresponds to a probability level of 5%.

...prophylaxis supports this view. Thus, physical methods are unlikely to be the choice for the future.

Anticoagulant Therapy

A large number of papers has recently been published claiming success or otherwise with various types of drug therapy: their results are summarized in table 4. Analysis of this data clearly shows a great deal of confusion because, in the majority of studies, clinical methods were used to assess the effectiveness of the agent used. The evidence that drugs such as aspirin and dipyridamole, known to interfere with platelet function, effectively reduce the incidence of deep vein thrombosis is unconvincing and these agents should probably not be used for the prophylaxis of venous thrombosis. However, the role of dextran is still uncertain and its efficacy in reducing the incidence of fatal pulmonary embolism remains to be determined. There is no doubt that drugs which are known to enhance naturally-occurring fibrinolytic activity — such as phenformin and ethyloestranol — are totally ineffective in preventing deep vein thrombosis in surgical patients (table 5).

Oral anticoagulant therapy, properly employed (starting before operation or immediately after admission to hospital), is the most effective and proved method of preventing venous thrombosis. However, the disadvantages of oral anticoagulants are the risk of hemorrhage and the need for strict laboratory control have undoubtedly contributed to the relatively limited acceptance of this form of prophylaxis among surgeons in general — at least in the USA and the United Kingdom.

A form of drug therapy which is both effective and without the drawbacks of oral anticoagulant therapy would therefore meet a real need. Ideally, any agent used for the prophylaxis of deep vein thrombosis should be well tolerated by the patient, be devoid of...

Table 4

Prophylaxis: Drugs Which Affect Platelet Function and the Incidence of Postoperative Deep Vein Thrombosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic technique</th>
<th>Incidence of DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control group</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Clinical</td>
<td>23/67 (34%)</td>
</tr>
<tr>
<td>Salaman, William and De Sanetis (1971)49</td>
<td>11H-fib. test</td>
<td>32/150 (22%)</td>
</tr>
<tr>
<td>M.R.C. (1972)34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextran</td>
<td>Clinical</td>
<td>13/25 (52%)</td>
</tr>
<tr>
<td>Johnson, Bygdeman and Eliasson (1967)74</td>
<td>Clinical/autopsy</td>
<td>59/600 (9.8%)</td>
</tr>
<tr>
<td>Atik77</td>
<td>Clinical/autopsy</td>
<td>14/90 (15.3%)</td>
</tr>
<tr>
<td>Brisman, Parks and Hailer (1971)95</td>
<td>Clinical/autopsy</td>
<td>14/40 (35%)</td>
</tr>
<tr>
<td>Kakkar (1973)46</td>
<td>11H-fib. test</td>
<td>15/140 (10.7%)</td>
</tr>
<tr>
<td>Bonnar and Walsh (1972)33</td>
<td>11H-fib. test</td>
<td></td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Clinical</td>
<td>7/334 (2.1%)</td>
</tr>
<tr>
<td>Browse and Hall (1969)74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Circulation, Volume 51, January 1975
Table 5

Phenformin and Ethyloestranol in the Prevention of Postoperative Venous Thrombosis*

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients over 40 + major operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
</tr>
<tr>
<td>No DVT</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>DVT</td>
<td>5 (11%)</td>
<td>5 (10%)</td>
</tr>
</tbody>
</table>

*Fossard et al., 1974.66

Group I = Placebo.
Group II = Phenformin + Ethyloestranol.

side effects, require no special monitoring and produce no bleeding in a clinical situation where the patient is subjected to trauma. One promising approach is the use of low-dose heparin given subcutaneously, a regimen which has been claimed to prevent thrombosis without increasing the risk of bleeding. Such proposals are not new. For many years there have been suggestions that small doses of heparin after surgery reduce the incidence of postoperative thrombosis.51, 52, 53 More than a decade ago, Sharnoff et al.44 suggest that low-dose heparin administered before, during, and after surgery may be effective in preventing postoperative thromboembolism. The regimen he recommended consisted of the administration of 10,000 IU of heparin subcutaneously at midnight prior to surgery; in his view, this dose provided an anticoagulant effect lasting approximately 12 hours. If surgery extended beyond this period, the coagulation time was determined, and if "critically short," additional heparin (rarely more than 2,500 IU) was administered subcutaneously during operation. At the completion of the operation, the coagulation time was repeated and usually 2,500 IU of heparin were administered subcutaneously every six hours until the patient was fully active or discharged. The findings of an uncontrolled study, published in 1970, suggested that this regimen was effective in preventing fatal pulmonary embolism. However, it had several drawbacks: it was not a randomly-allocated, controlled trial, and the results were therefore not suitable for statistical analysis. Secondly, with the regimen recommended by Dr. Sharnoff, the amount of heparin to be administered every six hours had to be tailored in accordance with the whole blood clotting time. It is obvious that such a regimen would be impractical as a wide scale practice.

The effectiveness of a standard regimen of subcutaneous heparin (table 6) in the prophylaxis of deep vein thrombosis was investigated by Kakkar et al.55 in 53 consecutive patients over the age of 50 undergoing inguinal hernia repair. The regimen employed consisted of 5,000 IU of heparin administered subcutaneously, starting two hours prior to surgery. This time interval for the initial heparin injection was selected because the findings of a quantitative and sensitive assay for heparin showed that it took 30 min for heparin in this dose to become demonstrable in the plasma and it reached a peak within two hours. This would allow for the heparin effect to be at its height prior to the operative incision. Deep vein thrombosis was detected, by means of the 125I-fibrinogen test, in seven (26%) of the control patients, while this was significantly reduced (4%) in 26 similar patients who received heparin. There was no unusual operative or postoperative bleeding.

Using the 125I-fibrinogen test, William56 assessed the efficacy of the Sharnoff regimen in 56 patients over the age of 50, subjected to major abdominal surgery (table 6). A 41% incidence of deep vein thrombosis in the

Table 6

Prophylaxis: Effect of Low Doses of Heparin on the Incidence of Postoperative Deep Venous Thrombosis (DVT) as Assessed in Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Control group</th>
<th>Treated group</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. studied</td>
<td>DVT</td>
<td>No. studied</td>
</tr>
<tr>
<td>Kakkar, Field and others (1971)</td>
<td>27</td>
<td>7 (26%)</td>
<td>26</td>
</tr>
<tr>
<td>Williams (1971)</td>
<td>29</td>
<td>12 (41%)</td>
<td>27</td>
</tr>
<tr>
<td>Gordon-Smith and others (1972)</td>
<td>50</td>
<td>21 (42%)</td>
<td>52</td>
</tr>
<tr>
<td>Kakkar, Corrigan and others (1972)</td>
<td>39</td>
<td>17 (42%)</td>
<td>39</td>
</tr>
<tr>
<td>Nicolaides, Dupont and others (1972)</td>
<td>122</td>
<td>29 (24%)</td>
<td>122</td>
</tr>
<tr>
<td>Gallus and others (1973)</td>
<td>118</td>
<td>19 (16%)</td>
<td>108</td>
</tr>
</tbody>
</table>

* A trial comparing two different regimens.
† Double-blind randomly allocated trial.
control group was reduced to 15% in the heparin-treated patients; all four patients in the heparin group who developed thrombi were from a group of seven patients subjected to prostatectomy.

Gordon-Smith et al.,⁵ using the ¹²⁵I-fibrinogen test and heparin prophylaxis in a manner similar to that of Kakkar, divided 161 patients over the age of 40, admitted for major elective surgery, into three groups in a prospective, randomized trial. Group 1 received no heparin and had a 41% incidence of deep vein thrombosis; group 2 received only three 12-hourly doses of 5,000 IU of heparin subcutaneously, starting before surgery, and had a 13.5% incidence of thrombosis; group 3, given 5,000 IU of heparin every 12 hours starting before operation and continued for five days, had an 8.3% incidence of venous thrombosis. Groups 2 and 3, both separately and together, had a significantly lower incidence of positive scans than the control group, but the difference between the two heparin-treated groups was not statistically significant.

In a second study by Kakkar and his associates,⁶ low-dose heparin was evaluated in 261 patients, divided into three groups. A prospective, double-blind, randomized trial was carried out in 78 patients over the age of 40 who were subjected to major elective abdominal, pelvic, and orthopedic surgery. The regimen of heparin prophylaxis employed consisted of 5,000 IU subcutaneously, begun two hours preoperatively and continued every 12 hours for seven days. The frequency of deep vein thrombosis was 42% in the 39 control patients and 8% in the 39 patients receiving heparin. None of the 78 patients developed pulmonary emboli. The same heparin regimen was also administered to another group of 133 consecutive patients over the age of 40 who had major elective surgery (table 6). The over-all incidence of deep vein thrombosis in this group was 9.7%. The results were less encouraging in patients undergoing total hip replacement: 4 (27%) of 15 such patients developed thrombosis. Similarly, the results were also unsatisfactory in 50 patients subjected to emergency surgery for fractures of the femoral neck. In this group, all patients received heparin and the incidence of thrombosis was 40%. In the entire series of 226 “at risk” patients, however, only one patient had clinically recognized emboli which proved fatal, and in the five other deaths, no pulmonary emboli were found at necropsy.

Nicolaides et al.⁷ also investigated the effectiveness of Kakkar’s heparin prophylaxis regimen in 251 surgical patients over the age of 40 undergoing major abdominal and thoracic surgery. The 24% incidence of deep vein thrombosis in the control group was reduced to 0.8% in the heparin-treated patients. In addition, heparin prophylaxis also reduced the frequency of the dangerous extending thrombi, which are often responsible for pulmonary emboli, from 7.4% to nil.

Similarly, Ballard et al.⁸ studied the effect of prophylactic heparin in 110 patients undergoing major gynecological operations who were randomly assigned to two equal groups. The treated patients were given 5,000 IU of heparin subcutaneously 1 to 2 hours before operation and every 12 hours thereafter for seven days. There was no significant increase in operative and postoperative bleeding in the heparin-treated patients and only two out of the 55 patients in this group developed deep vein thrombosis, compared with 16 patients in the comparable control group. The difference in the incidence of isotopic deep vein thrombosis was highly significant (P < 0.001).

Finally, Gallus et al.⁹ modified Kakkar’s regimen by giving 5,000 IU two hours before surgery and then repeating this dose three times rather than twice daily, beginning 8–10 hours after the preoperative dose. In 226 patients undergoing major elective surgery, they reduced the incidence of deep vein thrombosis from 16% to 2%. In 46 patients with hip fractures, heparin treatment also reduced a 48% incidence of deep venous thrombosis to 13%. Clinically significant bleeding was not increased in heparin-treated surgical patients, though the blood requirements of transfused patients were moderately increased and treated patients had a slightly lower postoperative hematocrit. In addition, the blood requirements of transfused patients were moderately increased following elective abdomino-thoracic surgery, by a mean amount of 518 ml. While Gallus and his colleagues did not regard increased bleeding as a major problem on a regimen of 5,000 IU three times a day, it is likely that the amount of heparin used is the maximum that can be given to surgical patients without significant hemorrhagic complications.

In nearly 1,200 patients entered in seven trials — most of them randomized — the incidence of deep vein thrombosis in those treated with low-dose heparin was significantly lower than in the control patients. Despite the heterogeneity of the patients and the varied nature of the surgery, the prophylactic effectiveness of low-dose heparin was such that the over-all incidence of deep vein thrombosis was three times higher in the untreated patients. This success was achieved with a more or less standard dose of heparin (10,000 or 15,000 IU per day) and without significant hemorrhagic complications. The fact that a standard regimen is not totally effective and that it is not yet certain that preventing postoperative isotopic deep vein thrombosis will also prevent death from pulmonary embolism should not detract from recogni-
tion of the highly significant advance in the prophylaxis of postoperative venous thrombosis that these studies collectively represent.

The failure of low-dose heparin in the prophylaxis of deep vein thrombosis among patients undergoing hip surgery (particularly total hip replacement) was disappointing (table 7). However, this result could have been anticipated; in traumatic operations of this magnitude, the stimulus to intravascular coagulation in terms of tissue damage (especially the release of intra-medullary fat and the elaboration of activated clotting factors that may be absorbed into the circulation) must be considerable. It would seem reasonable to suggest that failure of heparin prophylaxis in these patients may be due to the inadequacy of the dose schedule used.

It is interesting to note that low doses (10,000 IU daily) as used by Kakkar et al. also failed to protect patients subjected to emergency operations for fracture of the femoral neck. However, Gallus et al., who gave a 50% higher dose of heparin (15,000 IU a day instead of 10,000 IU) succeeded in reducing postoperative deep vein thrombosis in this group of patients to 15% compared with a control incidence of 48%. Our observations and those of others (Dechavanne M, Ville D, Viala JJ, Kher A, Faivre J, et al. Controlled trial of platelet anti-aggregating agents and subcutaneous heparin in prevention of postoperative deep vein thrombosis, unpublished observations) also indicate a schedule of 5,000 IU of heparin three times a day is much more effective in protecting patients undergoing total hip replacement. Excessive bleeding has not been observed with this regimen though different findings have been reported by Hume et al. These recent observations tend to indicate that when the coagulation sequence has already been activated beyond the stage of thrombin genera-

tion (as happens in patients with hip fractures before heparin prophylaxis is started) or when the stimulus to thrombin generation is overwhelming, 5,000 IU of heparin every 12 hours represents inadequate prophylactic therapy. However, when neither of these conditions is present, a b.i.d. regimen of low-dose heparin represents for the surgeon "... an antithrombotic approach tailor-made for primary care for patients subjected to operation, comparable in safety to penicillin prophylaxis for rheumatic fever or to a vaccine to prevent poliomyelitis, whereby thousands of individuals can be treated to prevent a single patient fatality."

The question that arises is — is low-dose heparin prophylaxis much more effective than other drugs which have already been claimed to be highly effective in preventing fatal pulmonary embolism? Most recent trials already published or still in progress are directed toward answering this question. In a recent prospective trial reported from the Netherlands, 50 patients were given low-dose heparin and another 50 patients were given an oral anticoagulant (Sintrom) following mainly abdominal surgery (table 8). The incidence of deep vein thrombosis, as diagnosed by the 125I-fibrinogen test, was 2% in the heparin group and 18% in the oral anticoagulant group. The unexpectedly high incidence of thrombosis in patients receiving oral anticoagulants may be due to the fact that therapy was started after surgery. Our studies of the natural history of postoperative deep vein thrombosis have shown that most thrombi detected by the radioactive fibrinogen test become manifest within the first 1–2 postoperative days, and as oral anticoagulants take longer than that for an antithrombotic effect to be achieved, it is not surprising that the incidence of deep vein thrombosis was so high in these patients. A true comparison must await the results of

<table>
<thead>
<tr>
<th>Table 7</th>
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<tbody>
<tr>
<td>Incidence of Deep Vein Thrombosis (DVT) with Different Regimens of Low-dose Heparin in Patients Undergoing Total Hip Replacement</td>
</tr>
<tr>
<td>Study                      </td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Kakkar et al. (1972)</td>
</tr>
<tr>
<td>Kakkar et al. (1974)</td>
</tr>
<tr>
<td>Nicolaides et al. (1974)</td>
</tr>
<tr>
<td>Dechavanne et al. (1974)*</td>
</tr>
</tbody>
</table>

randomized, controlled trials where oral anticoagulants are administered for 36-48 hours before surgery.

In another randomly-allocated recent trial, the efficacy of low-dose heparin was compared with Dextran-70 infusion (table 9) begun before surgery and continued during the first three postoperative days. 67 Of the 382 patients included in this study, 130 acted as controls, 126 received heparin and a further 126 received dextran infusion. Computer analysis showed that the three groups were well-matched so far as factors likely to influence the incidence of deep vein thrombosis are concerned. The incidence of thrombosis in the control group was 37%, in those receiving 5,000 IU of heparin twice a day it was 12%, and in those receiving Dextran-70 infusion, 25%.

The efficacy of low-dose heparin has also been compared with agents known to affect platelet function (Dechavanne et al., unpublished observations). Sixty patients over the age of 50, undergoing Charnley-Muller total hip replacement for osteo-arthritis, were randomly allocated to a control group, a group that received a combination of 150 mg of dipyridamole and 1.5 gm of acetyl salicylic acid per day, and a third group receiving 5,000 IU of calcium heparin (Calciparine, Laboratoire Choay), two hours before surgery every 12 hours for the first 48 hours, and subsequently, every eight hours for the next eight postoperative days. In the control group, 12 (40%) developed deep vein thrombosis while the incidence of thrombosis in those receiving dipyridamole was 5%; in those receiving dipyridamole and acetyl salicylic acid, it was 50%. The differences observed were statistically significant (table 10). Excessive blood loss during surgery was not observed in any of the patients.

Analysis of recently-published studies indicates that low-dose heparin prophylaxis fails to protect only approximately 10% of patients undergoing major surgery. Can these findings be taken as evidence that low-dose heparin prophylaxis will prevent postoperative pulmonary emboli, and in turn, death? Further analysis of these trials fails to provide an unequivocal answer to this question. The incidence of fatal and nonfatal pulmonary embolism is known to be low. Accordingly, a patient population of many thousands would be required for a prospective, multicenter, randomized trial to establish the prophylactic value of low-dose heparin in the prevention of postoperative pulmonary embolism: such a trial is now in progress.

In this trial, patients over the age of 40, undergoing major elective surgery, are being randomly allocated to a control or treated group. To date, 3,500 patients have been admitted to the trial, 1,800 in the control group and 1,700 in the treated group. Computer analysis has shown that the two groups are well matched for age, sex, presence of malignancy, type of operation performed, and other factors likely to influence the incidence of thrombo-embolism. In the control group 11 patients had massive fatal pulmonary embolism, while one of the patients in the heparin group died due to extensive emboli. These early results in a limited number of patients suggest that the regimen of low-dose heparin prophylaxis investigated may be effective in preventing fatal pulmonary embolism in surgical patients.

Data from trials already reported or still in progress has raised important ethical problems: in the future, is it justifiable to withhold a form of prophylaxis which

**Table 8**

<table>
<thead>
<tr>
<th>Oral anticoagulants</th>
<th>50</th>
<th>9 (18%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>50</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis.

**Table 9**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of pts studied</th>
<th>Developed DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>130</td>
<td>48 (37%)</td>
</tr>
<tr>
<td>Heparin</td>
<td>126</td>
<td>15 (12%)</td>
</tr>
<tr>
<td>Dextran-70</td>
<td>126</td>
<td>31 (25%)</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis.

**Table 10**

<table>
<thead>
<tr>
<th>Control</th>
<th>8 (40%)</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin + Dipyridamole</td>
<td>10 (50%)</td>
<td>10</td>
</tr>
<tr>
<td>Heparin</td>
<td>1 (5%)</td>
<td>19</td>
</tr>
</tbody>
</table>

Control vs. heparin: P < 0.025.
Control vs. aspirin + dipyridamole: NS.
Heparin vs. aspirin + dipyridamole: P < 0.010.

has been shown to be quite safe and effective? What should be the role of a practicing physician — should he await the outcome of these trials or has sufficient information already been collected to justify the recommendation of low-dose heparin prophylaxis for general use?

Published evidence and clinical experience now indicate that low-dose heparin prophylaxis be recommended as primary prevention for all adults who are subjected to major abdominal, pelvic, or thoracic but not, as yet, orthopedic surgery. A standard regimen fulfills most of the criteria demanded of an ideal prophylactic agent: it is well tolerated by the patient, is free of side effects and requires no monitoring other than that the patient receives the drug appropriately, and finally, does not produce excessive bleeding when the patient is subjected to major tissue trauma.

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DEEP VEIN THROMBOSIS

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