A SEGMENTAL APPROACH
TO THE
PROBLEMS OF VENOUS THROMBOEMBOLISM

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The work contained in this Thesis is my own, except that the haematological estimations carried out on patients on fibrinolytic drugs was carried out by Dr. D. Ogston and Dr. N.B. Bennett. I was, however, responsible for the management of these patients. Many of the patients in the earlier series were operated on by Mr. G.E. Mavor and Mr. W. Michie, but the review and analysis of the results in these cases was carried out by me.

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ABSTRACT OF THESIS

Many problems in the management of venous thromboembolism remain unsolved because there has been a failure to undertake adequate study of the correlation of clinical and pathological events, and to determine the natural history and prognosis of the disease against which the results of treatment may be measured.

This thesis is based on study of a large series of cases of venous thromboembolism in which the pattern of venous involvement was determined by venography and/or surgical exploration. From the results of this study it is concluded that a segmental concept of venous thromboembolism is fundamental to the understanding of the clinical manifestations and to a rational approach to the many problems that are encountered.

The study demonstrates the arrangements of the collateral circulation which determine the varying clinical picture with venous occlusion at different levels in the deep venous system. The collateral circulation to the femoro-popliteal segment is always adequate and venous insufficiency does not result. In the iliofemoral segment, the collateral arrangements are inadequate and venous insufficiency results.

Contrary to popular belief thrombosis in the iliofemoral venous segment is frequently primary not secondary to propagation from the lower leg. Thrombosis of the upper segment is not only the most important type of thrombosis in regard to leg morbidity but is the common source of major pulmonary embolism. On the basis of the results of these studies a rational approach to treatment is proposed, emphasis being placed on the importance of venography in diagnosis and management.

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The problems of the management of venous thromboembolism remain largely unsolved. These problems have been obscured for more than a quarter of a century by the illusion of safety created by the anticoagulant drugs. These drugs, despite their undeniable value in prophylaxis, have failed to fulfill their early promise as a therapeutic measure, in that they do not prevent embolism in a significant number of cases and that they have no influence on leg morbidity.

The idea that anticoagulants were a panacea for all forms of venous thromboembolic disease has delayed study of the correlation of clinical and pathological events. Such correlation is essential if a rational approach to management is to be found, because the results of treatment are meaningful only against a background of the natural history and prognosis of the disease.

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The study is presented in six sections:

(1) A historical review.

(2) An anatomical and venographic study of the collateral arrangements of the deep venous system of the lower limb and their influence on acute and chronic symptoms of venous occlusion.

(3) A study of the clinical pathology of venous thromboembolism.
INTRODUCTION

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emphasis being placed on the importance of venography in diagnosis and management.

(4) The results and problems of management by surgery and fibrinolytic therapy are discussed.

(5) An experimental study of venous reconstruction with autogenous vein, and consideration of the indications for venous reconstruction in chronic venous insufficiency.

(6) Summary and conclusions.
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Interest in the disease increased in the 17th century and full-blown phlegmasia dolens was described in detail (Wissmann, 1676). The early accounts were of cases complicating pregnancy. Perhaps the exclusion of doctors from the practice of midwifery, the restricted nature of surgery and the high septic rate had prevented earlier study of the disease. Wissmann did not speculate about the causes of the condition and although apparently familiar with thrombosis in crisis, did not relate the two. At this time the humoral theory was current and it was thought that the acutely swollen limb in relation to pregnancy was due to an uncleaned constriction of lochia in the posterior ax. Constitutional effects were ascribed to the retained placenta. Fages (1789) attributed the condition to an excess of milk accumulating in the lower limbs.

This state of confusion and mystique persisted until Davis presented his classic account of the Prominent Cause of the Disease called Phlegmasia Dolens to the Medical and Chirurgical Society of London in 1829.

He examined the veins of the lower limb at post-mortem of 5 patients who had died from phlegmasia dolens following parturition. His description of the pathological findings is detailed and has probably not been improved upon since. He proposed the diagnosis could be made by the appearance of the limb:

"The left lower extremity presented an uniform edematous enlargement, without any external discoloration from hip to foot..."
Historical Review

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"The left lower extremity presented an uniform oedematous enlargement, without any external discolouration from hip to
foot. This was found, on further examination, to proceed from the ordinary anasarous effusion into the cellular substance. The inguinal glands were a little enlarged, as they usually are in a dropsical limb; but pale coloured, and free from the slightest sign of inflammation. The femoral vein from the ham upwards, the external iliac and the common iliac veins as far as the junction of the latter, with the corresponding trunk of the right side, were distended and firmly plugged with what appeared externally a coagulum of blood. The femoral portion of the vein, slightly thickened in its coats, and of a deep red colour, was filled with a firm blood coagulum closely adhering to the sides of the tube, so that it could not be drawn out. As the red colour of the vein might have been caused by the red clot everywhere in close contact with it, it cannot be deemed a proof of inflammation. The trunk of the profunda was distended in the same way as that of the femoral vein; but the saphena and its branches were empty and healthy. The substance filling the external iliac and common iliac portions of the vein was like the laminated coagulum of an aneurismal sac, at least with a very slight mixture of red particles. The tube was completely obstructed by this matter, more intimately connected to its surface than in the femoral vein; adhering, indeed, as firmly as the coagulum does to any part of an old aneurismal sac. But in its centre there was a cavity containing about a tea-spoonful of a thick fluid of the
consistence of pus of a light brownish red tint, and pultaceous appearance. That the substance occupying the upper part of the venous trunk, and the fluid in its central cavity had been deposited there during life from inflammation of the vessel does not admit of doubt. I am also decidedly of the opinion, in consequence of its firmness and close adhesion to the vein, that the red coagulum in the femoral vein was the result of a similar affection extending along the tube; and that the passage of blood through it in the whole tract submitted to examination, must have been completely obstructed before death."

Elsewhere in his essay David clearly describes pulmonary embolism both clinically and pathologically although he did not appreciate the condition in that in Case IV he says,

"During the gradual development of the succedding hot fit, she experienced a pain on the left side of the chest which increased rapidly in intensity." The episode being accompanied by rapid pulse and general distress and restlessness. "In the evening of the sameday, unequivocal symptoms of phlegmasia dolens declared themselves."

At autopsy:

"The pleura costalis of the left thoracic cavity was found slightly inflammed, and lined in two or three places with a delicate tunic or lymph. There was also an effusion of about six ounces of a nearly transparent serosity into the
cavity itself. The lung of the same side was of a dark red hue. The right cavity of the chest and its contents were healthy."

It is likely that yet another of his cases died of massive pulmonary embolism, because:

"Her death took place instantaneously, whilst in the act of changing the recumbent for a sitting position, in the expression of a little merriment at the expense of something ludicrous which her waiting woman had said to her."

Of the clinical presentation Davis pointed out that it had frequently been observed that groin pain preceded swelling.

"Further I have myself met some cases where the pain first and most complained of has been in the calf of the leg or some other inferior part of the affected extremity; but in all such cases I have also found, that upon application of the gentlest pressure to the corresponding groin and iliac region, the patient has instantly flinched from the touch."

With the increase in range and number of surgical procedures which followed the advent of antiseptic and later aseptic techniques post-operative deep vein thrombosis assumed increasing importance. Pulmonary embolism was recognised by Spenser Wells in 1866. With improvement in the control of the inflammatory and metabolic complications of surgery, pulmonary embolism has accounted for an increasing proportion of post-operative deaths and has become the single most feared condition for the surgeon.
By 1924 when Aschoff delivered his famous lectures the concept of femoral and iliac venous thrombosis with or without pulmonary embolism, was well established. He pointed out that fatal emboli virtually always arose from this area and that these vessels were the only ones of sufficient size to give rise to such large emboli. He showed that the tributaries of the internal iliac vein, though frequently the site of thrombosis, could not be the source of major embolism.

With more careful autopsy studies it became apparent that thrombosis of the deep veins of the calf was a common occurrence, more common that thrombosis of the femoral or iliac veins (Frykholm, 1940). At the same time it became increasingly apparent that pulmonary embolism, fatal and non-fatal, was frequently unaccompanied by signs of venous thrombosis in the form of phlegmasia dolens. Homans (1934) described 4 cases where the earliest signs indicated thrombosis in the veins of the calf and where embolism subsequently developed, being fatal in two instances. He suggested that thrombosis beginning in the calf veins propagated as a "free floating thrombosis" into the popliteal and femoral vein, and that detachment of this floating thrombus resulted in embolism. He proposed that ligation of the femoral vein below the entrance of the saphenous vein was a sound therapeutic measure. The venographic studies of Bauer (1940) supported this idea of proximal propagation of calf vein thrombosis and this has remained the accepted theory until the present time.

With this concept of the development of D.V.T. and the encouraging reports of the use of anticoagulants by Craaford (1939), Jorpes (1939) and Bauer (1940), increasing attention was paid to early signs in the calves in the post-operative period and increasing evidence of the efficacy of
anticoagulant drugs was presented. So great was the enthusiasm that any calf discomfort in the post-partum or post-operative period represented a D.V.T. and was treated with anticoagulants. Many patients were consequently erroneously diagnosed as having a deep vein thrombosis and the efficacy of such treatment became exaggerated.

Because of the failure of anticoagulants to control embolism in a significant number of cases venous interruption has been extensively practiced in the United States of America. Due to uncertainty of preventing embolism by interruption at other levels, the inferior vena cava has become the site of choice. Unfortunately leg morbidity is severe after vena cava ligation (Dale, 1958), and the early hopes that partial interruption or plication might avoid it (DeWeese and Hunter, 1963) are unfortunately not being maintained (De Meester et al., 1967).

More recently attention has been focused on the importance of the iliofemoral venous segment in thrombo-embolism by the pathological studies of McLachlin and Paterson (1951), Gibbs (1957) and Sevitt (1959). Gibbs showed that calf vein thrombosis was a common event, its incidence increasing with age and duration of bed rest, so that it was present in 75 - 80% of patients who were confined to bed for two weeks or more. All of these workers showed, however, that although calf vein thrombosis was more common, iliofemoral thrombosis was more important in that it gave rise more frequently to symptoms and was the source of most major emboli.

When thrombosis involves major vessels like the femoral and iliac veins surgical removal of the thrombus is a justifiable means of attempting to relieve symptoms and prevent embolism. This operation of venous thrombectomy was first performed by Schepelmann in 1910, but although used by a few workers
in France and Germany, it has never been popular.

The work of Sevitt and Gallagher (1959) showed that prophylactic anticoagulants can prevent venous thrombosis and embolism. They were concerned specifically with lower limb fractures where haematoma formation, although troublesome, is not dangerous. This does not obtain after intra-abdominal procedures, or where there has been extensive retroperitoneal dissection so that general surgeons have not adopted their methods.

Despite these recent advances the position for the average practitioner is unchanged from that in 1954 when DeBakey wrote:-

"...... few conditions in medicine have been subjected to so much analysis with so little elucidation" so that "the problem remains practically as baffling to-day as it has been during the past 50 years. Whereas many factors have undoubtedly contributed to this continuing state of confusion, the most important ones are concerned with the lack of precise knowledge about the aetiology and pathogenesis of the disease, its protean, clinical and pathological manifestations and the difficulties in establishing an accurate diagnosis."

It is hoped that the work contained in this thesis will reduce this confusion.
COLLATERALS OF THE DEEP VENOUS CIRCULATION OF THE LOWER LIMBS

"The tedious process for the establishment of a new and circuitous circulation is an evil of great and almost inscrutable magnitude." - Davis 1922.

The difficulties in diagnosis of deep venous thrombosis are a direct consequence of failure to correlate clinical findings with the underlying pathology. The clinical effects of deep venous occlusion are obviously related to the extent and location of the obstruction, and depend on the capabilities of the collateral circulation provided by existing alternative venous pathways. Despite this, knowledge of these collateral venous channels is lacking and current text book descriptions of the venous anatomy of the lower limb are incomplete and inaccurate.

The standard description of the venous system of the lower limb is that the venae comitantes of the three arteries of the leg, the anterior and posterior tibial and the peroneal, enter the popliteal fossa to form the popliteal vein. This vein runs with its companion artery to the hiatus in the adductor magnus to become continuous with the femoral vein. The latter extends to the inguinal ligament then becoming the external iliac vein. The profunda femoris vein is described as originating from muscle veins and running with its companion artery to end in the femoral vein in the femoral triangle. The description of the profunda vein is usually sketchy and tends to suggest that it is a small minor tributary of the femoral vein. Lact's Textbook of Anatomy especially written for the surgeon in training has no description of this vein. The presence of venae comitantes of the popliteal and femoral arteries is not mentioned.
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The standard description of the deep veins of the lower limb is that the venae comitantes of the three arteries of the leg, the anterior and posterior tibial and the peroneal, unite at the lower end of the popliteal fossa to form the popliteal vein. This vein runs with its companion artery to the hiatus in the adductor magnus to become continuous with the femoral vein. The latter extends to the inguinal ligament there becoming the external iliac vein. The profunda femoris vein is described as originating from muscle veins and running with its companion artery to end in the femoral vein in the femoral triangle. The description of the profunda vein is usually sketchy and tends to suggest that it is a small minor tributary of the femoral vein. Last's Textbook of Anatomy especially written for the surgeon in training has no description of this vein. The presence of venae comitantes of the popliteal and femoral arteries is not mentioned. The
impression thus created is that the popliteal and femoral veins are the only veins draining the lower leg, and other veins which may on occasion serve as collaterals are not described.

At surgical exploration of the femoral vessels it is apparent that the profunda femoris vein is a vessel of considerable size, not infrequently almost as large as the femoral. For this reason surgeons have preferred the term the superficial femoral vein for the deep vein from the adductor hiatus to its junction with the profunda, corresponding to the surgical terminology of the arteries, the profunda being considered as a separate major vessel. Secondly, venae comitantes of the femoral artery are apparent on surgical exploration. These are generally small but present in most instances, and with numerous cross connecting channels. Depending on their peripheral connections these two systems, the profunda vein and the venae comitantes of the popliteal and femoral arteries, may act as collateral channels for the femoro-popliteal segment.

In an attempt to assess the importance of the collateral venous system in the presence of venous interruption or occlusion at different sites in the main deep veins of the lower limb, anatomical and venographic studies have been made and the clinical implications of the findings investigated.

Certain terms which lack anatomical precision have attained general acceptance in the literature of thromboembolic disease and clearer definition is required. In particular this applies to the term "pelvic veins" which while not anatomical still finds present-day usage (B.M.J. 1966a, 1966b, and Richards, 1966a). Aschoff (1924) described venous thrombosis as occurring in the femoral vein and to a lesser extent in the external and common iliac veins. He showed that the tributaries of the hypogastric (internal iliac)
vein though frequently the site of thrombosis were not a significant source of embolism, and that as thrombosis occurred so frequently in the absence of embolism their co-existence was insufficient evidence of origin. Sevitt showed that the internal iliac vein itself was rarely the site of thrombosis and virtually never the source of embolism (Sevitt and Gallagher, 1961).

The term "pelvic veins" is therefore vague and confusing and if iliac venous involvement is being described, the phrase "iliofemoral" (or upper) segment is more precise.

As will be seen there are strong anatomical, pathological and clinical reasons for regarding the deep vein as two segments and new descriptive terms have been introduced which are used throughout this study. The term "upper or high or iliofemoral segment" refers to the deep vein above the termination of the profunda femoris, i.e. the common femoral, external iliac and common iliac in continuity. The term "lower or peripheral segment" refers to the deep veins below the termination of profunda, more especially the popliteal—superficial femoral vein.

The results in the present study are considered in the light of this segmental concept, and are presented in two parts: firstly, an anatomical demonstration of collaterals in relation to the lower segment, and secondly venographic demonstrations of collateral channels in relation to both upper and lower segments.

Anatomical Study

The collateral venous channels of the lower segment were studied in dissections carried out on 22 limbs. Special attention was paid to:

(a) Connection of the profunda femoris vein with the veins of the popliteal fossa.
(b) Presence of popliteal and femoral venae comitantes and their level of termination.

For the profunda femoris vein to act as a collateral to the femoropopliteal segment it must have a connection, direct or indirect, with the veins of the popliteal fossa (i.e. the popliteal vein or the venae comitantes of the popliteal artery). If the venae comitantes of the popliteal and femoral arteries are to act as significant collaterals of the lower segment they must communicate with each other and the femoral venae comitantes must empty into the upper part of this segment or even higher. The results, therefore, were tabulated under 3 headings (Table I and II) dealing with these separate points.

1. Connections of the profunda femoris vein with the veins of the popliteal fossa.

2. Communication between the venae comitantes of the popliteal and femoral arteries.

3. Level of termination of the venae comitantes of the femoral artery.

Results

The profunda femoris vein has a direct communication with the popliteal vein in 38% of cases and in a further 48% via one of the latter's tributaries (Table II). Thus in 86% of cases the profunda vein is a potential bypass collateral to the femoro-popliteal or lower segment. In 3 cases there was no connection between the popliteal and profunda veins, but in 2 of these there was a communication between the venae comitantes of the popliteal artery and the profunda (Table I limbs 22 R and 30 R). Thus in only 1 leg (5%) the profunda had no connection with the venous plexus of
the popliteal fossa and was incapable of acting as a collateral channel to the lower segment.

Venae comitantes of the popliteal and femoral arteries were found in every case. The exact origin of the venae comitantes of the popliteal artery is not certain. They arise from a variable plexus of veins at the level of the two heads of the gastrocnemius and in a number of cases, probably most, have connections with the venae comitantes of the posterior tibial artery. In 86% of cases the venae comitantes of the popliteal artery communicated with those of the femoral (Table II). In one of the three legs where this connection was not found the venae comitantes of the popliteal artery communicated with the profunda vein (Table I limb 22 R), so that in all but 2 cases (11%) the venae comitantes of the popliteal artery were involved in a collateral system to the femoro-popliteal segment. In 89% of cases in which the information was available the venae comitantes ended above half way to the profunda termination (Table II). In two of these they did not communicate with the venae comitantes of the popliteal artery and therefore did not form a bypass of the lower segment. However, in 78% of cases this connection did exist and therefore the venae comitantes constituted a bypass from the lower leg to the proximal part of the superficial femoral vein or higher. In these cases the venae comitantes terminated usually near the profunda termination or less rarely in the profunda. In only 2 limbs (11%) did the bypass extend beyond the profunda termination (Table II).

In every limb there was a bypass of the femoro-popliteal segment. In 80% there were two alternative bypasses and in 2 cases (11%) there were three separate routes. These considerations do not include the long
saphenous system which provided a constant long bypass because of its communications with deep veins above and below the knee.

These collaterals have been represented diagrammatically in Figures 1B and 2B, where they are compared with classical pictures of the deep venous system (Figures 1A and 2A).

**VENOGRAPHIC PATTERNS OF VENOUS COLLATERALS OF THE LOWER LIMB**

Because of difficulty in interpretation the value of venography has not been apparent in the study of venous occlusion, and conclusions based on venographic evidence tend to be viewed with suspicion. These difficulties are, however, less apparent above the knee, where the vessels visualised can be accurately correlated with those found on dissection.

Two venographic techniques have been employed, namely ascending functional venography without a tourniquet and direct femoral venography. In the first, injection via the saphenous vein at the ankle is carried out and serial films taken following calf pumping exercises. This gives good filling of the lower and upper deep venous segments. The second technique involves direct femoral vein puncture just below the inguinal ligament for visualisation of the upper or iliofemoral segment.

The present information is extracted from a series of 334 cases of deep venous thrombosis, 206 of which had venographic studies carried out. Many of these patients had venous thrombectomies of the upper segment carried out, some followed by ligation and division of the femoral vein just distal to the profunda termination. Venographic studies were undertaken in early and late postoperative assessment.
Lower Segment Collaterals

The venous collaterals which are regularly demonstrated on venography in the presence of lower segment venous occlusion are the profunda femoris vein, the venae comitantes of popliteal and femoral arteries, and the long saphenous vein. The profunda femoris vein is regularly the major collateral channel of the lower segment (Figs. 3 and 4). It extends from the popliteal fossa to its termination in the femoral vein about the level of the lesser trochanter (Fig. 5). Although visualised in the majority of normal venograms it is smaller and its connection with the popliteal fossa less distinct than in the presence of superficial femoral vein occlusion.

The venae comitantes of the popliteal and femoral arteries show considerable enlargement (Figs. 3, 4, 5 and 6), with numerous cross communications which is typical of venae comitantes (Figs. 3, 5 and 11). They extend from the popliteal fossa to about the level of the profunda termination. Alternatively they may terminate in the profunda vein (Fig. 3), the common femoral vein (Figs. 4 and 5), or more rarely the external iliac, or common iliac veins.

The other major collateral of the lower segment is the long saphenous vein (Figs. 5 and 11). Its distal connection with the main deep channel is not shown, but is via one or more of the perforating or communicating veins below the lower limit of the occlusion. The extent to which it acts as a collateral varies with the size and efficiency of the deep collaterals (c.f. Figs. 4 and 5).

These collateral channels are all markedly enlarged when compared with their size in the normal limb. They are also more direct and linear. It is of importance that even in the presence of such marked enlargement the
valves may remain competent (Fig. 4).

The extent to which each collateral enlarges varies in individual cases. With the passage of time the number of collaterals decreases, and the ones which remain become large and direct, so much so that in the case of the venae comitantes they may well be mistaken for the original main channel or a "recanalised" main channel (Figs. 4 and 6).

The collaterals illustrated appear adequate and competent venographically. These patients had no venous insufficiency of the poor collateral circulation type (vide infra), i.e. they had clinically adequate venous collateral circulation.

Upper Segment Collaterals

The collaterals of the upper segment (Fig. 7) can be divided into two groups.

1. Ipsilateral Collaterals
   (a) Internal iliac vein and its tributaries, notably the obturator, and cruciate anastomoses.
   (b) Ascending lumbar veins bypassing the common iliac on the same side.
   (c) Venae comitantes of the external and common iliac arteries opening into the ascending lumbar vein or inferior vena cava.
   (d) Lateral femoro-iliac circle - which is formed by anastomosis of medial femoral circumflex and deep circumflex iliac veins.
   (e) Inguino-Axillary Anastomoses.

2. Contralateral (or Crossover) Collaterals
   (a) Superficial
      (i) Scrotal/vulvar plexuses - connecting the superficial
epigastric and superficial pudendal tributaries of the long saphenous veins of each side.

(b) Visceral - bladder, prostate and broad ligament plexuses.

(c) Presacral plexus.

These crossover collaterals connect the internal iliac vein or its tributaries on the obstructed side with the internal iliac system of the other side, so that the venous drainage of one leg ultimately returns by way of the contralateral ilio-femoral segment.

The collateral vessels available in the upper segment vary with the site and extent of occlusion. In limited external iliac vein occlusion the collaterals which develop are those without crossover, but not the ascending lumbar. The bypass here is direct, involves somatic veins and is reasonably efficient. In occlusion limited to the common iliac vein the collaterals which are opened up are the crossover veins via the main trunk of the internal iliac vein and the ascending lumbar system (Figs. 8a, 9 and 10). The collateral circulation here is dependent to a large extent on poorly supported visceral veins and is inefficient. In complete iliofemoral or upper segment occlusion the only collaterals available are the crossover anastomoses involving the tributaries of the internal iliac vein, not the main trunk (Figs. 8b, 11 and 12) and the collateral circulation is therefore of small venous type and inadequate.

The lateral femoro-iliac circle (Figs. 12 and 13) though stressed as a collateral by Edwards and Robuck (1947) is a small and very indirect bypass. The openings into the main vein are only approximately 4 cms. apart, and thrombosis at this level is rarely limited to such a short segment which would be necessary for it to function as a satisfactory collateral.
The iliac venae comitantes are not often seen on venography but were found to be very large on both sides in two cases (Fig. 13). Here the venae comitantes have increased in size over a prolonged period and now provide an adequate collateral circulation. On cursory inspection these venae comitantes could easily be mistaken for recanalised and disorganised external and common iliac veins.

In all cases illustrated there was clinical venous insufficiency of the poor collateral circulation type though much less marked in the limited occlusion (Figs. 9 and 10) than in the extensive iliofemoral occlusion (Figs. 11 and 12). This venous insufficiency exists despite the opening up of the available collateral channels, and clinically affects both lower leg and thigh. It is a general rule that where there are direct collateral channels without crossover, the venous insufficiency is limited (Fig. 13), but where crossover collaterals are in evidence and venous return is via the contralateral iliofemoral venous segment, the venous insufficiency is severe, and remains so, although even in such cases there is some variation in degree, depending on whether or not direct communications to the ascending lumbar system exist.

**General Considerations**

There are, therefore, potential bypass collaterals to the lower venous segment, and the veins which provide this bypass are macroscopic veins even in the normal limb. As clearly demonstrated by Dale (1958) such collaterals are capable of enlarging to act as major channels in the presence of major vein obstruction. It has been assumed too readily and on insufficient evidence that dilatation of a vein would invariably render its valves incompetent. While this is so in collateral routes valved as venous circles
and in primary varicose veins this is not necessarily an effect of dilatation for in the former the valves must be rendered incompetent before flow will result and in the latter valvular incompetence may precede dilatation. Provided flow is in the direction determined by the valves, enlargement does not invariably result in valve incompetence as clearly demonstrated by Kelly (1950) in his classic case of radio-cephalic arterio-venous fistula (Fig. 14).

The collateral bypass to the lower segment depends on the venae comitantes and the profunda femoris vein, of which the profunda is the larger, and more important. The importance of the venae comitantes as direct collaterals, almost replacing the deep veins has probably not been realised previously. This is a very common alternative circulation in the lower segment, and in many instances in the literature, these vessels have been mistaken for recanalised deep veins. Whether or not linear or consecutive recanalisation in the deep vein over a considerable segment results in a good functional channel has never been adequately shown. In our own series of venograms amounting to nearly 500 films it has never been observed. Bauer (1940) never saw it in his venographic studies and was of the opinion that it did not occur. Studies which have claimed that it is a common phenomenon have been pathological (e.g. Edwards and Edwards, 1937) and are open to criticism in certain respects. Firstly although apparently adherent thrombus has been demonstrated on histological section it has not been shown to obstruct the venous flow. Further, although channels may be shown at several levels on section there is no proof that these are connected to form a functional channel.

Many of the collateral venous channels to the upper segment are poorly
supported, smaller and less direct than in the lower segment. In addition they are valved as venous circles, i.e. the valves drain away from the site of anastomosis (Fig. 15). For them to act as collateral channels they must dilate to a size which renders their valves incompetent. For these reasons although many collateral channels of the upper segment exist they may be functionally inadequate.

The extent of ilio-femoral occlusion has a direct influence on the availability of collateral venous channels, and consequently the severity of venous insufficiency. With complete occlusion of the upper segment, the collateral circulation is at its most indirect and inadequate with venous drainage via small superficial and visceral veins to the contralateral ilio-femoral venous segment. In this instance venous insufficiency is most severe. With limited external iliac occlusion a more direct collateral venous circulation utilising cruciate and gluteal anastomoses provides drainage into the internal iliac system of the same side. The resulting venous insufficiency is less severe. Such a limited external iliac thrombosis, however, is an uncommon clinical occurrence.

More common and more important is common iliac occlusion, where the venous collateral is partly crossover and partly via the ascending lumbar veins. The adequacy of this depends on the size and connections of the ascending lumbar vein, and where this is directly connected to the common iliac vein venous insufficiency is minimal. However there are a small number of cases (8%) where this communication does not exist (Davis, Milloy and Anson, 1958) and here venous insufficiency is more severe.

Thus the anatomical capabilities of the collateral venous circulation decreases as the site of venous obstruction becomes more proximal in the
deep vein of the lower limb. The critical level is the termination of the profund a femoris vein. The collateral reserve is adequate with thrombosis below this level, but inadequate when venous occlusion is more proximal.

For these reasons it is important always to consider in clinical cases whether deep vein thrombosis is proximal, involving the iliofemoral segment, or distal, involving the lower segment. Such considerations divide deep vein thrombosis into two groups which differ greatly in acute and late morbidity, and which in our opinion should differ greatly in regard to treatment, particularly in the acute phase. If deep vein thrombosis remains peripheral, conservative measures are adequate. In iliofemoral venous thrombosis, on the other hand, a more aggressive approach is essential if some control of early and late morbidity is to be achieved. Such an approach is of course offered by the operation of venous thrombectomy.

Post-Phlebitic Syndrome

It has long been recognised that varicose veins, lower leg skin changes and the heavy leg of venous insufficiency were related in some way to the effects of deep vein thrombosis. However, the correlation between clinical findings and the pathology of the deep venous system has not yet been clarified, and the term post-phlebitic syndrome is a general term which covers a diverse group of conditions.

Cockett and Jone (1953) demonstrated that skin changes and ulceration in the lower leg result from perforator incompetence, arising from post-thrombotic valvular damage. A high pressure venous leak into the superficial venous system results and this in turn produces secondary varicosities of the tributaries of the long saphenous vein and dilatation of the long saphenous itself. Elsewhere perforator incompetence can produce
similar changes in the superficial system and the overlying skin.

Less attention has been paid to the pattern and extent of the venous occlusion and the role of the collateral venous circulation. Where venous occlusion, in most instances due to thrombosis or surgical ligation, is limited to the lower segment, the collateral circulation is adequate, venous return good and evidence of generalised venous stasis absent. In such limited venous thrombosis the only type of venous insufficiency that can result is related to perforator damage.

The situation with iliofemoral venous thrombosis, however, is vastly different. Here, in most cases, the collateral circulation is inadequate, and particularly where the main drainage is by cross-channels the morbidity as regards the leg is severe. Varicosities of the long saphenous vein and its tributaries may develop but these are rarely marked except in the pubic region. Venous insufficiency due to inadequate collateral channels and poor drainage is always present, and symptoms of heaviness, tiredness and swelling of the lower leg and thigh are persistent. As would be expected these signs and symptoms increase with standing or sitting when the calf muscle pump is inactive and improve with exercise, particularly of the calf muscle; elevation always helps the leg and any increase in environmental heat and other factors which increase peripheral arterial flow are detrimental.

The venous tributaries of the calf, in particular the soleal plexuses are known to be the site of initial involvement in many cases of deep vein thrombosis (Murley, 1950; Cotton and Clark, 1965). This is particularly common in the elderly where the soleal sinuses are more numerous and more dilated, and occurs in 70 - 80% of patients confined to bed for two weeks
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or more (Gibbs, 1957). It is also known that after involvement of the lower segment, the thrombotic process can spread in continuity to involve the upper segment. But such a picture, originally suggested by the work of Bauer (1940), is by no means wholly representative of venous thrombosis in the lower limb and has probably been overstressed (Gibbs, 1957). In many instances the deep vein thrombosis can commence in the ilio-femoral segment, particularly on the left side, remaining restricted to this segment or subsequently spreading distally to involve the lower segment.

It is therefore possible to recognise clinically three different groups of patients with the post-phlebitic syndrome. Firstly, the patient with skin changes and ulceration or near ulceration in the lower leg, the leg itself being of normal calibre. There are no marked symptoms of aching and tiredness and no leg swelling. There are often marked secondary varicose veins in the lower limbs. Such patients have perforator damage as the result of an old peripheral or lower segment deep vein thrombosis, perhaps of very limited extent. In all instances the collateral venous circulation is adequate. The second group constitutes patients with symptoms of aching and tiredness in the limb, often marked in the calf, and with swelling of both the lower leg and thigh. The skin is intact, and secondary varicose veins are not marked. The background pathology is one of old ilio-femoral venous thrombosis with an inadequate collateral circulation. As there has been no peripheral deep vein thrombosis, the perforator veins are competent and the skin intact. A third clinical group corresponds to the end result of extensive venous thrombosis involving both lower and upper venous segments and clinically the presence of both perforator incompetence and an inadequate venous collateral circulation results in skin involvement in the lower leg and symptoms of tiredness and heaviness.
associated with swelling of the lower leg and thigh.

Summary

By means of detailed anatomical dissections and venographic studies, it has been shown that the deep venous system of the lower limb is best considered as two segments, the high or ilio-femoral segment and the low or peripheral segment, the profunda termination being the line of division, where the functional anatomical reserves of the collateral circulation and the clinical effects of venous obstruction are vastly different.

In the lower segment the potential bypasses provided by the profunda-popliteal connections, the venae comitantes of the popliteal and femoral arteries, and the long saphenous vein are direct. In the presence of obstruction these veins dilate and in time become more linear. Valvular function is frequently retained even when there is marked dilatation. This collateral circulation is always adequate so that acute and chronic venous insufficiency never results, and the only sequelae result from perforating vein incompetence, which, although distressing, is effectively managed by subfascial ligation of these vessels.

In the upper segment, in contrast, the collateral circulation depending on cross communications between the two internal iliac and two saphenous systems, is provided by poorly supported tortuous channels, and vessels valved as venous circles. It is functionally poor and even when fully developed venous insufficiency due to poor drainage results in symptoms of heaviness, tiredness and swelling of the lower leg and thigh which are persistent.
It has been shown that as a result of the collateral venous arrangement, the effects of deep venous occlusion are markedly different in the two segments of the deep venous system of the lower limb. Because it appeared that certainly widely accepted concepts regarding the site of inception and mode of propagation of deep venous thrombosis, and their clinical importance could not be substantiated by the pathological evidence available it was decided to study the major problems in the pathology of venous thrombosis, namely the site of inception and propagation of thrombosis and the production of pulmonary emboli, on this segmental basis.

The study is based on the operative findings in 399 patients; 390 patients had venous thrombectomies for iliofemoral thrombosis, 36 being bilateral, and 3 had venous ligation for peripheral venous thrombosis (Appendix I and II). The extent of the venous thrombosis and the nature of the thrombus removed were noted. On the basis of this information the site of origin and the extent of propagation were determined in these cases. Where the thrombus removed was white and laminated (Fig. 16) it was thought to have come from a site of inception of the thrombotic process, and where it consisted of fresh, coagulated blood (Fig. 17) it was considered to have resulted from propagation.

Venographic studies, by direct puncture of the femoral vein or introduction of the greater trochanter or during venous thrombectomy, were carried out in 200 cases. Throughout, emphasis has been laid on venographic demonstration of the iliocostal venous segment, and figures rela-
PATHOLOGY OF DEEP VENOUS THROMBOSIS

SITE OF ORIGIN AND PROPAGATION

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The study is based on the operative findings in 259 patients; 228 patients had venous thrombectomies for iliofemoral thrombosis, 24 being bilateral, and 31 had bilateral superficial femoral vein ligation for peripheral venous thrombosis (Appendix I and II). The extent of the venous thrombosis and the nature of the thrombus removed were noted. On the basis of this information the site of origin and the extent of propagation were determined in these cases. Where the thrombus removed was white and laminated (Fig. 16) it was thought to have come from a site of inception of the thrombotic process, and where it consisted of fresh coagulated blood (Fig. 17) it was considered to have resulted from propagation.

Venographic studies, by direct puncture of the femoral vein or intra-osseous injection of the greater trochanter or during venous thrombectomy were carried out in 200 cases. Throughout, emphasis has been laid on venographic demonstration of the iliofemoral venous segment, and figures rela-
ting to the involvement of this segment are calculated on the basis of operative and venographic findings.

Results

The distribution of thrombosis and the site of inception of the thrombotic process in the 259 patients operated on for deep venous thrombosis is shown in Table III. Although these figures are true for the site of origin of the iliofemoral venous thromboses, the number of peripheral deep vein thromboses, which remained localised to the lower segment, is artificially reduced as many of these patients were treated conservatively and are therefore excluded. Thus far fewer than 44% (24 of 55) of peripheral venous thrombosis propagated into the upper segment. However this criticism is not valid for the figures in Table IV in that these patients initially presented with pulmonary embolism without leg signs and were therefore unselected. From Table IV it is apparent that in this unselected group only 2 out of 38 (5%) of iliofemoral thromboses originated in the peripheral segment, and only 2 of 19 (11%) of peripheral venous thromboses propagated to involve the iliofemoral segment.

Discussion

Peripheral Deep Vein Thrombosis

Extensive post-mortem dissections by Gibbs and Sevitt have demonstrated the usual pattern of thrombosis in the deep veins of the leg (Gibbs, 1957; Sevitt, 1960; Sevitt and Gallagher, 1961). Sevitt has shown that there are six common sites of thrombus formation (Fig. 18), the iliac veins, the common femoral vein, the profunda termination, the popliteal vein about the adductor hiatus, the posterior tibial veins and
the soleal sinuses. Simultaneous involvement of two or more sites is common. Many observers have confirmed that the venous sinuses of the calf muscles are frequently the site of thrombus formation (Murley, 1950; Gibbs, 1957; Sevitt, 1960; Sevitt and Gallagher, 1961; Cotton and Clark, 1965). This finding in association with the venographic work of Bauer (1940) and the prophylactic value, claimed for superficial femoral vein interruption by Homans (1934), has given rise to the belief that calf vein thrombosis is of clinical importance in so far as it is the usual site of thrombus formation, and as the disease progresses propagation of the clot occurs along the deep vein, popliteal and femoral, to involve in due course the iliofemoral segment. Hence the suitability of anticoagulant therapy which is supposed to curtail this dangerous propagation and arrest the disease. However, it is surprising that it has never been adequately demonstrated that such propagation does occur; or if it does, how frequently; and whether therefore peripheral deep vein thrombosis is of clinical importance or not. Bauer's theory of proximal propagation from the peripheral segment, now so universally accepted as the usual pattern of progression, was based on one venographically illustrated case, showing a patent superficial femoral vein, and 36 hours later no visualisation of the same vein. This evidence was deduced as demonstrating proximal obliteration and propagation (Bauer, 1940). However, the iliofemoral segment was not visualised and its condition not commented on. In fact all Bauer's line drawings which illustrated venograms are limited to below the groin.

In 63 pathological examinations in which Gibbs (1957) found femoral vein thrombosis, he found conclusive proof that the thrombosis had originated there in 37.7% of instances, and discovered no case in the "act of
propagation" from the lower leg veins. Popliteal thrombosis in continuity with the leg veins was seen several times, but the thrombus did not extend beyond the adductor opening. The significance of the detailed dissections of Gibbs (1957) and Sevitt and Gallagher (1961) showing the frequent simultaneous involvement of the iliofemoral segment in the majority of cases of peripheral involvement with clinical signs has not been realised. Our experience in venous thrombectomy with removal and examination of thrombus at operation from the iliofemoral and peripheral segments has confirmed that it is usual to remove old laminated clot from the proximal segment (Figs. 16 and 17) and rare to remove such clot from superficial femoral vein (Fig. 17). In only 24 out of 252 instances of iliofemoral thrombosis did the distribution of clot suggest that propagation had occurred from peripheral to proximal segment (Table III). In 55 cases presenting with pulmonary embolism without leg signs, and therefore unselected as regards an initial site of thrombosis, evidence at surgery or from venography showed that in all but 2 of the cases which subsequently developed iliofemoral thrombosis, thrombus formation had commenced in the segment (Table IV). Although it is appreciated that the age of thrombus cannot be determined accurately by macroscopic or microscopic examination, it is possible to determine where there is white thrombus and lamination that this is from a site of initial thrombosis and has not resulted from propagation.

Furthermore, anatomical dissections show that in some legs the venous arrangements are such that there is less possibility of direct propagation along the posterior tibial and popliteal veins to the superficial femoral vein than to the profunda femoris. This is not to suppose that thrombosis may not commence about the adductor hiatus area; in fact this
is a recognised initial site (Sevitt and Gallagher, 1961). Further, venous inflow at the common femoral area via the long saphenous vein, the profunda femoris, and venae comitantes is always considerable, and diminishes the changes of propagation from peripheral to proximal segment.

Pulmonary embolism originating in the peripheral segment is not usually significant, cannot be massive and can only become serious because of the cumulative effect of repeated small emboli leading to pulmonary hypertension and right heart failure. Of 144 patients with pulmonary embolism, 7 out of 113 showing an origin in the iliofemoral segment died, while in the remaining group of 31 with embolism arising peripherally, there were no deaths (Table V). This group of peripheral venous thromboses represent the more severe cases, in that operation was reserved for those with recurring embolism. A far greater number where clinical and/or venographic evidence indicated that venous thrombosis was limited to the peripheral segments were treated conservatively and in no instance was there a fatal outcome.

The belief that the important site of deep vein thrombosis is "in the veins of the soleal muscle" (Ochsner, 1967) must be contested. The real clinical significance of diagnosing peripheral deep vein thrombosis lies in the fact that it should alert the clinician to the possibility of simultaneous iliofemoral thrombosis.

**Iliofemoral Thrombosis**

In our experience thrombosis involving the iliofemoral segment commences in the segment, and is not the result of extension from the peripheral segment. The common iliac vein is usually initially involved, the left more so that the right in a ratio of 3:1 (Table VI). The reasons for this are mainly embryological and anatomical and relate to the overlay of
the right common iliac artery on the left common iliac vein and also to abnormalities in the structure, length and course of the vein and the condition of its terminal caval orifice (McMurrich, 1906/8; Ehrich and Krumbhaar, 1943; Cockett, Thomas and Negus, 1967).

Pulmonary embolism is common as a complication of iliofemoral venous thrombosis, in two-thirds of all cases of major pulmonary embolism this segment being the site of origin of the embolus. When the right side is affected, embolism is more common, the indirect transverse lie of the left common iliac vein and the narrowing of its terminal orifice presumably having a protective effect. Embolism may be massive and fatal and may occur without leg signs, part of the "silent leg" syndrome. It is the failure to appreciate this "silent leg" syndrome, with non-occlusive iliofemoral thrombosis that has caused considerable confusion. Clinico-pathological correlation shows that deep vein thrombosis is symptom-free in the majority of cases (nearly 2 out of 3) and in most of the limbs (about 3 out of 4), even to the most watchful observer, no matter how minimal the diagnostic criteria (Sevitt and Gallagher, 1961). This high incidence of "silent" venous thrombosis is the same in cases with and without pulmonary embolism. Such "silent leg" cases may have peripheral thrombosis or non-occlusive iliofemoral thrombosis. Iliofemoral venous thrombosis is often a slow insidious process, and the stage of partial or incomplete occlusion of the vein, detectable only by venography may be present for weeks or months. Clot formation in fact may be extensive without occlusion (Sevitt and Gallagher, 1961) (Fig. 19). With such a condition the patient is obviously under severe risk of major pulmonary embolism, particularly during abdominal straining such as with difficult defaecation or micturition, which is a much
more common trigger for embolism than any peripheral muscular activity.

In many cases of pulmonary embolism without leg signs, the patient eventually develops an iliofemoral venous occlusion, the "late leg" syndrome. Of the 113 cases of iliofemoral thrombosis with pulmonary embolism, this sequence occurred in 24 or 21% of cases (Tables IV and VII). It has generally been assumed that this has resulted from the extension of silent thrombosis of the peripheral segment into the proximal segment. In our series of 55 cases presenting with pulmonary embolism without leg signs this sequence of events occurred on only 2 occasions, while in 22 instances an initially non-occlusive iliofemoral occlusion became complete (Table VII). When iliofemoral thrombosis became obstructive thrombectomy was carried out in 12% of instances before distal propagation had occurred (Table VIII) and this was demonstrated venographically in a number of instances (Figs. 20 and 21). In such circumstances there can be no doubt of the proximal inception of the occlusive thrombosis. The insidious and often prolonged non-obstructive thrombotic phase, with "silent legs" creates a further problem in regard to venous thrombectomy. It is apparent that even when iliofemoral occlusion is of recent clinical origin, old adherent thrombus may be present and to some extent this may compromise complete clearance.

At venous thrombectomy the common finding is common iliac venous occlusion with varying degrees of distal propagation, so that either the iliofemoral segment in its whole length is occluded or the iliofemoral segment together in continuity with a varying part of the peripheral segment. In the 24 instances (10% of cases) in which old clot was present in the superficial femoral vein, thrombosis may have commenced about
adductor hiatus level (Table VIII). There were also 20 cases in the series in which the initial site of thrombosis was either in the common femoral or external iliac vein.

Further evidence of the proximal inception of thrombosis is provided by study of the femoral vein at thrombectomy. The theory of peripheral onset of venous thrombosis proposed that proximal spread results because occlusive distal thrombus prevents inflow to the more proximal area and that propagation of the thrombus occurs in the resulting stagnant column. Were this the case it would be logical to expect that the thrombosed common femoral vein would be small because of this reduced inflow. The opposite is the case. At thrombectomy the femoral vein is large, frequently being as much as 3 - 4 cm. in diameter. This is in keeping with proximal occlusion, producing distension with retrograde extension into this area.

The evidence is therefore considerable that where there is extensive deep venous occlusion involving iliofemoral and peripheral segments, the initial occlusion occurs in the iliofemoral segment.

Another problem in the pathology of venous thrombosis relates to whether or not the internal iliac vein or its tributaries are the site of significant thrombosis. There is little doubt that the venous plexuses of bladder, prostate and uterus are commonly the site of thrombus formation, but there is no evidence to suggest that such clot extends into the iliofemoral segment or gives rise to significant emboli. Aschoff (1924) pointed out that the plexuses draining to the internal iliac vein, while often the site of thrombosis, could not give rise to major embolism. Sevitt and Gallagher (1961) found the internal iliac trunk to be the site of thrombosis in only 5.5% of limbs and 8.6% of patients. In iliofemoral venous thrombosis the
ipsi-lateral internal iliac system acts as the main collateral drainage and can generally be visualised by venography to be free of thrombus (Fig. 22). Furthermore, the internal iliac system is often the source of the "bleed back" at thrombectomy, which may be considerable even in the presence of common iliac occlusion (Fig. 23).
Summary

The evidence that the iliofemoral segment is not only the serious site for venous thrombosis, but also the common site of inception of such thrombosis is considerable. From a study of the thrombus removed at operation it has been shown that 90% of iliofemoral venous thromboses originate in the segment. Contrary to popular belief it is rare for a lower segment thrombosis to propagate to involve the iliofemoral segment. In a group of cases which were unselected, in that they presented with pulmonary embolism initially without evidence of venous thrombosis, only 11% of peripheral thromboses showed proximal propagation. Only 24 out of 252 iliofemoral venous thromboses commenced in this way. The femoral vein at operation is usually enlarged, commonly being 3 - 4 cm. in diameter, in keeping with proximal occlusion and distension prior to thrombosis, rather than distal occlusion and reduced inflow. Finally in 12% of cases with occlusive iliofemoral thrombosis operative and venographic findings demonstrated that thrombosis was limited to the upper segment.
THE IlioFEMORAL VENOUS SEGMENT AS A SOURCE OF PULMONARY EMBOLI

The iliofemoral segment has been shown to be the important site of inception of venous thrombosis in regard to clinical deep vein thrombosis and its significance as a source of pulmonary embolism has been referred to. It is proposed to consider this in more detail and, on the basis of the results obtained, present a rational approach to the management of this serious disease.

The source of pulmonary emboli is generally agreed to be the deep veins of the legs and to a lesser extent the veins of the pelvis and abdomen (Brig., med. J., 1966a; 1966b; Richards, 1966a). This vague description has led to considerable confusion so that it is now generally accepted that emboli arise from the veins of the calf or from tributaries of the internal iliac vein in the pelvis. Treatment is accordingly decided on this assumption.

However, it must be pointed out that calf vein thrombosis is a common pathological entity, it rarely gives rise to leg disability and the evidence that it is a common source of pulmonary embolism is not conclusive.

The venous channels of the pelvic organs are essentially the site of thrombus formation. Nevertheless, sealing at these sites, though common, is seldom followed by pulmonary embolism and the evidence that they are a significant source of embolism is incomplete. Aschoff (1924) pointed out that the internal iliac system, while often the site of thrombosis, could not give rise to major pulmonary embolism.

The fact that venous thrombosis may commence in two or more sites independently (Sewitt and Gallagher, 1961) has not been fully appreciated. Gibbs (1937) reported that although the calf veins were the commonest site
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The fact that venous thrombosis may commence in two or more sites independently (Sevitt and Gallagher, 1961) has not been fully appreciated. Gibbs (1957) reported that although the calf veins were the commonest site
of thrombosis, that most emboli originated in the thigh or iliac veins, and McLachlin and Paterson (1951) reported that 73% of thrombi began in veins of the thigh or iliac veins, and that 56% of the patients affected had an associated pulmonary embolus. Yet, despite these reports the significance of the iliofemoral segment as a site of venous thrombosis and subsequent pulmonary embolism is not fully appreciated. Richards (1966b), in fact, rejects the view that iliofemoral thrombosis takes precedence over calf vein thrombosis as a cause of pulmonary embolism.

Patients and Methods

Of the 259 patients undergoing operation for deep venous thrombosis 144 had suffered pulmonary embolism. 113 of these were treated by venous thrombectomy, often combined with superficial femoral vein ligation, the remaining 31 had superficial femoral vein ligation alone. Many of these patients (81 or 71%) had been treated at first with anticoagulants and were referred because of failure to control embolism (Table IX). Venographic studies either by direct puncture of the femoral vein at the groin or by intraosseous injection of the greater trochanter, or during venous thrombectomy, were carried out in 120 instances.

Throughout, emphasis was laid on venographic demonstration of the iliofemoral venous segment, and figures relating to the involvement of this segment were calculated on the basis of operative and venographic findings.

Results

Clinical Findings

Thrombus was present in the iliofemoral segment in 113 of the patients (78%) in whom surgical exploration of the iliofemoral vein was carried out.
At operation, the character of the thrombus removed from the proximal or iliofemoral segment and from the distal or femoro-popliteal segment was recorded. The presence of old white thrombus (Fig. 16) in the proximal segment was taken as evidence that it had originated there, rather than as a result of propagated coagulation from the distal tree, particularly when the thrombus from the distal tree consisted of fresh coagulated whole blood (Fig. 17), or where there was no thrombus in the superficial femoral vein.

Of the 113 patients who had iliofemoral thrombus, it was considered to have originated at that site in 96, and in a further 11 there was old thrombus both proximally and distally with fresh thrombus in between suggesting a dual origin. Hence in 107 instances (94%) of iliofemoral venous thrombosis associated with pulmonary embolism, the site of thrombus inception was in the iliofemoral segment. Expressed in another way, in 144 patients with pulmonary embolism, the clot had originated in the iliofemoral segment in 74%, and the segment was the source of the embolae in a further 4% (Table X).

Clinical examination showed iliofemoral venous thrombosis in 99 patients. Clinically, the thrombus was thought to have originated in this segment in 83 (58% of all the patients). In 17 (14%) the thrombosis remained proximal without distal propagation. In the remaining 66 (44%) there was evidence of distal propagation. In some, this was very limited, but in others it extended to the level of the popliteal fossa or even the calf veins.

In 36 patients the thrombus was thought to have a peripheral origin on clinical grounds. Of this group, the clot remained peripheral in 20, and in 16 there was evidence of proximal propagation (Table X). The
remaining 25 patients had "silent" legs, i.e. there was no clinical evidence of deep vein thrombosis, either peripheral or high. Of this group, 14 were found to have proximal thrombus, insufficient to produce occlusion and therefore symptoms. The remaining 11 were assumed to have asymptomatic peripheral venous thrombosis - an assumption supported by the findings that after bilateral femoral vein ligation the affected side became symptomatic on 6 occasions.

In 56 patients signs of deep vein thrombosis preceded the onset of pulmonary embolism. In the remaining 88 patients embolism was the presenting symptom, but in 33 signs of deep vein thrombosis were present but unrecognised when the patient was first examined on account of embolism (Table XI). The extent of this figure is partly accounted for by the fact that a practitioner thought the patient had a deep vein thrombosis, but did not refer him until embolism confirmed it; but there were still a number of patients in whom deep vein thrombosis was not diagnosed until some time after its appearance. The high proportion of these patients with iliofemoral thrombosis is a striking feature (Table XI).

Of the 55 patients with embolism but without leg signs at the onset ("silent legs") the legs remained "silent" throughout in 25. In the remainder leg signs developed later ("late leg" cases) 22 high, and 8 peripheral. The iliofemoral segment was thrombosed in 38 (69%) of the 55 patients with initially clinically "silent" legs (Table IV).

Partial or Incomplete Iliofemoral Venous Thrombosis

McLachlin and Paterson (1951), Gibbs (1957) and Sevitt (1960) have shown that the iliofemoral venous segment is a common source of pulmonary emboli and the source of almost all major pulmonary emboli. In 107 out of 144 of
our patients thrombus formation began in the iliofemoral segment. The frequency of iliofemoral thrombosis originating at this level explains the high failure rate of bilateral superficial femoral vein ligation as a prophylactic measure. In this series, ligation would have failed to prevent embolism in 74% where the thrombus originated above this level. This accords very closely with the necropsy findings of McLachlin and Paterson (1951) where it would not have been adequate prophylaxis in 21 (62%) of the 34 cases in which deep venous thrombosis was present.

Peripheral deep vein thrombosis is not as common a source of severe pulmonary embolism as is often supposed. While 9 out of 113 cases with pulmonary embolism from the iliofemoral segment died, there were no deaths in the 31 peripheral cases treated by superficial femoral vein ligation. This group of peripheral venous thromboses were the more severe cases for whom operation was reserved, while a far greater number, where clinical and venographic evidence indicated that thrombosis was limited to the peripheral segment were treated conservatively with no fatalities. Though these veins are seldom the source of major embolism they may give rise to recurrent small emboli, resulting in pulmonary hypertension and right heart failure. If embolism is oft repeated as judged by recurring symptoms, persistent fever, raised E.S.R., deteriorating chest X-rays, pulmonary scanning, or electrocardiographic evidence of right heart strain then, provided the patency of the iliofemoral segments has been determined by venography, bilateral superficial femoral vein ligation will arrest embolism and at the same time be without morbidity, the collateral venous circulation having been preserved.

There remains the "silent leg" cases. These are cases where embolism
occurs in the absence of any clinical evidence of deep vein thrombosis. As has been shown, leg signs involving the iliofemoral segment will subsequently develop in nearly half of these cases. This finding, together with the common finding at venous thrombectomy in iliofemoral thrombosis of old, white, partly organised thrombus from the common iliac veins (Fig. 16) suggests that iliofemoral venous thrombosis is at times slow and insidious in onset, and that there is a period when occlusion is incomplete and pulmonary embolism can occur without signs of venous insufficiency in the legs. Later, when thrombosis and occlusion become complete, acute venous insufficiency and leg signs rapidly develop. That such a state of incomplete iliac occlusion does exist has been demonstrated by bilateral femoral venography in several patients with recurrent pulmonary embolism and "silent" legs (Fig. 24). Further evidence that this incompletely occluding thrombus was the source of recurrent emboli lies in the fact that its removal by femoral thrombectomy without venous interruption was a satisfactory therapeutic measure. Moreover, the nature of the thrombus, consisting of old, hard, laminated thrombus with recent fresh coagulated whole blood on the surface, supports its aetiological role (Fig. 25).

Discussion

In the past it has been customary to assume that pulmonary emboli, arising in the absence of leg signs, have originated from a silent thrombosis (phlebothrombosis) of the peripheral veins for it was mistakenly believed that iliofemoral thrombosis always gave rise to symptoms. This has continued despite the clinico-pathological studies of Sevitt and Gallagher (1961) who showed that iliofemoral thrombosis was clinically silent, at least for a time, in 60% of cases. They suggested that in
such cases the thrombus did not occlude the vein. The venographic
demonstration of such incomplete iliofemoral venous thrombosis (in living
patients) in this series confirms this and makes it imperative that, in all
cases of severe pulmonary embolism without leg signs, the state of the
iliofemoral segments by displayed by means of venography. In this way
early incomplete occlusions of the iliofemoral segment can be detected and
appropriate therapeutic measures taken. If, on the other hand, the ilio-
femoral segments are clear, it can be safely assumed that the functionally
and clinically less important distal segment is the source of the embolism.

A plan of investigation and treatment of pulmonary embolism can now
be formulated. First, when iliofemoral venous thrombosis is diagnosed
clinically, femoral thrombectomy under venographic control is indicated.
At this operation the patency of the contralateral iliofemoral segment is
checked by venography as the disease is frequently bilateral. Secondly,
when there is clinical evidence of peripheral deep vein thrombosis, bilat-
eral femoral venography should be undertaken to exclude a coexistent non-
occlusive iliofemoral thrombosis, when conservative treatment can be safely
recommended. The progress of peripheral thromboembolism can be assessed
clinically. If, despite conservative measures which may include anti-
coagulant therapy, further pulmonary embolism occurs, bilateral superficial
vein ligation should be carried out, the continuing patency of the ilio-
femoral segments being checked by venography at the time of operation.
Finally, where there are no leg signs ("silent" leg cases), bilateral
femoral venography is required in order to display the iliofemoral seg-
ments. The presence of thrombus incompletely occluding the vein (Figs. 19
and 24) is an indication for venous thrombectomy, because these patients
are at risk from embolism, the severity of which is related to the size
of the non-occlusive thrombus, and the development of a complete ilio-
femoral occlusion with its accompanying dangers of massive embolism and
severe leg morbidity. If both iliofemoral segments are normal, there is
no risk of major embolism and the case can be treated as a peripheral venous
thrombosis. This plan of investigation and treatment is based on the
importance of the iliofemoral segment as a site of origin of venous throm-
bosis and a source of pulmonary embolism. Femoral venography is an impor-
tant diagnostic procedure, which must be carried out bilaterally. It is
without risk and the results obtained allow a measure of control not other-
wise attainable. The fact that 71% of the patients in the present series
were referred with continuing embolism despite anticoagulant therapy
indicates that major embolism can probably not be controlled adequately
without precise knowledge of the source of embolism.

Inferior vena caval ligation and plication have been advocated as
methods of treating pulmonary embolism (Dale, 1958; DeWeese and Hunter,
1963). Although these measures control embolism, the mortality is not
insignificant (Dale, 1958), and the resulting morbidity where plication is
performed in the presence of partial or complete iliofemoral thrombosis is
severe, in contrast to prophylactic plication when this is absent (DeMeester
et al., 1967).

Venous thrombectomy, by restoring the integrity of the iliofemoral
venous segment, aims to remove the source of embolism and overcome the
venous insufficiency. Emphasis in treatment should be on restoration of
venous patency, which both in theory and practice is preferable to venous
interruption, partial or complete.
Detachment of Pulmonary Emboli

Before leaving the problems of the pathology of pulmonary embolism it is relevant to consider the mode of detachment of thrombus from the deep veins, because it is this that gives deep vein thrombosis its deadly sting. Despite this little attention has been paid to this aspect of the problem.

The studies of Paterson (1962) which showed that the blood fibrinogen level was significantly lower in the 3 weeks period before death in 22 cases of thrombosis with embolism than in 18 cases of thrombosis without embolism, are interesting and support the suggestion that the risk of embolism is greatest where the fibrin component of the thrombus is defective. In the present study embolism following thrombectomy was much more common in patients with embolism before operation and no deaths occurred in those without pre-operative embolism (Table XXIX). Clearly, the thrombus or its attachment to the vein wall is different in the two groups.

Little attention has been paid to mechanical and haemodynamic factors in dislodgement. A factor contributing to this is the impression which is prevalent that the so-called "tail" of deep venous thrombosis is "floating" and free all round and therefore capable of being detached by very minor trauma. This is an uncommon situation. The tail of non-occluding thrombus is adherent to at least one point of the vein wall and must be stripped from this attachment before embolism results (Fig. 26).

It is well recognised that embolism frequently arises following straining at difficult defaecation or micturition or unaccustomed straining involved in the Valsalva manoeuvre altered the venous pressure in the lower limb and suggested
that this was an important factor in the production of pulmonary embolism. In addition the Valsalva manoeuvre causes distension of the veins (Fig. 27 a and b) which leads to stripping of the thrombus from its attachment to the vein wall. The increase in venous return which follows release of proximal pressure drives the thrombus centrally (Fig. 27c).

**Summary**

Iliofemoral venous thrombosis is a very serious disease with a high mortality from pulmonary embolism. Massive pulmonary embolism arises from the iliofemoral segment, the thrombosis originating at that level. For a variable period iliofemoral venous thrombosis may be non-occlusive and give rise to pulmonary embolism, which depending on the size of the thrombus may be massive and fatal, without producing leg signs. Pre-occlusive iliofemoral venous thrombosis can only be diagnosed by bilateral femoral venography which is therefore an important diagnostic procedure.

When thrombosis is limited to the peripheral segment massive pulmonary embolism does not occur and therefore provided there is proof that the iliofemoral segments are clear conservative measures will suffice. The only risk is recurrent small emboli leading to pulmonary hypertension and death from right heart failure. In such cases bilateral superficial femoral vein ligation will arrest embolism, and at the same time be without morbidity, the collateral venous circulation having been preserved.

A rational plan for the management of pulmonary embolism, based on the importance of the iliofemoral segment as the source of pulmonary embolism and depending on adequate bilateral visualisation of the iliofemoral segments by femoral venography has been proposed. Where there is iliofemoral thrombosis with or without occlusion and therefore signs, venous throm-
bectomy is the treatment of choice, for it will arrest embolism and relieve leg morbidity. Where the iliofemoral segments are clear, conservative measures will suffice unless embolism is oft repeated when bilateral superficial femoral vein ligation should be carried out.
CLINICAL DIAGNOSIS OF DEEP VEIN THROMBOSIS

Early diagnosis of deep vein thrombosis is still a major problem and many patients still die suddenly from massive pulmonary embolism without the attending doctor detecting any evidence of deep vein thrombosis. In the past it was customary to invoke distant and clinically undetectable sites of thrombosis such as the veins of the plantar aspect of the foot or those of the muscles of the arm or the pleurae of the pelvic viscera. Post mortem studies (Gibbs, 1957 and Sevitt and Gallagher, 1962) have shown that all cases of pulmonary embolism have thrombosis of the deep veins of the lower limbs and that in many instances this involves the major veins even if this is not detectable on routine clinical examination. This is not to suppose that thorough clinical examination is of no value, rather that in cases of doubt more elaborate investigations such as venography should be undertaken. Failure to look for high signs of deep vein thrombosis which leads to error and in our own series there was a failure to diagnose the condition in 17% of cases even though definite high signs were present. 23% of these having even sustained a pulmonary embolism (Table XII).

It is traditional to state that the early features of thrombo-embolic disease are related to the calf. In our experience serious venous thrombosis affects the iliocaval segment rather than the calf veins. Nonetheless it is important to carefully examine all patients with calf pain and try to elicit tenderness there. In many instances such discomfort results not from an inflammatory process round a thrombosed calf vein but from congestion of these veins, one of the earliest features of venous obstruction at a higher level, and in many cases tenderness in the grain
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It is traditional to state that the early features of thrombo-embolic disease are related to the calf. In our experience serious venous thrombosis affects the iliofemoral segment rather than the calf veins. Nonetheless it is important to carefully examine all patients with calf pain and try to elicit tenderness there. In many instances such discomfort results not from an inflammatory process round a thrombosed calf vein but from congestion of these sinuses, one of the earliest features of venous obstruction at a higher level, and in many cases tenderness in the groin
or supra-inguinal region can be detected (Fig. 20), a point appreciated by Davis (1822) (see page 6). In other instances it may result from calf vein thrombosis and this should alert the clinician to the fact that such patients have a thrombotic tendency and are therefore at risk from more serious and potentially fatal iliofemoral thrombosis.

Pre-occlusive iliofemoral venous thrombosis is not detectable clinically and can only be diagnosed venographically, which at this stage is usually indicated an account of pulmonary embolism. In a few cases incomplete occlusion may produce a minor degree of venous obstruction with discomfort and slight swelling of the leg (Fig. 28). Where there is less thrombus it may not proceed to complete occlusion and in such cases minor degrees of venous insufficiency are late sequelae when organisation of the thrombus results in narrowing of the vein (Fig. 29). These patients are more liable to further attacks of venous thrombosis, a feature which has been noted in a number of cases.

Where iliofemoral venous occlusion is complete the clinical picture varies from a very benign state with slight calf discomfort, minimal swelling and slight groin or supra-inguinal tenderness, through the severe blue leg to massive venous gangrene. The severity of the clinical picture is related to the extent of occlusion and the collateral capabilities of the individual patient. In a series of 228 patients treated by thrombectomy 152 (67%) had a phlegmasia caerulia dolens (Table XIII).

Groin and supra-inguinal tenderness which frequently precede leg swelling by some hours or even days, must always be sought, and the femoral vein is often palpable.

Too great a reliance has been placed on the presence or absence of ankle
oedema. Not infrequently, despite fairly marked leg swelling, pitting oedema is minimal or absent, the swelling involving the deeper tissues, muscles and fascia, to a greater extent than the skin and subcutaneous tissues, especially those of the ankle. Gross oedema of the muscle bellies is often marked at venous thrombectomy. This is detectable clinically as an increased firmness of the muscles best demonstrated by light "ballottement" of the muscles of the thigh and calf.

Reliance has often been placed on finding equal measurements for the thigh and calf on both sides. This suffers from several defects in that the affected leg may normally have been thinner than its companion (Fig. 74), and that the natural hollows of the antero-medial aspects of both thighs and lower leg may be filled out to a considerable extent without any increase in circumferential measurement (Fig. 30). None-the-less regular measurements of thigh and calf are valuable.

Increase in the superficial venous patterns especially on the anterior aspect of the upper thigh has received inadequate attention but is a valuable confirmatory sign of venous occlusion.

There is considerable variation in the activity of the disease process in deep vein thrombosis. In many instances the disease is bland with minimal constitutional upset, low grade fever and E.S.R. range from 20 - 40 mm. fall. There is, however, a minority of cases where the disease is excessively acute and active. Symptoms and signs are marked, fever and sedimentation rate much raised, the course protracted and severe complications like recurrent pulmonary embolism, caval thrombosis, and venous gangrene more common. Both iliofemoral segments may be involved, and the superficial veins are often intensely phlebitic. Pulmonary embolism
is a common accompaniment, recurrence over the years usual, and morbidity and mortality high. Treatment of whatever type usually fails to halt the disease. In such cases thrombectomy is usually unsuccessful, and if clearance is obtained, rethrombosis is common. In this series the incidence of this type of severe disease has been about 8%. Several patients have had severe episodic disease over the years, and mortality has been due to pulmonary embolism or followed surgery for pulmonary embolism or to venous gangrene, or in one case to mesenteric venous occlusion during a subsequent pregnancy (Table XIV).

**Superficial Thrombophlebitis**

Consideration of the clinical aspects of deep venous thrombosis would be incomplete without mention of superficial thrombophlebitis of the long saphenous vein. This is a common condition, which often remains localised, usually runs a short benign course and is readily treated by supportive bandaging and activity. However, the condition may give rise to pulmonary embolism (Zollinger et al., 1962) and there are numerous reports of a fatal outcome from this complication (Barrow, 1957; Gjores, 1962; Zollinger et al., 1962; Hafner et al., 1964; Totten, 1965). The precise source of pulmonary embolism in such cases is less well known.

Three patients with extensive thrombophlebitis of the long saphenous vein associated with pulmonary embolism have been studied, and in each case the iliofemoral segment was involved in thrombus formation (see Appendix III). Management in such cases therefore must take the condition of the iliofemoral segment into consideration.

High ligation of the long saphenous vein in cases of thrombophlebitis involving the thigh has been recommended for many years (Martin et al., 1956).
Such treatment should not be delayed because frequently thrombus in the vein has extended much higher in the thigh than is clinically obvious, and when thrombus reaches the sapheno-femoral junction the risk of spread into the deep vein is considerable and pulmonary embolism may result.

Now that the iliofemoral segment is being recognised as the significant source of pulmonary embolism, and that clinically silent, non-occlusive thrombosis of this segment may give rise to embolism it is important that high saphenous ligation be combined with venography to determine the state of the iliofemoral segment. In these circumstances the source of embolism may not be the inflamed superficial vein, but thrombus in the iliofemoral segment. It may be continuous with the thrombus in the phlebitic segment and extending through the sapheno-femoral junction (Fig. 31) or it may be a simultaneous, discontinuous, silent non-occlusive thrombus of the ipsi- or contra-lateral iliac veins (Figs. 24 and 32). It is therefore essential to demonstrate that the iliac veins on both sides are free of thrombus by means of venography. On the side with the phlebitis this can be done by the introduction of a catheter through the stump of the long saphenous vein, the contralateral side being demonstrated by direct femoral vein puncture at the time of high saphenous ligation. When iliac thrombus is present thrombectomy will arrest the disease. By means of venography used in this way some of the fatal outcome reported in the literature would almost certainly have been averted (Hafner et al., 1964).

Summary

If the diagnosis of deep vein thrombosis is to be improved then attention must be directed to the iliofemoral segment which has been shown to be the area where thrombosis produces most severe leg symptoms, and is the usual
source of pulmonary embolism. Signs of iliofemoral venous thrombosis are thigh and calf swelling, increased superficial venous markings, and a variable degree of skin discolouration. Groin and suprainguinal tenderness frequently precede other signs and must always be sought. Ankle oedema is commonly absent and its absence is not a reliable means of excluding the diagnosis of deep vein thrombosis. Whenever doubt in diagnosis exists bilateral iliofemoral venography by direct puncture or intra-osseous injection of the greater trochanter is indicated.

Finally phlebitis of the long saphenous vein may give rise to thrombosis propagating into the iliofemoral segment or may be coexistent with, but not necessarily causative in the production of, a discontinuous iliac thrombosis. In treating saphenous thrombophlebitis involving the thigh, therefore, venographic visualisation of the iliofemoral segments is essential, especially if there is pulmonary embolism. Ligation of the saphenous vein at its termination will hasten resolution of the phlebitic process. If there is iliofemoral thrombus it must be removed, either through the stump of the saphenous vein or a separate venotomy in the common femoral vein.
That gangrene could be produced by venous obstruction in the absence
of arterial disease is said to have been recognized as early as 1593 by
Fabricius Hildanus. Many terms relating to this condition, such as
"Phlegmasia Caerulea Obliterans" (Gregoire, 1938), "Gangrene of Venous Origin"
(Andier and Haimovici, 1938), "Acute Massive Venous Occlusion" (Yosi et al.,
1951) and "Psammomatoid Phlebitis", have been introduced into the litera-
ture over the years without precise definition being given. As a result
of this there has arisen considerable confusion so that the same title has
been used to describe different conditions. Thus Boyd and Clark (1962)
reporting from the Lahey Clinic described six cases of Phlegmasia Caerulea
Obliterans, without gangrene or mortality, while Laccennati and May (1963) in a
report under the same title described five cases all of which developed
venous gangrene, four of them having the same mortality. Clearly the latter authors
restricted the title to cases where gangrene developed while the first used
it to describe cases with extensive venous thrombosis associated with blue-
case of the leg, a feature of many cases of iliofemoral venous thrombosis.

In the cases reported under these various titles the thing that is
common is the underlying pathology, namely iliofemoral venous thrombosis with
or without proximal or distal extension. This is borne out by most of the
cases in the literature where evidence has been sought and by those in the
present series (Table XV).

Six cases of venous gangrene have been treated, (Appendix IV) and the
results are summarized in Table XVI.
That gangrene could be produced by venous obstruction in the absence of arterial disease is said to have been recognised as early as 1593 by Fabricius Hildanus. Many terms relating to this condition, such as "Phlegmasia Caerulia Dolens" (Gregoire, 1938), "Gangrene of Venous Origin" (Andier and Haimovici, 1938), "Acute Massive Venous Occlusion" (Veal et al., 1951) and "Pseudoembolic Phlebitis", have been introduced into the literature over the years without precise definition being given. As a result of this there has arisen considerable confusion so that the same title has been used to describe different conditions. Thus Boyd and Clark (1962) reporting from the Lahey Clinic described six cases of Phlegmasia Caerulia Dolens, without gangrene or mortality, while Loewenthal and May (1965) in a report under the same title described five cases all of which developed gangrene, four of them having a fatal outcome. Clearly the latter authors restricted the title to cases where gangrene developed while the first used it to describe cases with extensive venous thrombosis associated with blueness of the leg, a feature of many cases of iliofemoral venous thrombosis.

In the cases reported under these various titles the thing that is common is the underlying pathology namely iliofemoral venous thrombosis with or without proximal or distal extension. This is borne out by most of the cases in the literature where evidence has been sought and by those in the present series (Table XV).

Six cases of venous gangrene have been treated, (Appendix IV) and the results are summarised in Table XVI.
Discussion

Pathogenesis

Considerable controversy has centred on the mode of production of tissue necrosis in venous gangrene. Reflex arterial spasm has been implicated (Leriche and Kunlin, 1934; Ochsner and DeBakey, 1940; Edwards, 1958), and lumbar sympathectomy performed in an attempt to relieve it. However, experience has shown that it produces no benefit in severe ilio-femoral thrombosis. The experimental studies on which it was based (DeBakey, Burch and Ochsner, 1939) are open to criticism and those of Brockman and Vasko (1966) have shown that sympathectomy has no influence on experimental phlegmasia caerulea dolens. The disparity in size between the femoral artery and vein was taken as a sign of arterial spasm. However, as previously noted (p. 53) it is the vein that is distended as a result of proximal occlusion, and the artery is of normal calibre.

The vasospastic theory is not supported by the clinical appearances of the leg. The peripheral pulses are full and bounding early in the course of the disease. The superficial veins are distended, and the rate and degree of accumulation of fluid is very great. Arteriography in venous gangrene shows no reduction in the calibre of the main vessels at least (case 3). The fact that the gangrene remained the same and the leg as a whole improved after external iliac artery ligation in case 2 indicates that it is not a defect of arterial inflow but of venous outflow.

Recently more attention has been directed to purely mechanical factors. Jepson as early as 1926 showed that the increased tissue tension following experimental massive venous occlusion could lead to tissue necrosis. The successful clinical application of this work by Cywes and Louw (1962) who
used relieving fasciotomies in 2 cases of incipient gangrene adds support to this.

Massive obstruction of the venous outflow track of the limb results in a raised capillary pressure and an outpouring of fluid into the tissues. This gives rise to a state of hypovolaemic shock. The combination of reduced arterial pressure and raised tissue pressure lowers the transmural pressure below the critical closing pressure (Burton, 1951) and flow ceases (Brockman and Vasko, 1966; Snyder et al., 1967). In experimental studies the transmural pressure may be reduced to as little as 12 mmHg. (Snyder et al., 1967).

Management

Venous gangrene is a life threatening condition. Death may result from pulmonary embolism, hypovolaemic shock or gangrenous toxaemia. Considering the underlying pathology of the disease and the pathogenesis of the tissue necrosis the logical form of treatment is venous thrombectomy which removes the risk of embolism, averts tissue necrosis, and by allowing reabsorption of tissue fluid corrects hypovolaemia. Of the 4 cases in this series treated in this way, 3 survived the episode of venous gangrene, although 2 subsequently died of their underlying disease. Thrombectomy was incomplete in the only patient who died (case 2).

Although even limited clearance at thrombectomy will frequently result in rapid resolution of swelling and pain (page 73), it is essential in such circumstances to proceed to caval thrombectomy to ensure complete clearance and so avert the risk of rethrombosis as occurred in case 2. In the only case treated in this way clearance was complete and the patient not only survived but had no chronic venous insufficiency. Experience in 7 caval
thrombectomies has shown that complete clearance can be maintained following this operation (Table XXXIV). The decision to proceed to caval thrombectomy should be made on the operative venographic findings.

Anticoagulant therapy has been the treatment of choice in most large series of cases, but where gangrene is established they are not only ineffectual but dangerous.

From a study of the literature it would appear that at least 60% of patients were adequately anticoagulated when gangrene developed (Table XV), as were 3 of the 6 cases in the present series. There are strong theoretical reasons for not using anticoagulants in a condition where sequestration of essential coagulation factors and platelets leads to a potentially haemorrhagic state (Rosenberg and Zullo, 1958). The capillary pressure is so great as to produce petechiae and many have advised against anticoagulants on this basis (DeBakey and Ochsner, 1949; Veal et al., 1951; Catchpole, 1957).

A number of cases which have developed 'gangrene' while on anticoagulants and have subsequently progressed to a satisfactory outcome may have merely had haemorrhage into a congested leg as a result of anticoagulants, as in the following case.

Case Report*

A 31 year old patient was given warfarin for 2 episodes of pulmonary embolism, one 24 hours before and the second 24 hours after delivery. There was not clinical evidence of deep vein thrombosis. Two and a half days later she developed severe pain in the right leg and foot. The leg rapidly became swollen

* This case is not considered a case of venous gangrene and is not included in Tables XV and XVI.
and tight below the knee and the 2nd toe became black and swollen. At this stage she was referred as a case of venous gangrene.

Faint bruising was noted over the right lower leg and the possibility of bleeding from anticoagulant therapy was considered. One stage prothrombin time was found to be 2 mins. 40 secs.

Two hours later after 20 g. of Vitamin K₁ intravenously the prothrombin time fell to 28 seconds and bilateral femoral venograms were performed. These showed normal iliofemoral segments (Fig. 41), ruling out venous gangrene. Anticoagulant therapy was discontinued and the leg returned to normal within 4 days, without loss of tissue.

The value of femoral venography in these circumstances is apparent.

Intensive active and passive exercises have been advocated (Veal et al., 1951). Although these are an essential part of the after care following thrombectomy, in the absence of venous clearance the risk of precipitating pulmonary embolism is grave (Edwards, 1958).

Sequestration of blood and plasma in the limb leads to severe hypovolaemia in many instances (cases 1 and 2) (Fig. 33) and active fluid replacement is required in such circumstances (Catchpole, 1957). Snyder found that in 6 hours 6% of the body weight could collect in the leg of the dog with experimental venous gangrene. Where, despite continued infusions, hypovolaemia is not corrected, ligation of the external iliac artery will reduce the inflow to the limb and arrest the loss of fluid as shown in Case 2 (Fig. 33). Although a desperate measure it may on occasion be essential. Emergency amputation has been advocated (Brockman and Vasko, 1965) but it would seem prudent to ligate the artery and delay amputation for in many
instances gangrene is superficial and with a conservative attitude to amputation tissue loss may eventually be small as in Cases 3 and 5.

It is inevitable that the overall results of treatment will always be poor when so many cases are associated with underlying malignant disease, frequently in an advanced stage (Ross et al., 1961; Loewenthal and May, 1965; Sutton, 1966). However, it may develop in otherwise healthy patients, or follow a minor operation or pregnancy, and if managed adequately in the early stages life can be saved, major amputation avoided and good functional recovery obtained.

Summary

Venous gangrene results from total venous outflow obstruction of the limb, in the absence of arterial disease, and in the lower limb is produced by iliofemoral venous thrombosis in its most severe form. Gangrene results from the accumulation of tissue fluid under pressure, which reduces the transmural pressure in the small arteries below their critical closing level: vasospasm, though frequently invoked as the cause of the tissue necrosis, is not important. Death from massive pulmonary embolism, hypotension due to fluid sequestration or gangrene occurs in over 50% of cases.

The logical treatment is iliofemoral venous thrombectomy which will arrest embolism, and restore fluid balance and the circulation to the limb, when clearance is complete. If complete clearance, as judged by operative venography, cannot be achieved from the femoral approach, then caval thrombectomy should be undertaken. In 3 of the 4 cases treated by thrombectomy in this series clearance was complete and the acute episode was controlled in each. In one case clearance was via the inferior vena cava.
If thrombectomy fails, external iliac artery ligation, which will not necessarily compromise the limb, may be life saving by preventing further fluid loss.
The results of treatment of venous thromboembolic disease have remained unsatisfactory. For 30 years the anticoagulant drugs have been the short
umber of therapy in this country, but despite many reports indicating the
beneficial effects in individual groups of cases neither the mortality nor
the morbidity has been influenced by these drugs (Morrel, Truslove and Barr,
1963). None-the-less an uncritical approach to their use continues.

There are considerable difficulties in controlling anticoagulant therapy
and many patients are only transiently within what is generally considered to
be a therapeutic range. In four spot checks of prothrombin estimations
in the laboratory of our own service only 30% of patients were within the
therapeutic range on any one occasion. Although this figure may be exag-
gerated by including a number of patients in the process of being
"tailed off" from therapy it still indicates a high error in dosage. When
this is considered in the light of the variation in prothrombin coagulation tests
between hospitals where variations may be as great as 40-50% (Brit.
med. J., 1960) then the dangers of drawing firm conclusions about dosage,
control and efficacy of treatment are apparent.

The theoretical basis for anticoagulant therapy is unsound. These
drugs were employed in an attempt to prevent propagation from the distal to
the proximal segment on the basis that this was the usual course of the
disease. This has been shown to be a rare occurrence. The second
advantage of anticoagulant therapy was that it reduced the risk of pulmonary
embolism during the critical 3-5 days when the thrombus was "free-floating",
before it became adherent to vein wall (Hauer, 1960). Though theoreti-
cally attractive this is not borne out in practice. Embolism is freq-
The results of treatment of venous thromboembolic disease have remained unsatisfactory. For 30 years the anticoagulant drugs have been the sheet anchor of therapy in this country, but despite many reports indicating the beneficial effects in individual groups of cases neither the mortality nor the morbidity has been influenced by these drugs (Morrel, Truelove and Barr, 1963). None-the-less an uncritical approach to their use continues.

There are considerable difficulties in controlling anticoagulant therapy and many patients are only transiently within what is generally considered to be a therapeutic range. In four spot checks of the prothrombin estimations in the laboratory of our own service only 30% of patients were within the therapeutic range on any one occasion. Although this figure may be exaggerated by including a number of patients who were in the process of being "tailed off" from therapy it still indicates a high error in dosage. When this is considered in conjunction with the lack of standardisation of such tests between hospitals where variations may be as gross as 40-50% (Brit. med. J., 1966c) then the dangers of drawing firm conclusions about dosage, control and efficacy of treatment are apparent.

The theoretical basis for anticoagulant therapy is unsound. These drugs were employed in an attempt to prevent propagation from the distal to the proximal segment on the basis that this was the usual course of the disease. This has been shown to be a rare occurrence. The second advantage of anticoagulant therapy was that it reduced the risk of pulmonary embolism during the critical 2-3 days when the thrombus was "free-floating", before it became adherent to vein wall (Bauer, 1960). Though theoretically attractive this is not borne out in practice. Embolism is freq-
uently continuous over weeks or even months and anticoagulant drugs frequently are not effective in preventing embolism, in that 81 out of 113 (71%) of patients operated on in this series for pulmonary embolism were referred because embolism continued despite anticoagulants (Table IX). 121 (52%) of the 228 patients with iliofemoral thrombosis were referred because of anticoagulant failure (Table IX).

So much reliance has been placed on the anticoagulant drugs that other beneficial measures such as elevation, supportive bandaging and calf pumping exercises have been largely abandoned, despite the reduction in venous stasis which they produce (Wright and Osborne, 1952; McLachlin, McLachlin, Jory and Rawling, 1960). Many young clinicians ignore such details of patient care. Attempts to combat venous stasis by early ambulation are criticised because several reports have suggested that they do not significantly lower the incidence of deep vein thrombosis (Blodgett and Beattie, 1946; Powers, 1947). However, careful study of these reports reveals that the patients were not really ambulant in the early postoperative period but were left for prolonged periods in the sitting position which has been cited as a cause of deep venous thrombosis (Homans, 1954).

Of the surgical measures available in the management of venous thromboembolism, thrombectomy and venous interruption, the former is more attractive in that if adequate it will not only arrest embolism but restore the normal venous drainage of the limb. Venous interruption, on the other hand, although it may prevent embolism, will not improve venous function and may further jeopardise it by increasing venous stasis. The iliofemoral segment is the functionally important site of venous thrombosis both in relation to pulmonary embolism and leg morbidity. Accordingly treatment
must be concentrated on this segment. Venous interruption must be at the
deferred site. Venous interruption must be at the
level of the inferior vena cava in iliofemoral thrombosis and under such
circumstances it is attended by high morbidity (DeMeester et al., 1967).

**ILIOPHLEMORAL VENOUS THROMBECTOMY**

The operation of venous thrombectomy is aimed at removing all thrombus
from the iliofemoral segment and, consequently, the risk of major pulmonary
embolism, and restoring completely and permanently the patency of the ilio-
femoral segment, so that symptoms of acute and chronic venous insufficiency
due to an inadequate collateral venous circulation can be overcome. The
functional importance of a patent iliofemoral segment makes this procedure
a soundly based and justifiable operation. However, how often and to what
extent a satisfactory result can be achieved is not clear from the literature
(Fontaine, 1957). Experience suggests that incomplete clearance, and early
rethrombosis are important hazards. The recognition of these difficulties
has led to improvements in technique as the use of balloon catheters (Fogarty,
1966; Little, Loswenthal and Mills, 1966) and the approach from the inferior
vena cava.

The desire to introduce some measure of objective control into the
procedure, both as an aid to the progress of thrombectomy and as a means of
accurate assessment of the early result of the venous clearance, has led to
the routine use of venography during operation and in the immediate post-
operative phase in the last 83 patients in whom thrombectomy was carried out.
No complications have been noted during these venograms.
Technique of Iliofemoral Venous Thrombectomy under Venographic Control

General anaesthesia is used whenever possible, but the procedure can and frequently is performed under local anaesthesia. The common femoral vein is exposed by a vertical incision which crosses the groin crease. The superficial circumflex iliac vein is divided, and the portion of this vein leading to the saphenous vein is preserved and marked in order that a catheter can be led through it to the sapheno-femoral junction for local infusion of heparin or fibrinolytic agents postoperatively and to facilitate postoperative venography. The common and superficial femoral and profunda femoris veins are isolated and controlled by capillary rubber tubing. Other tributaries such as the medial and lateral circumflex femoral veins may also be controlled. The venae comitantes of the femoral artery are frequently in evidence and every attempt is made to preserve these vessels. A 1 - 2 cm. phlebotomy is made in the common femoral vein just at its origin, this site being chosen because it facilitates clearance of all three vessels.

Thrombus is removed by forceps and suction from the first 5 - 6 cm. of the common femoral and external iliac veins. Then, via a Portex catheter, introduced to a distance of 2 cm. into the common femoral vein, a venogram is performed to show the extent of proximal thrombosis and the collateral venous drainage. This and subsequent venograms are carried out using 10 - 15 ml. of 60% urografin. Thereafter thrombus is removed from the upper segment as completely as possible using Portex suction catheters and Fogarty catheters (Fig. 42). When it is felt that a clear channel has been made to the inferior vena cava or when no more progress can be made, a further venogram is taken. From this film the location of any remaining thrombus can be determined and attempts at clearance accurately directed. In most
instances two venograms will suffice, but in difficult cases as many as five may be required before a satisfactory result is achieved.

When the best possible clearance of the upper segment, as determined by venography, has been achieved, heparin saline is instilled into the upper segment, and a Blalock clamp is then applied across the vein proximal to the phlebotomy. Using the Fogarty catheter and polythene suckers the superficial femoral and profunda femoris veins are emptied of thrombus in turn. The success of clearing the less important distal segment is determined purely by the bleed-back obtained. If a good, free, distal bleed is not obtained, or there are difficulties in passing the catheter in a retrograde manner, clots are milked from the lower segment by firmly applying an Eamarch bandage from the ankle to the level of the incision. The profunda and superficial femoral veins are then controlled with Blalock Clamps. After checking the proximal bleed-back, the area between the clamps is thoroughly irrigated with heparin saline, the phlebotomy closed with continuous 5/0 arterial silk, and the clamps released.

The stump of the superficial circumflex iliac vein is then cleared and cathererised with a 6 FG Portex intravenous catheter. This is passed to the sapheno-femoral junction and the distal end is brought out through a separate incision lateral to the wound and connected to a heparin saline infusion (10,000 units heparin per 500 ml. normal saline). 20,000 - 30,000 units heparin are infused daily depending on the clotting time, which is kept just below an effective systemic level (usually at 15 - 20 mins.). The heparin saline infusion is continued for a period of 8 - 12 days. Both legs are bandaged firmly with crepe from just behind the toes to the level of the tibial tuberosity. The legs are placed on an elevator at 45°. Immediately
on recovering consciousness the patient is encouraged to do calf muscle exercises, continued for 5 minutes in every waking hour throughout the period of inpatient treatment. Blue line elastic webbing bandages are worn for 2 - 3 months postoperatively. Two or three venograms are carried out via the indwelling catheter during the early postoperative phase, the final one immediately before the infusion is discontinued.

**Observations on Technique of Iliofemoral Venous Thrombectomy**

Only by such venographic methods as have been outlined it is possible to obtain precise information about the state of the iliofemoral segment during and after thrombectomy. During thrombectomy the progress of venous clearance can be observed (Fig. 43). In an increasing number of cases complete clearance is obtained (Figs. 43, 44 and 45).

In difficult cases where there is uncertainty about the route taken by the Fogarty catheter a film taken with the balloon distended with urografin can give valuable information. In many instances it proves that the catheter has traversed the common iliac vein and has entered the inferior vena cava (Fig. 46). In others it shows that the catheter has been deflected into the ascending lumbar vein (Fig. 47) or has been bent upon itself. This is most likely to occur in the presence of old standing common iliac occlusion.

Operative venography also gives information about the collateral venous circulation. When the iliofemoral segment is completely cleared these collateral channels do not fill. However, with a persisting common iliac occlusion, which is particularly liable to occur on the left, the demonstration of a large ascending lumbar vein indicates a partial success which is likely to be attended by relief of venous insufficiency both in the acute and good visualization of the inferior vena cava.
phase and the long term (Fig. 48).

There is a theoretical risk of infection resulting from the maintenance of a catheter in the saphenous vein for 12 days. In practice this has not resulted, only 3 cases showing delayed wound healing. Before dismantling the infusion a blood culture has been taken through the catheter and a swab taken from tip of the catheter on six occasions. No growth was obtained on aerobic or anaerobic culture.

**Postoperative Venography**

Through the sapheno-femoral catheter postoperative venograms are carried out, in the patient's own bed, using a portable X-ray machine. Usually three venograms are undertaken in the first 12 postoperative days. Indications for more frequent venograms are continued elevation of E.S.R., or temperature or the persistence or recurrence of leg or chest signs. Late follow-up venograms to visualise the iliofemoral segment have been carried out by direct femoral vein puncture at the groin, or by the intraosseous pertrochanteric route at periods ranging from 3 months to 14 years following thrombectomy.

**Details of Present Series**

Details of age distribution, sex incidence and leg involvement in the present series of 223 patients are shown in Tables XVII, XVIII and XIII. 252 thrombectomies were carried out, 24 patients having bilateral operations. In 113 cases or 40% pulmonary embolism was an associated complication and 141 cases or 62% had plegmasia caerulea dolens and 4 had venous gangrene (Table XIII). Predisposing factors are listed in Table XIX.

In this study complete clearance of the iliofemoral segment is determined on venographic evidence and denotes no evidence of residual iliac thrombus and good visualisation of the inferior vena cava. The filling defect prod-
uced by the overlay of the right common iliac artery on the left common iliac vein may lead to difficulty in interpretation (Fig. 49). Partial clearance indicates that a filling defect is present in the external or common iliac vein, the latter partially or completely occluding the lumen. The inferior vena cava may not be directly visualised but in all instances direct channels, particularly a large ascending lumbar vein, are present.

The 252 iliofemoral thrombectomies in this series are divided into two groups.

**Group A**

This group consists of 159 legs operated on before the introduction of operative venography and without the Fogarty balloon catheter. In 76 instances the superficial femoral vein was ligated at a site just below the profunda termination, a procedure now regarded as being of no therapeutic value in that it will not affect the incidence of pulmonary embolism in iliofemoral thrombosis, nor will it alter the late morbidity as regards venous insufficiency, the peripheral femoro-popliteal segment having an adequate collateral arrangement. In Group A cases venous clearance was assessed on the basis of "bleed-back" from the common femoral vein, and the clinical improvement as regards leg swelling. Operative venography shows that "bleed-back" is an inaccurate means of assessing operative clearance, as bleeding from the proximal vein will be considerable even when common iliac occlusion persists, coming in such instances from the internal iliac and ascending lumbar veins (Fig. 23). Likewise improvement in leg swelling is usually dramatic whether or not clearance is complete. Therefore, in the absence of venography, it is not possible to give accurate figures as regards the effectiveness of clearance in Group A cases.
Late clinical follow-up was carried out in 104 of the Group A cases at periods varying from 2 to 14 years after thrombectomy (Table XX). If the results in the 36 cases with venographic follow-up (Table XXI) are utilised in assessing the whole follow-up group, complete clearance was probably maintained in 42%, and partial clearance with direct channels in a further 25%. Only 10% of these patients had marked venous insufficiency (Table XX).

**Group B**

This group consists of 83 patients in whom thrombectomy was carried out under venographic control and with the use of Fogarty balloon catheters. The postoperative sapheno-femoral catheter technique using continuous heparin therapy was employed in 67 patients and in these venographic studies show that complete clearance of the iliofemoral segment was achieved in 65% of cases, and that rethrombosis occurring during the early postoperative period reduced this patency to 55% at the end of 14 days (Table XXII). Partial clearance was achieved in a further 37% of patients, but here rethrombosis in the early postoperative period was significant and occurred in 36% of cases (Table XXII).

Venographic and clinical follow-up studies were undertaken in Group B cases from 3 months to 5 years after thrombectomy. 25 cases were studied venographically and the correlation of venographic and clinical findings is shown (Table XXIII). In 52% of cases a normal iliofemoral segment was found, and in a further 28% limited occlusion with an excellent clinical result. A further 29 had clinical follow-up studies only (Table XXIV). Late rethrombosis occurred in 12% and a further 8% had further episodes of venous thrombosis (Table XXV).
When the iliofemoral segment was patent, and the venogram showed no evidence of collateral channels (Figs. 49 and 50), there was no chronic venous insufficiency of the poor collateral circulation type. No information is available in such cases of valvular competence as regards the external iliac vein, but it would seem evident that a clear iliofemoral segment means an adequate venous return and normal function. The second clinical group classified as having "minimal symptoms" had no increase in girth of calf or thigh, no oedema, and no persisting signs suggesting venous insufficiency of the poor collateral circulation type. The leg was normal however in that the patient noted occasional tiredness, cramps, or thigh or calf discomfort. In these patients venography revealed persistent iliac involvement, the striking feature being the presence of direct collateral venous channels, such as a large ascending lumbar vein, or iliac venae comitantes (Figs. 10, 13, 45, 51 and 52). It would seem clear that such direct channels are important in limiting venous insufficiency. In the third group of patients symptoms of chronic venous insufficiency affecting thigh and lower leg were marked, and swelling of the whole leg apparent. These clinical findings correlated in most instances with a venographic finding of complete occlusion of the iliofemoral segment, the main venous return being by large crossover veins to the contralateral internal iliac system.

Early Postoperative Venography

The use of the sapheno-femoral catheter enables venographic observations of the iliofemoral segment to be carried out over the first two postoperative weeks. In this way early rethrombosis can be detected. In such instances the use of fibrinolytic agents have been investigated.
obtained at thrombectomy, rethrombosis is uncommon (Table XXII). When
clearance is partial rethrombosis in the immediate postoperative period is
more frequent (Table XXII), especially when the external iliac vein remains
affected (Table XXVI). The incidence of complete rethrombosis even with
incomplete clearance is only 12% (Table XXVI).

Observations on Thrombectomy

As has been noted previously the beginnings of iliofemoral venous
thrombosis may antedate clinical evidence of venous occlusion by weeks or
months. It is not possible therefore to set any time limit beyond which
thrombectomy is not justifiable, because the period between the onset of
clot formation and complete occlusion of the vein is unknown. Obviously
the fresher the thrombus the easier it is to achieve complete clearance.

However, even if thrombectomy is undertaken immediately after diagnosis,
when occlusion is complete, there may be technical difficulties in removing
old adherent thrombus which has accumulated over several weeks, during the
pre-occlusive phase of the disease (Fig. 16). Thrombectomy should always
be considered where the thrombophlebitic process is still active as evidenced
by fever, elevated E.S.R. or continued embolism. Where there are continuing
leg symptoms despite adequate elevation, bandaging and exercises it may be
indicated many weeks afterwards for if leg signs persist, occlusion must be
extensive and the collateral reserve poor in the particular individual. In
these late cases pre-operative bilateral venography is indicated to visualise
the contralateral iliofemoral segment and the inferior vena cava (Fig. 19).
In these cases partial clearance, especially if the ascending lumbar collateral
route can be opened, may be a worthwhile aim, that can be achieved in 80% of
cases. Rethrombosis is more common under these circumstances (Table XXVII)
but the clinical result is in most cases much superior to the severe venous insufficiency of extensive iliofemoral occlusion.

In addition to improving the venous return, thrombectomy will often bring the systemic disturbances in thrombophlebitis under control (Fig. 53). This is most striking when clearance is complete but occurs in 80% where there is only partial clearance (Table XXVIII). Cases of the severe progressive type of thrombo-embolism described previously (p. 49), account for a significant number of the remainder.

Thrombectomy in Management of Pulmonary Embolism

Of the 228 patients with iliofemoral venous thrombosis, 113 or 49% also suffered from pulmonary embolism. Of the 113 cases with embolism, 38 or 33% presented with this complication, 24 developing leg signs later, "late leg" cases, and 14 remaining silent throughout, the diagnosis being made venographically before venous occlusion and leg signs developed (Table IV).

The occurrence of pulmonary embolism in association with iliofemoral thrombosis did not alter the decision to operate, although in many instances continued embolism despite anticoagulants was the reason for surgical referral. This of course does not apply to the patients with incomplete iliofemoral occlusion where embolism was the only symptom and the indication for operation. Pulmonary embolism occurred in 25 or 11% of patients after thrombectomy. In 18 (8%) it was non-fatal and was fatal in 7 (3%). Embolism was more common after thrombectomy if there had been embolism before operation, occurring in 19% of those with pre-operative embolism and only 3% of those without (Table XXIX). There were no fatalities in the cases without embolism before operation. This supports the suggestion that in some individuals the venous thrombus is more friable and is more liable to fragment, and may be related
to its fibrin content (Paterson 1966).

Post-thrombectomy embolism, both fatal and non-fatal, was less common when the operation was performed within 2 weeks of the onset of thromboembolism (Table XXX). Of the 7 instances of fatal postoperative pulmonary embolism in the series, 2 cases suffered fatal pulmonary embolism at 7 weeks and 10 weeks after thrombectomy. This is in sharp conflict with the often quoted statement that within a few days thrombus is so adherent to the vein wall that embolism does not occur (Bauer, 1940).

In all 14 cases where thrombectomy was carried out for embolism, in the absence of leg signs, iliofemoral thrombosis having been demonstrated by preoperative venography, clearance was complete at operation and embolism was controlled. In one of the 14 cases thrombectomy was carried out via the right common iliac vein to facilitate clot removal from the vena cava.

There is no doubt that further embolism was related to the technical success of operation (Table XXXI). Where clearance of the segment was complete embolism was controlled in nearly all cases. When there was only partial clearance, usually with residual thrombus in the common iliac vein, embolism was controlled in about 80% of cases. Of the failures, noted over a three month postoperative period, recurrent embolism was seldom major and rarely fatal. Where thrombectomy was a total failure because of old standing complete occlusion, recurrent postoperative embolism was common occurring in 35% of cases (Table XXXI).

Where rethrombosis occurs following thrombectomy further embolism is a hazard. Embolism is therefore related to the causes of failure of thrombectomy, namely old standing and persistent thrombo-embolic disease, where clearance is incomplete and also to the severity of thrombo-
However, many instances of failure in the past have been the result of inadequate appreciation of the fact that iliofemoral thrombosis may be bilateral while only one side is symptomatic, and a consequent over-dependance on clinical signs of deep venous thrombosis. It is now our practice to assess both iliofemoral segments and the inferior vena cava by bilateral iliofemoral venography in all cases of pulmonary embolism, and to base management on these findings (Fig. 19).

Immediate Clinical Response to Thrombectomy

The response to venous thrombectomy both in regard to venous return and pulmonary embolism is striking. Leg swelling decreases over the course of a few hours (Figs. 39 and 40) and pain disappears almost immediately. In some instances the reabsorption of fluid from the limb is so rapid that pulmonary oedema results (Brockman and Vasko, 1965). In severe phlegmasia caerulia dolens, where the limb is cold and sensation depressed with impending venous gangrene these effects are reversed within 4 - 6 hours. This is most marked where clearance is complete but occurs where only a limited thrombectomy has been possible, especially if direct collaterals such as the ascending lumbar have been opened.

A notable feature of pulmonary embolism is the persistence of pleuritic pain in the absence of other evidence of further embolism. The relief from this pain following thrombectomy is dramatic, the patient frequently remarking that it has gone immediately on recovery from anaesthesia. That this is not a psychological effect from anaesthesia is shown by the fact that bilateral femoral venography under general anaesthesia does not produce this relief. Whether this is due to arrest of continuing embolism which Allison and his
co-workers claim is a feature of the disease is not certain (Allison, 1967, Morrell and Dunhill, 1968).

Apart from improving venous return and preventing embolism, thrombectomy often brings the systemic disturbance in thrombophlebitis under control (Fig. 53). This is most important when clearance of the segment is complete, but occurs in the majority of instances of partial clearance (Table XXVIII).

Complications of Thrombectomy

Mortality

Over a 3 month post-operative period 9 patients died, representing a mortality for the whole series of 4%. Two deaths occurred during thrombectomy and were thought to result from embolism, although proof of this was not found at autopsy in one of them. The other 7 deaths were related to recurring embolism. Two of them followed inferior vena caval ligation, one at operation and the other in the immediate post-operative period, both resulting from hypotension which developed immediately after the cava was tied. All of these patients had partial or failed thrombectomies.

Incomplete Clearance of the Iliofemoral Segment

Difficulties in achieving complete clearance of the iliofemoral segment are encountered mainly on the left side (Table XXXIII). The oblique lie of the left common iliac vein, abnormalities about its caval orifice (McMurrich, 1906; Ehrich and Krumbhaar, 1943) and the overlying right common iliac artery make clearance from below difficult. In a number of instances extensive iliofemoral thrombosis is superimposed on previous limited common iliac thrombosis or narrowing (Fig. 29), (Cockett et al., 1967), and in these cases clearance of the common iliac vein is rarely achieved. The introduction of
the Fogarty balloon catheter has improved the results but on occasions repeated attempts at passing it meet with failure, the catheter being deflected up the ascending lumbar vein (Fig. 47) or returning on itself.

Caval Thrombectomy

In 7 patients in the present series thrombectomy was carried out from the inferior vena cava (Fig. 54). In 6 a right transverse incision with an extraperitoneal approach was used, the cava and right common iliac veins being mobilised. The phlebotomy was made on the right antero-lateral aspect of the cava, conveniently placed to facilitate thrombectomy via the orifice of the left common iliac vein. In one case transperitoneal approach was used and the venotomy was made in the upper part of the right common iliac vein.

All 7 patients suffered from severe and extensive iliofemoral thrombosis, and marked systemic manifestations with established or threatened venous gangrene. Two cases had pulmonary embolism and in two cases there was bilateral iliofemoral involvement. In 6 of the 7 cases caval thrombectomy was carried out after failure to achieve adequate clearance from the femoral approach. All 7 cases survived without complications although 2 died later of their primary disease. Follow-up venography in the 5 survivors showed patency of the iliofemoral segment in all cases (Fig. 38 and Table XXXIV).

Caval thrombectomy has been reserved for the most severe cases of thromboembolism where femoral thrombectomy has not been successful, as determined by operative venography. The decision to proceed to caval thrombectomy is made on the basis of the patient's clinical condition. In some cases the presence of venous gangrene or impending gangrene makes clearance of the segment imperative. In other instances severe embolism with per-
sistent extensive caval thrombosis may be the indication for the caval approach.

This limited experience of caval thrombectomy has been uniformly successful and possibly such an approach should be considered more frequently. However, it should only be taken after failure from below, in that it requires a general anaesthetic to be given to a very ill patient and converts a minor to a major operation. With the introduction of balloon catheters of a bigger capacity failure to clear the cava is becoming increasingly rare.

Postoperative Rethrombosis

Postoperative rethrombosis remains a serious complication of venous thrombectomy. When it occurs, the final result as regards venous insufficiency is compromised and the risk of major pulmonary embolism returns. In most instances rethrombosis is due to the presence of residual clot (Table XXII).

Other factors which increase the tendency to rethrombosis are causes of iliac vein compression such as results from a distended urinary bladder (Carlsson and Garstein, 1960; Smith, Gluck and Kallen, 1963), faecal impaction, the presence of pelvic malignancy and iliac vein kinking (Fig. 55 and 56).

It has been a general rule not to transfuse whole blood, either during surgery or in the postoperative period. Initially it was assumed that increasing the haematocrit might predispose to thrombosis as occurs in polycythaemia. Inadvertently one patient received 4 units of whole blood over a 24 hour period in treatment of anaemia (Hb. 60%) on her 8th postoperative day. Previously postoperative venography had shown that clearance of the iliofemoral segment was satisfactory. Within 24 hours of transfusion,
extensive rethrombosis had occurred (Fig. 57). This may also be related to the considerable increase in platelet adhesiveness which occurs after blood transfusion (Bennett, 1968). Whether such a reaction can be prevented by the use of dextran 70 or not, it would seem that blood transfusion is best avoided during the management of patients with iliofemoral thrombosis.

**Thrombectomy in Antepartum Cases**

Antepartum iliofemoral thrombosis represents a special and difficult problem. It is not so uncommon as has been supposed (De Vita, Wiener and Massumi, 1965) and there were 19 cases in the present series (Table XXXV). The nature of the thrombus removed in cases treated early in the postpartum period suggested that many of these cases also originated before delivery. Not only is pre-operative and post-operative venography contra-indicated, so that control is poor, but the presence of the gravid uterus, causing inferior vena caval compression (Scott and Kerr, 1963; Kerr, Scott and Samuel, 1964) and possibly also iliac vein kinking from the pull of the broad ligament, makes rethrombosis a great hazard (Fig. 56). Thrombectomy should not be undertaken without termination of pregnancy, and if the pregnancy is advanced the need for thrombectomy should probably be taken as an indication for early caesarian section. The risk of major pulmonary embolism being precipitated by the abdominal straining of normal delivery should be avoided.

**Discussion**

In the past, series dealing with the treatment of thrombo-embolic disease have related results only to the control of the immediate signs of
the disease, and no interest has been shown in long term morbidity, particularly as it relates to the leg. In the present series results have been related to control of pulmonary embolism, the relief of acute venous insufficiency, and the restoration of a patent iliofemoral segment or a segment with good direct collateral venous channels, both circumstances being associated with normal or near normal venous return in the long term.

The results in the present series with a mortality of 4% compare favourably with other series treated by other methods. Anticoagulant therapy carries a published mortality of 10 - 25% (Barker, 1959; Donaldson, Linton and Rodkey, 1961) and caval interruption 10 - 15% (Moses, 1946; Collins, MacCallum, Nelson, Weinstein and Collins, 1951; Dale, 1958). Each case in this series has been of established iliofemoral venous thrombosis, which represents the clinically serious type of deep vein thrombosis, both in relation to risk from embolism and interference with venous function (Table V). As stated earlier a large number of patients with clinical and venographic evidence of thrombosis limited to the lower segment have been treated conservatively, frequently without anticoagulants, with no deaths. It is therefore, not comparable to other series where many cases of peripheral deep vein thrombosis are included, and in many instances the diagnosis, depending on clinical assessment, often of transient symptoms, is in considerable doubt. Nevertheless, the results obtained with thrombectomy compare more than favourably with results of treatment with anticoagulant drugs.

In the past, thrombectomy has often been reserved for the severe phlegmasia caerulia dolens. While an aggressive approach by thrombectomy supplemented by caval exploration in difficult cases, is certainly indicated in such circumstances, the dramatic results only serve to emphasise the need
for a wider application of the operation. Thrombectomy should be used as the treatment of choice in all cases of iliofemoral thrombosis, whether occlusion is complete or not. Where embolism is the presenting symptom, occlusion incomplete, and the patient at major risk, thrombectomy will eliminate the risk and curtail the disease.

Thrombectomy, by restoring the patency of the iliofemoral segment or by opening up direct collateral channels, such as the ascending lumbar vein, overcomes venous insufficiency. With improvement in surgical technique emphasis in treatment should be more and more on restoration of venous patency, as against any venous interruption, partial or complete. Certainly there is no justification for routine venous ligation at any point above the profunda femoris termination, nor for routine plication of the vena cava.

In cases where thrombectomy either femoral or caval has failed, there is still a role for venous interruption, but to use such methods widely in the presence of established iliofemoral thromboembolism is to court serious morbidity (Dale, 1958; DeMeester, 1967).
Summary

With the realisation that the iliofemoral venous segment is the significant segment in thromboembolism, the theoretical basis for the use of anticoagulant drugs in management is unsound. For this reason and because of the frequent failure of the anticoagulants drugs to control venous thromboembolism and unsolved problems in laboratory control and dose regulation the routine use of these drugs in venous thromboembolism has been abandoned in favour of venous thrombectomy. This operation, by removing all thrombus from the iliofemoral segment, eliminates the risk of major pulmonary embolism, and restores normal venous drainage, thereby relieving acute and chronic venous insufficiency. The efficacy of this procedure is dependent on the clearance achieved, and the latter can be accurately determined only by operative venography. This aim is achieved in 100% of cases operated on in the pre-occlusive phase. With improvements in technique such as the use of the Fogarty balloon catheter and the approach from the inferior vena cava complete clearance is obtained in 75% of cases operated on within 2 days of the onset of occlusion. Operative mortality is 0.9% for the whole series and both were in-patients who had had repeated embolism over a prolonged period before operation producing right heart failure.

The immediate clinical response to thrombectomy is striking. Relief of pain is almost immediate and leg swelling disappears within a few hours. Where persisting pain is a feature of pulmonary embolism it is frequently relieved immediately. Control of embolism however is not complete. It recurred after thrombectomy in 11% of patients and was fatal in 7 (3%). Apart from improving venous return and preventing embolism, thrombectomy often brings the systemic disturbance of thrombophlebitis under control. All of
these effects are most marked when clearance of the iliofemoral segment is complete, but occur in the majority of instances of partial clearance.

The incidence of post-thrombectomy rethrombosis can be determined only by venography, and this has been carried out during the early postoperative period via a small indwelling sapheno-femoral catheter, and in late follow-up at periods of from 3 months to 14 years after operation, either by direct puncture of the femoral vein or intraosseous injection of the greater trochanter. The results indicate that in most instances rethrombosis is due to the presence of residual clot at the completion of thrombectomy. The incidence of rethrombosis was 10% when clearance was complete while it was 32% when it was not.

Delay between complete occlusion of the iliofemoral segment and operation compromises results. Where the delay is greater than 14 days clearance is complete in only 50% of cases and rethrombosis of some degree occurs in 50%. However, this has appeared worthwhile in that the existing venous insufficiency has been relieved to a significant extent and the systemic disturbance associated with the phlebitic process has been controlled.

The results where there has been delay leave room for considerable improvement, and it was felt that a new approach to the problem was required. Consequently the value of fibrinolytic agents has been investigated and the results are presented in the next section.
Despite improvements in the technique of iliofemoral venous thrombolysis such as the introduction of operative venography and the use of high-dose thrombolytic agents, complete clearance of the iliofemoral segment is not achieved in 77% of cases (Table XXII), although the clearance obtained relieves venous insufficiency in almost all instances (Table XXVIII).

Where clearance of the iliofemoral segment is complete, thrombolysis is rare, but it occurs in 12% of cases with incomplete clearance, and this complication is not eliminated by the use of heparin.

By the introduction of purified fibrinolytic agents in vivo thrombolysis has become feasible. Recent opinion favours the use of agents which convert the inactive plasma globulin, plasminogen, to the proteolytic enzyme plasmin (Fig. 36) (Douglass, 1953). Of the two plasminogen activators available for thrombolytic therapy, streptokinase, a bacterial product, has the disadvantage of being relatively cheap and readily available. The alternative human product, urokinase, is neither toxic nor antigenic but is expensive. Experimental studies have shown that these agents will induce thrombolysis when administered at a distance from the site of thrombosis in a dosage which induces systemic fibrinolytic activity or when infused in lower dosage at the site of the thrombus. The latter method avoids the possible haemorrhagic complications of hyperplasminemia which may result from the high dose method (Alkjaersig, Fletcher and Sherry, 1959).

Lack of venographic control largely invalidates the conclusions of most previous clinical trials of fibrinolytic agents in the management of deep vein thrombosis. In contrast to the peripheral segment, venograms can
Despite improvements in the technique of iliofemoral venous thrombectomy such as the introduction of operative venography and the use of the Fogarty catheter, complete clearance of the iliofemoral segment is not achieved in 37% of cases (Table XXII), although the clearance obtained relieves venous insufficiency in almost all instances (Table XXVIII).

Where clearance of the iliofemoral segment is complete rethrombosis is rare, but it occurs in 32% of cases with incomplete clearance, and this complication is not eliminated by the use of heparin.

By the introduction of purified fibrinolytic agents in vivo thrombolysis has become feasible. Recent opinion favours the use of agents which convert the inactive plasma globulin, plasminogen, to the proteolytic enzyme plasmin (Fig. 58) (Douglas and McNicol, 1964). Of the two plasminogen activators available for thrombolytic therapy, streptokinase, a bacterial product, has the disadvantage of being both pyrogenic and antigenic but is relatively cheap and readily available. The alternative human product, urokinase, is neither toxic nor antigenic but is expensive. Experimental studies has shown that these agents will induce thrombolysis when administered at a distance from the site of thrombosis in a dosage which induces systemic fibrinolytic activity or when infused in lower dosage at the site of the thrombus. The latter method avoids the possible haemorrhagic complications of hyperplasminaemia which may result from the high dose method (Alkjaersig, Fletcher and Sherry, 1959).

Lack of venographic control largely invalidates the conclusions of most previous clinical trials of fibrinolytic agents in the management of deep vein thrombosis. In contrast to the peripheral segment, venograms can
be accurately interpreted when the iliofemoral venous segment is the site of venous thrombosis. The indwelling sapheno-femoral catheter technique described previously provides for frequent venography during the administration of fibrinolytic agents, and allows a meaningful assessment of the extent of thrombolysis produced.

Three separate studies with fibrinolytic agents have been carried out:

(1) A study using local, low dose infusion of urokinase in the management of incomplete thrombectomy and rethrombosis after thrombectomy.

(2) A study using local, high dose streptokinase in the management of post-thrombectomy rethrombosis.

(3) A study using local, high dose streptokinase without thrombectomy in the management of late cases of occlusive iliofemoral thrombosis.

These studies were carried out consecutively, and the results and conclusions drawn from each are presented separately, because these conclusions determined the form of the next investigation. Finally the present position of these drugs in our programme of management is explained.
LOCAL LOW DOSE UROKINASE IN ILIOFEMORAL VENOUS THROMBOSIS

In this study 10 patients were treated with urokinase following thrombectomy; four had residual thrombus and six patients had early rethrombosis (Appendix V). Following thrombectomy an indwelling saphenofemoral catheter was inserted and post-operative venography carried out (Fig. 99). When residual iliofemoral clot or rethrombosis was detected, treatment with urokinase was started. The critical activator concentration of urokinase was dissolved in 1 ml. of normal saline and infused through the indwelling catheter at a rate of 1 - 2 ml. per minute using a constant infusion Palmer pump (Yeapogos and Pluts, 1964). In later cases higher dosage was used (Table XXXVII).

Venograms were performed before, during and after each urokinase infusion. The venogram was considered the sole criterion of thrombolysis.

Laboratory Methods

Euglobulin lysis times were performed by the method of Nilsson and Glop (1963). Platelet plasmaglog was estimated by the coagulolytic technique of Roentgen and Cohen (1949) as modified by Alkjaerg et al. (1959). Plasma fibrinogen was assayed by a modification (Ogston and Ogston, 1960) of the method of Ratnoff and Menzie (1951). The critical activator concentration was determined as described by Pluts (1964).

Results

Table XXIV shows that local urokinase infusions had little or no effect on residual post-thrombectomy thrombus. Only in Case 1 was slight thrombolysis produced (Fig. 60).
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Venograms were performed before, during and after each urokinase infusion. The venographic appearance constituted the sole criterion of thrombolysis.

Laboratory Methods

Euglobulin lysis times were performed by the method of Nilsson and Olow (1962). Plasma plasminogen was estimated by the caseinolytic technique of Remmert and Cohen (1949) as modified by Alkjaersig et al. (1959). Plasma fibrinogen was assayed by a modification (Ogston and Ogston, 1966) of the method of Ratnoff and Menzie (1951). The critical activator concentration was determined as described by Flute (1964).

Results

Table XXXVI shows that local urokinase infusions had little or no effect on residual post-thrombectomy thrombus. Only in Case 1 was slight thrombolysis produced (Fig. 60).
The effect of urokinase on freshly reformed thrombus was more impressive (Table XXXVII; Figs. 61, 62, 63, 64 and 65). Only one case failed to show any thrombolysis, and this patient had proximal involvement of the inferior vena cava by a malignant tumour. In Case 10 lysis was produced in a segment which was completely occluded (Fig. 65).

No allergic manifestation or toxic effects were noted in any of the cases. No significant alterations occurred in the euglobulin lysis time, plasma plasminogen and plasma fibrinogen during the urokinase infusions. Wound healing was by first intention in all patients and there were no infective complications associated with the infusion.

Discussion

The aim of local low dose urokinase therapy is to administer sufficient urokinase directly to the site of thrombosis to induce thrombolysis but insufficient to produce systemic hyperplasminæmia with consequent risk of bleeding. The absence of significant change in the plasma fibrinogen, plasminogen, and euglobulin lysis time (Table XXXVIII) and the absence of toxic effects indicates the safety of this technique of urokinase administration.

The poor result obtained when urokinase was used to lye residual thrombus is disappointing through not unexpected. The susceptibility of a thrombus to thrombolytic agents decreases with its age (Back et al., 1958). It has been shown that clot in the iliofemoral segment may antedate clinical thrombosis by weeks or even months (p. 41), and it is this old, hard, white thrombus, composed of platelets and cellular matter with a low fibrin content that is most adherent at thrombectomy and remains as residual thrombus (Fig. 16).
Conclusive proof is presented that local urokinase therapy can stimulate lysis of recently formed in vivo thrombus. This demonstrates that urokinase administered in low dosage to the site of the thrombus has a thrombolytic action. In all cases, however, there was rethrombosis after therapy was discontinued. Prolonged anticoagulant therapy might have prevented this, but as yet there is no proof. Most authors have employed anticoagulants because of theoretical considerations (Fletcher et al., 1959 and McNicol et al., 1964) but Fletcher et al. said they noted no ill effects in the patients in whom the drugs were not given.

It is of interest that lysis was produced in a completely occluded segment of vein in one patient (Case 10) since it has been reported that occlusive venous thrombi are resistant to fibrinolytic agents (Rischlau, 1964; Browse et al., 1968).

The high cost of urokinase (£76 to £456 per patient in this series) underlines the importance of the careful assessment of its indications and limitations as a fibrinolytic agent. The results obtained indicate that at least in the dosage hitherto recommended local urokinase therapy is not a useful adjunct to thrombectomy in the management of iliofemoral venous thrombosis, although it may have a place in the management of rethrombosis.

At this stage in the investigation two problems presented themselves. First, would a higher dose of fibrinolytic agent produce more thrombolysis than the low dose used in this study, and still not give rise to serious complications? Second, would currently available anticoagulant drugs prevent rethrombosis when adequate thrombolysis had been achieved? In an attempt to resolve these problems the investigation presented in the next section was carried out. Because of the prohibitive cost of urokinase it was decided to use streptokinase in the higher dose scheme.
LOCAL HIGH DOSE STREPTOKINASE IN POST-THROMBECTOMY RETHROMBOSIS

In this study 9 patients received streptokinase, in a dosage designed to produce systemic fibrinolytic activity, for rethrombosis occurring within 14 days after venous thrombectomy (Appendix VI). Postoperative venography accurately established the time of rethrombosis (Table XXXIX). The streptokinase was administered through the indwelling saphenous-femoral catheter by means of a constant infusion Peristaltic pump, as in the previous study. Venograms, carried out via the saphenous-femoral catheter, were repeated before, during and after the streptokinase infusions.

Changes in venographic appearances provided the sole criterion of thrombolysis. All patients received heparin for 36 hours following streptokinase, and 6 received verapamil thereafter. The dosage was aimed at keeping the prothrombin ratios at 0.4. If the drug was continued for 6 weeks following streptokinase infusion.

The Titrated Initial dose was infused over a period of 30-50 minutes followed by a fixed dose of 750,000 units in the first 6 hours with 750,000 units in each subsequent 6-hour period of treatment. The infusion was discontinued if lysis was complete, if no further lysis had occurred in a period of at least 6 hours, or if laboratory study indicated that a potential haemorrhagic state existed.

The Titrated Initial dose is the quantity of streptokinase necessary to neutralise circulating inhibitor and any antibody to streptokinase resulting from previous streptococcal infection. It is assessed by determining the minimum amount of enzyme producing lysis of a 1 ml. platelet clot in 18 minutes at 37°C, and multiplying this value by the assumed blood volume.

Regular coagulation and fibrinolytic assays were carried out during and
LOCAL HIGH DOSE STREPTOKINASE IN POST-THROMBECTOMY RETHROMBOSIS

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Change in venographic appearances provided the sole criterion of thrombolysis. All patients received heparin for 36 hours following streptokinase, and 8 received warfarin thereafter. The dosage was aimed at keeping the prothrombin ratio at 2.5 - 3.5 times normal, and the drug was continued for 6 weeks following streptokinase infusion.

The Titrated Initial Dose of streptokinase was infused over a period of 20 - 30 minutes followed by a fixed dose of 750,000 units in the first 4 hours with 750,000 units in each subsequent 8 hour period of treatment. The infusion was discontinued if lysis was complete, if no further lysis had occurred in a period of at least 8 hours, or if laboratory study indicated that a potential haemorrhagic state existed.

The Titrated Initial Dose is the quantity of streptokinase necessary to neutralise circulating inhibitor and any antibody to streptokinase resulting from previous streptococcal infection. It is assessed by determining the minimum amount of enzyme producing lysis of a 1 ml. plasma clot in 10 minutes at 37°C. and multiplying this value by the assumed blood volume.

Regular coagulation and fibrinolytic assays were carried out during and
after the infusion of streptokinase. Euglobulin clot lysis time and fibrinogen and plasminogen levels were estimated as described in the previous section. Quick one-stage prothrombin times and thrombin clotting times were carried out using citrated plasma. The above 5 assays were carried out on all patients serially during and for 24-48 hours after streptokinase therapy.

Fibrin plates prepared after the method of Astrup and Mullertz (1952) and heated fibrin plates as described by Lassen (1952) were used to detect the presence of free plasma activator and free plasma plasmin throughout the infusions in the first 4 cases. Kaolin-cephalin clotting times were performed in several patients in whom a marked fall in plasma fibrinogen occurred and who might therefore have shown evidence of consumption of other coagulation factors.

Results

Clinical

Details of the results of streptokinase therapy are presented in Table XXXIX. Eight of the 9 cases showed radiographic evidence of lysis; in the majority this was extensive (Figs. 66, 67, 68, 69 and 70). In 3 of the 5 cases where the main vein was completely occluded a patent main channel was produced (cases 3, 4 and 8) and in the two others (cases 2 and 4) the ascending lumbar vein was opened to act as a direct collateral. Of the non-occlusive thrombi one (case 6) showed complete and another (case 1) almost complete lysis, another (case 5) was markedly improved and the fifth (case 9) was unaltered by streptokinase.

Cases 2 and 3 showed significant lysis of thrombi proved venographically to be 12 and 30 days old; in the latter case patency of the main vein was re-established (Fig. 68).
The time of maximum lysis varied considerably and in cases 1, 2, 3 and 5 venographic evidence of continued lysis was obtained 41, 116, 35 and 24 hours after termination of the streptokinase infusion (Table XXXIX). 

Rethrombosis occurred in 2 cases and in one of these (case 8) this occurred after extensive thrombolysis and while streptokinase was still being infused.

The complications of therapy are shown in Table XL. Cases 1 - 6 received no steroid prior to streptokinase and of these, 3 had severe reactions in the form of fever, rigors, muscle pain or nausea. These were controlled by steroid therapy. The last three cases (cases 7 - 9) received 20 mg. prednisone orally prior to treatment and no reactions were noted. Case 8 had profuse bleeding from his wound at the end of and for some hours after cessation of the streptokinase infusion, and received 5 units of whole blood by transfusion. This wound subsequently broke down. Small wound haematomas occurred in 4 patients, but required no treatment and did not prevent wound healing by first intention. Pulmonary embolism was not observed.

Three patients died, case 1 three weeks after streptokinase of gastric carcinoma with extensive hepatic metastases, case 3 six days after cessation of streptokinase of an extensive empyema which had been present for some time before treatment and case 4 three days after treatment as a result of a myocardial infarction. This last case, a diabetic woman of 73, developed chest pain and acute left ventricular failure about 24 hours after completion of streptokinase therapy; post mortem examination showed that the major coronary arteries were severely stenosed by calcific atheroma, but were completely free of thrombus.
Details of dosage and duration of therapy are present in Table XII.

Follow-up venography was carried out on case 5, 2 months after the streptokinase infusion. A patent main channel had been maintained and the residual caval thrombus had decreased so that the vein appeared normal (Fig. 70).

**Laboratory**

In all cases clear evidence of the presence of systemic fibrinolytic activity was obtained in the first assays carried out after commencement of streptokinase infusion. Marked shortening of the euglobulin clot lysis time occurred (pre-infusion euglobulin clot lysis times ranged from 180 - 1000 minutes and the shortest lysis times attained during treatment varied from 5 - 40 minutes) and was maintained throughout each infusion. Free activator was present in whole plasma throughout the infusions, but free plasmin was detectable only rarely and in small quantity where estimated by heated fibrin plate assay. Plasma plasminogen fell to very low levels soon after the start of therapy and remained at levels approaching zero throughout, returning to approximately pre-infusion values over the 2 days after the termination of the infusions. Moderate to marked prolongation of the thrombin clotting time occurred during therapy in all cases (Fig. 71).

Progressive depression of plasma fibrinogen levels occurred during treatment and in case 4 this continued for 24 hours after the end of treatment. The mean initial fibrinogen level was 448 mg./100 ml. and the mean fall during treatment was 228 mg./100 ml. In cases 1, 4 and 6 low levels were reached, 80, 80 and 130 mg./100 ml. respectively at the end of, or on the day following, cessation of streptokinase. The one-stage prothrombin time showed no change or increases of up to 6.5 seconds during treatment
with the exception of case 6 in which prothrombin time increased from 18 to 32 seconds and remained prolonged during the streptokinase infusion.

The kaolin-cephalin clotting time was measured serially throughout treatment in case 1 and in cases 4 and 6 at the times of maximum depression of plasma fibrinogen levels; it was found to be normal in all cases. Alteration in coagulation factors was therefore confined mainly to depression of the plasma fibrinogen, the extrinsic clotting system as assessed by the one stage prothrombin time being markedly altered in one case only, and the intrinsic clotting system as assessed by kaolin-cephalin clotting time being normal where estimated.

The most extensive thrombolysis occurred in those cases showing greatest fall in plasma fibrinogen levels (cases 1, 3, 4 and 6). The only case showing no lysis had the least fall in fibrinogen level. Wound bleeding and wound haematomas occurred in the patients in whom alteration in the coagulation and fibrinolytic factor assays were least marked (Tables XL and XLI).

Discussion

Definite thrombolysis was produced in all but one of the 9 cases treated with local high dosage streptokinase therapy. Lysis was more marked than in the cases treated with low dose urokinase, and in many instances the circumstances were less favourable in that the thrombus was older and occluded the vessel. It would appear, therefore, that lysis produced by locally administered fibrinolytic agents is dependent on the dose of the drug. This is supported by the fact that lysis was most marked where there was most evidence of systemic fibrinolytic activity as indicated by the fall in plasma fibrinogen. The only case which failed to show significant lysis showed
least alteration in fibrinogen. The only other possible explanation of the difference between the two series is that streptokinase is a more effective fibrinolytic agent but numerous experimental studies have failed to show such a difference.

It is of interest that significant lysis was achieved in thrombi demonstrated to be 12 and 30 days old and that in the latter case patency of the main vein was re-established. Although the susceptibility of thrombus to fibrinolytic agents probably decreases with the duration of the thrombosis (Back, Ambrose, Simpson and Shulman, 1958), these results suggest that in clinical venous thrombosis the age of the thrombus is not invariably critical and that successful lysis of relatively old thrombi may be achieved.

Occluding venous thrombi are said to be much less susceptible to lysis by streptokinase (Browse, Thomas and Pim, 1968) and by the proteolytic enzyme from Aspergillus oryzae (Roschlau, 1964). The explanation offered is that where the thrombus is occlusive diffusion of the fibrinolytic agent through the thrombus is poor. The results in this study indicate re-establishment of the main channel in 3 of 5 cases of occlusive thrombosis and lysis of an occluding thrombus was achieved by local low-dose urokinase in one case. In the present study delivery of streptokinase into the iliofemoral segment may have contributed to lysis of the occlusive thrombi in spite of the intention of achieving thrombolysis by inducing systemic fibrinolytic activity. Local delivery resulting in a high concentration of the agent at the site of thrombus may aid diffusion into it and so increase thrombolysis.

In at least four cases lysis continued for some time after streptokinase therapy was stopped and after evidence of systemic fibrinolytic activity had
subsided. The most extreme example of this was case 2, where clot lysis was maximal 5 days after the onset of therapy and 4 days after cessation. Further information is required as to whether local application does confer advantages in relation to clot lysis and implications as to a possible shorter dosage scheme.

All of these findings suggest that higher dosage of fibrinolytic agents is more effective in producing thrombolysis and that local delivery of the drugs may confer advantages. The latter suggestion is supported by early experimental experience (Karmody, 1969). There remains the question of the safety of higher dosage.

The aim was to achieve thrombolysis by inducing systemic fibrinolytic activity, but to avoid bleeding by close laboratory control of total dosage. Significant hypofibrinogenaemia developed in 3 patients and treatment was discontinued because of this in 2 cases. These patients, however, showed no haemorrhagic manifestations other than minor oozing from venepuncture sites. Those patients who did show haemorrhagic features had the least marked alteration in their coagulation and fibrinolytic assays, and it is difficult, therefore, to relate their bleeding to thrombolytic therapy alone. Four of these patients received streptokinase within 5 days of operation and this clearly may be a factor of importance in the development of bleeding.

High dosage of fibrinolytic agents, therefore, may safely be employed provided there is adequate laboratory monitoring of therapy to avoid the development of dangerous hypofibrinogenaemia. Recent surgery complicates matters and such high dose infusions should be avoided within a few days of operation. For this reason it would be unsafe to employ such therapy for residual thrombus after thrombectomy, as was done with low-dose urokinase
in the previous study.

Conventional anticoagulant therapy was employed in all cases in accordance with accepted practice (Alkjaersig et al., 1959; Douglas and McNicol, 1964). Despite this early rethrombosis occurred in 2 cases (cases 7 and 8), although in one (case 8) the process had started while streptokinase was still being infused. However it is apparent that rethrombosis still presents a problem, in which the intense inflammatory reaction in the vein wall commonly observed at thrombectomy may well be detrimental.

Because streptokinase will lyse old occlusive thrombus, and thrombectomy is least effective in cases of occlusive iliofemoral venous thrombosis presenting late, it was decided to investigate the value of local high dose streptokinase in such cases without attempting thrombectomy.
LOCAL HIGH DOSE STREPTOKINASE WITHOUT THROMBECTOMY IN Ilio-Femoral Venous Thrombosis

In this study 4 patients were treated by infusing streptokinase, in a dosage designed to produce systemic fibrinolytic activity, into the ilio-femoral segment without thrombectomy (Appendix VII). The saphenous vein or one of its tributaries was cannulated at the groin and the catheter manipulated so that the tip was at the sapheno-femoral junction. The infusion was delivered by the constant infusion pump. Dosage, venography and laboratory monitoring were the same as in the previous study. All patients received anticoagulant drugs following the infusion.

In two cases the infusion was given for late exclusive ilio-femoral thrombosis, and in the other two the patient's cardio-pulmonary state was so poor that thrombectomy could not be undertaken.

Details of the cases and the results of treatment are given in Table XLIII. These show that extensive thrombolysis was produced in all 4 cases, and in three of the four the ilio-femoral segment was cleared. In the two cases with cardio-pulmonary decomposition this was rapidly corrected.

Discussion

The results in these four cases confirm the efficacy of streptokinase as a thrombolytic agent in venous thrombosis (Figs. 72 and 73). Until these studies were undertaken it had never been conclusively shown that thrombolysis could be achieved under such conditions.

Many problems remain in regard to control and dosage of the drug and the prevention of rethrombosis where lysis has been achieved. The extensive literature on fibrinolytic agents has been confined to studies of the
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Discussion

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Many problems remain in regard to control and dosage of the drug and the prevention of rethrombosis where lysis has been achieved. The extensive literature on fibrinolytic agents has been confined to studies of the
physiology of fibrinolysis and the safety of such therapy. However, objective evidence of clinical effect has been lacking and many unwarranted assumptions have been made. It has been assumed too frequently that where fibrinolytic activity, as judged by reduced euglobulin clot lysis time, fibrin plate lysis and fibrinogen destruction, has been induced in the systemic blood that a thromolytic state has been produced. This is not necessarily so. Further it has been shown experimentally that fibrinolytic agents when infused locally will produce lysis of a thrombus without fibrinolytic activity being detected in the blood, and that similar lysis could be produced by systemic infusion inducing fibrinolytic activity. It has been too readily assumed that there is no advantage in giving the higher dose locally. The results in the present series show that this may not be so.

‘Fibrinolytic activity’ so called does not necessarily mean thrombolytic activity, it merely represents a state where artificial fibrin clots will be lysed in the laboratory and nothing more. Such assays are a measure of the activity produced but not of the therapeutic effect produced. They provide a guide to the margin of safety from haemorrhagic complications. This simple point is of fundamental importance if further progress towards rational use of these drugs in practice is to be made. Only if objective evidence of lysis is produced should the term thrombolysis be used.

The meaning of certain laboratory tests is also in doubt where fibrinolytic agents have been administered. In particular the value of thrombin clotting time as a guide to when heparin therapy may safely be employed is uncertain. It is known that certain fibrinogen degradation products (F.D.P.S.) have a heparin-like effect. They alter the thrombin clotting time, interfere with fibrin polymerisation and may give rise to haemorrhagic com-
plications. However, the extent to which they alter in vitro thrombin clotting time is not necessarily a measure of their efficiency in preventing in vivo thrombus formation in the presence of intimal damage resulting from severe phlebitis, as shown in case 4 (Fig. 73). It is of interest that whole blood clotting was normal while the thrombin clotting was prolonged at the time when this rethrombosis occurred (Table XLIII).

It may be that heparin therapy started immediately after streptokinase will prove ineffective in preventing rethrombosis, or it may give rise to serious haemorrhagic complications. It is important, however, to establish if this is the case, so that other means of preventing rethrombosis such as the use of the new anticoagulant drug Arvin or anti-platelet agents, like Dextran 70, may be explored.

Summary and Conclusions

Fibrinolytic agents have a place in the management of iliofemoral venous thrombosis. Local urokinase is disappointing in low dosage, and high costs prohibit its use in higher doses. Streptokinase, in a dosage sufficient to induce systemic fibrinolytic activity, produces significant thrombolysis when infused locally at the site of thrombosis. Complete clearance was achieved in 6 out of 13 cases of iliofemoral thrombosis. It is effective in lysis of old and occlusive iliofemoral thrombus as well as fresh thrombus reforming after thrombectomy. There appears to be considerable and hitherto unsuspected advantage in infusing the high dose of the drug locally. It should not be employed within a few days of operation because of the danger of haemorrhage from the wound and careful laboratory monitoring is essential to avoid dangerous hypofibrinogenaemia. Rethrombosis is no less a problem following thrombolysis than thrombectomy and requires more extensive study.
However, streptokinase has been incorporated into our current programme of management of iliofemoral thrombosis and is now our first line of management in late occlusive cases and in rethrombosis after thrombectomy. Where recurrent embolism has led to serious impairment of cardiopulmonary function, and thrombectomy is hazardous, streptokinase has proved effective both in lysing the iliofemoral thrombus and improving the lung lesion.
VENOGRAPHY IN IlioFemoral Venous Thromboembolism

Because iliofemoral venography has contributed so much to our knowledge of the pathology of deep vein thrombosis, its accurate clinical diagnosis, and assessment of therapeutic measures, it is proposed briefly to review this subject.

Much of the confusion that has surrounded the management of venous thromboembolism has been the result of difficulties in diagnosis and the failure to correlate clinical features with the causative pathological lesion. The introduction of venography by De Sauty (1950) offered hope of overcoming these difficulties. Unfortunately, attention has been focused on the veins below the knee (Bauer, 1950) and because of difficulties in interpretation of venograms at this level, venography has not been adopted as a routine diagnostic aid.

The realization that the iliofemoral segment is the area of significant venous thrombosis, both in regard to pulmonary embolism and severe acute and chronic venous insufficiency has emphasized that in the management of thromboembolic disease, it is essential to obtain precise knowledge of the state of the iliofemoral segment. This can readily be achieved by several venography, either in the course of venous thrombectomy, or by direct femoral vein puncture, or by intra-cannon injection via the greater trochanter.

Operative Venography

The technique of thrombectomy with venographiccontrol has been described elsewhere (p. 63), and 67 patients have been operated on in this summer without any complication arising from venography.

Discussion

Accurate information about the progress of venous insufficiency is only
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The realisation that the iliofemoral segment is the area of significant venous thrombosis both in regard to pulmonary embolism and severe acute and chronic venous insufficiency has emphasised that in the management of thrombo-embolic disease, it is essential to obtain precise knowledge of the state of the iliofemoral segment. This can readily be achieved by femoral venography, either in the course of venous thrombectomy, or by direct femoral vein puncture, or by intra-osseous injection via the greater trochanters.

Operative Venography

The technique of thrombectomy with venographic control has been described elsewhere (p. 63), and 67 patients have been operated on in this manner without any complication arising from venography.

Discussion

Accurate information about the progress of venous thrombectomy is only
available if the procedure is carried through under venographic control, and the early post-operative period monitored by frequent venography. In the absence of such control exaggerated claims have been made for the operation and many of the problems have been inadequately appreciated.

It is patently valueless to assess the result of the operation on the basis of the immediate clinical response as regards the relief of acute venous insufficiency alone, when knowledge of the collateral venous circulation is wanting. Clearance of the external iliac vein only, with opening of the ascending lumbar collateral circulation, will relieve venous insufficiency, and this finding at late venographic follow-up may be wrongly interpreted as evidence of postoperative rethrombosis.

Assessment of venous clearance on the bleed back from the proximal segment is misleading. Operative venography will demonstrate that free bleeding from the proximal vein will occur after clearance beyond the internal iliac vein, even in the presence of complete common iliac vein occlusion, and residual external iliac thrombus, the blood in such circumstances, coming from the internal iliac vein (Fig. 23). Such a situation is prone to early postoperative rethrombosis, occurring in 40% of cases (Table XXII). Modification, such as determining the flow after dilatation with forceps (Diethrich, 1967) add nothing and cannot compare with operative venography as a means of assessment.

The ability to insert a catheter a long and measured distance proximally in the deep vein is also imprecise as an indication of the extent of clearance. Venography has demonstrated that a catheter can pass readily for a considerable distance along a large ascending lumbar vein, especially in the presence of common iliac vein occlusion (Fig. 47).
Diagnostic Femoral Venography

The diagnosis of occlusive iliofemoral venous thrombosis is usually easy provided the significance of high signs is appreciated. However, in some cases in which the onset is insidious, tenderness may be minimal, oedema slight and increased girth not helpful because of pre-existing differences in leg size. Under such circumstances femoral venography either by direct puncture or by the intraosseous trochanteric route may give valuable information (Fig. 74).

Venography in the Management of Pulmonary Embolism

The significance of Sevitt and Gallagher's studies (1961) which showed that, for a time at least, 60% of iliofemoral venous thromboses are clinically silent has until now not been appreciated. Sevitt, rightly surmised, that in such circumstances the thrombus must be non-occlusive. The use of bilateral femoral venography as an aid to diagnosis in cases of pulmonary embolism without leg signs has confirmed that such a stage of non-occlusive iliofemoral venous thrombosis is not uncommon (Figs. 19, 24 and 28).

Clinical awareness of the pathologicallrole of the iliofemoral segments in pulmonary embolism without leg signs leads therefore to the need in many instances for bilateral femoral venography. In this way cases of early incomplete occlusion of the iliofemoral segment can be detected and appropriate therapeutic measures taken. If, on the other hand, there is no evidence of iliofemoral venous involvement, it can be assumed that the functionally and clinically less important distal segment is the site of venous thrombosis. The patient therefore is not at risk from major embolism.

Iliofemoral venous thrombosis is frequently bilateral. The pathological process does not proceed at the same rate on both sides and one may
give rise to symptoms of occlusion while the other is still silent. In the past many instances of failure of thrombectomy to control embolism have resulted from an over reliance on physical signs without adequate visualisation of the contralateral iliofemoral segment. It is now routine practice to assess both iliofemoral segments and the inferior vena cava by bilateral femoral venography in all cases of pulmonary embolism, and to base management on these findings.

Where pulmonary embolism complicates superficial phlebitis of the long saphenous vein it is important that attention is directed to the state of the iliofemoral segment and that high saphenous ligation is combined with bilateral iliofemoral venography and thrombectomy where appropriate (p. 64).

**Indwelling Sapheno-femoral Catheter**

The use of the indwelling sapheno-femoral catheter has been described previously (p. ). This technique allows assessment of progress following thrombectomy and during and after infusions of fibrinolytic agents. Such objective observation is essential if conflicting claims for various therapeutic measures are to be fully assessed. This technique provides a model system in which therapeutic advances may be tested.

**Venography in Follow-up Studies**

For full assessment of the long term results of venous thrombectomy venographic visualisation of the iliofemoral segment is essential. Correlation of venographic findings allows an adequate assessment of the effectiveness or otherwise of the collateral venous circulation. From such venographic studies it is possible to assess prognosis in cases of the poor collateral circulation type of postphlebitic syndrome and to assess those cases where venous reconstruction may be indicated. In general this will
be reserved for the patient with complete iliofemoral venous thrombosis in whom the venous return depends entirely on poorly supported visceral cross communications to the contralateral iliofemoral segment. The more limited common iliac segmental occlusion appears in most instances to be well compensated provided there are direct ascending lumbar channels, and although limited local surgery in the form of patch grafting (Cockett et al., 1965) may be technically easy it will not frequently be necessary. In any event the decision for or against reconstruction should probably not be made until several years following the thrombotic episode to allow the collateral circulation to develop to its full extent.
Summary and conclusions

With the realisation that the iliofemoral segment is the important region in venous thromboembolism, venographic visualisation of this segment is of fundamental importance. Iliofemoral venography can be performed in diagnosis by direct femoral puncture or by intraosseous injection of the greater trochanter. In control of management it is an integral part of the operation of venous thrombectomy. The use of the indwelling sapheno-femoral catheter is essential for adequate assessment not only of thrombectomy but of any other form of treatment such as thrombolytic therapy and only by the use of such objective observations will erroneous claims for various therapeutic measures be disproved. Iliofemoral venography, therefore, provides a measure of control of diagnosis and treatment of venous thromboembolism not hitherto available.
VENOUS RECONSTRUCTION

The incidence of chronic venous insufficiency following venous thrombectomy for iliofemoral thrombosis is 10% (Tables XX and XXIII) and with earlier referral in the acute phase this result will improve. Not all of the patients with venous insufficiency will have symptoms severe enough to warrant venous reconstruction and in the majority conservative measures, which include elastic support, avoidance of prolonged dependence and elevation of the feet at night, will suffice. However, in a minority of patients with severe venous insufficiency and marked venous hypertension, venous reconstruction if successful will afford considerable benefit. In an attempt to assess what success might be expected venous bypass grafts were inserted into the femoral vein in 30 days.

Material and Methods

VENOUS RECONSTRUCTION

Healthy mongrel dogs of weights varying between 15 and 25 kilograms were used. They were anaesthetised with intravenous nembutal (pentobarbital sodium) in doses of 5 mg./Kilo. The operations were conducted with careful aseptic technique and attention was paid to absolute haemostasis.

The right superficial femoral vein (donor) was exposed and all its tributaries divided and ligated with fine linen. Care was taken during dissection not to hold the vein and to remove all excess adventitia. Lengths of vein varying from 5 to 10 cm. were obtained. The vein was left in situ until the recipient left superficial vein was completely exposed. The donor vein was then excised and carefully washed free of blood with heparinised saline (12,500 u heparin/500 ml. saline).

The right femoral vein was then inserted as a side-to-end/end-to-side bypass graft of the left femoral vein below the level of the profunda
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Material and Methods

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The right superficial femoral vein (donor) was exposed and all its tributaries divided and ligated with fine linen. Care was taken during dissection not to hold the vein and to remove all excess adventitia. Lengths of vein varying from 6 to 10 cm. were obtained. The vein was left in situ until the recipient left superficial vein was completely exposed. The donor vein was then excised and carefully washed free of blood with heparinised saline (12,500 u heparin/500 ml. saline).

The right femoral vein was then inserted as a side-to-end/end-to-side bypass graft of the left femoral vein below the level of the profunda
femoris ostium. The recipient femoral vein was occluded above and below the anastomotic sites with light Blalock clamps and washed clear of blood with heparin saline. Careful technique was used throughout with minimal handling of the very edges of the vein and sacrifice of the small piece of vein traumatised by the forceps. The anastomoses were constructed using everting horizontal mattress sutures for the upper and lower corners of the anastomoses and a continuous over and over suture, taking "bites" of less than 1 mm. and sutures being 1 mm. apart (Mavor, 1963). Waxed 5/0 braided silk arterial sutures on 10 mm. straumatic needles were used throughout. The anastomoses were made twice the width of the recipient vein. Before releasing the clamps the recipient femoral vein was ligated with linen above the lower and below the upper anastomosis (Fig. 75 and 76). On releasing the clamps the graft was seen to distend and the graft was checked to see that adventitial snaring had not produced narrowing and that there was no funnelling of the anastomoses.

Vein patency was checked by means of venography carried out using 60% urografin injected through a peripheral vein (Fig. 77). Venograms were taken at 2 stages, namely early within 2-4 weeks of inserting the graft, and late at intervals varying from 6 months to 2½ years. Occasionally more frequent venograms were carried out. When the animals were sacrificed the vein graft was resected. It was checked macroscopically for patency (Fig. 78) and was then subjected to histological examination.

Results

The operation was completed on 20 dogs. There were no deaths in the series. The grafts were inserted in 3 series and the results are shown in Tables XLIV and XLV.
In the first 6 grafts a 50% patency rate was achieved, the first 2 thrombosing. In the second group 5 of the 6 remained patent and 100% patency was achieved in the Group III. In the latter group one graft (Dog No. 15) appeared thrombosed when venography was carried out at 4 and 8 weeks but was patent on exposure for removal and venography by direct femoral vein puncture showed a normal graft (Fig. 79).

Discussion

With increasing interest in reconstructive surgery of the venous system considerable experimental work has been undertaken. Most of this has been directed towards replacement of large veins such as the venae cavae (Bryant et al., 1958; Ohara and Sakai, 1957). Early experience was discouraging but reports of good results are increasing (Sauvage and Gross, 1960; John et al., 1961). Many of these reports are concerned with end-to-end anastomoses which will probably not be used in peripheral venous reconstruction, and various substances such as anticoagulants and dextrans have been used in an attempt to reduce the incidence of graft thrombosis (Eadie and De Takats, 1966). Eadie and De Takats experiments were on very short segments of vein (0.5 cm.) inserted as end to end grafts. Such small grafts are difficult to handle and the high thrombosis rate in their series in cases not given adjuvant therapy confirms this. It was proposed to study this in the present series but the results in the control group (Group III) were uniformly good so that it was not possible to carry out such a comparison. Experience has shown that anticoagulant drugs do not affect the outcome of arterial reconstructions and that adjuvant therapy such as dextrans has little influence. In clinical venous reconstruction, therefore, such therapy will probably have no place.
Dale showed that, with increasing experience of the delicate technique required in handling vein as a graft material predictably good results could be obtained in the arterial system (Dale, 1960).

The present series confirms that this is true of the venous system also. Table XLV shows the grafts in chronological sequence and shows that the only failures occurred in the first eight grafts, and two of these were the initial attempts at the operation. During this period the operator and assistant became increasingly proficient in handling the grafts and during the same period the operator developed an increasing experience of the use of vein as a graft material in the reconstruction of human arteries so that technique at the end of the series was vastly superior to that at the beginning. Extremely delicate technique is required, for the femoral vein of the dog is a much less rigid and thinner walled vessel than the human saphenous vein, the most useful vessel for clinical venous reconstruction. The work of Robertson and his co-workers (1959) has shown that minor trauma to vein will encourage thrombus formation and for this reason the corners of the grafts, where they had been held by forceps, were excised. The lightest Blalock clamps were used for the same reason.

Where the vein graft was patent at early venographic follow-up it remained patent until the animal was sacrificed (Table XLV). There was no tendency for the graft to become narrower or to contract in length. If early thrombosis due to technical difficulties can be avoided it would appear that long-term patency can be anticipated in human veno-venous grafts.

Considerable attention has been focused on the question of recanalization of a vein graft in the venous system which has thrombosed in the early postoperative period. Experience of experimental and clinical vein by-pass
grafts in the arterial system and of thrombosis in the arterial system and venous system suggests that such an occurrence is unlikely. This phenomenon has not been observed in this series, but the observations made on Dog No. 15 in this series may explain some instances, at least, of apparent recanalisation (Fig. 79). This highlights the difficulty of assessing graft patency by venography utilising injection of a superficial peripheral vein, because in such circumstances the dye may all pass into the abundant collateral channels. It may be that in some instances thrombus is laid down at the suture lines and narrows the ostium, making it easier for dye to pass into the collateral channels. With the decrease in this thrombus that occurs with organisation, the orifice will become wider and the graft will then be visualised. This, however, is a different phenomenon from that implied by the term recanalisation as used in the literature.

Dale (1960) pointed out that the walls of a vascular graft were prevented from collapsing by the intraluminal pressure and not their inherent rigidity. Ligation of the superficial femoral vein in the dog does not result in a sustained rise in venous pressure distal to the site of ligation, the pressure reverting to normal in 6 hours (Fig. 80). Despite this the vein grafts remained patent. In clinical venous insufficiency, where vein by-pass grafting will be of value there is venous hypertension, and this will help to maintain graft patency.

Attention has been focused on the importance of retaining valvular function in vein grafts (DeWeese and Niguidula, 1960). Because of the adequate venous collateral circulation to the lower segment, venous insufficiency is not a problem here. Reconstructive surgery will only be required for extensive chronic iliofemoral occlusion. This region is
without valves in 28% of normal people (Powel and Lynn, 1951) and the haemodynamic studies of Højensgaard and Sturup (1952) suggest that valves have little functional importance above the level of the popliteal vein, these veins merely acting as conducting tubes. Preservation of valve function in the graft, therefore, is probably not critical.

In this series the grafts were all examined histologically. If the graft was patent the normal architecture was maintained and there was only minimal increase in fibrous tissue (Figs. 81 and 82). There was no detectable increase in this in the grafts removed after 6 months, 8 months or 2 years. The endothelium of donor and recipient fused, so that the sutures appeared to be subintimal at the suture line (Fig. 82). In a vein, the site of previous thrombophlebitis, the intima may not be capable of proliferation to bridge the defect and the risks of rethrombosis may be thereby increased.

In clinical venous reconstructive surgery for chronic venous insufficiency the cross-over vein graft utilising the long saphenous vein on the asymptomatic side will probably be the operation of choice (Dale, 1966). However a number of problems remain. The routing of such a graft across the front of the pubis is difficult. The exact tension required to allow the anastomoses to lie correctly is not easy to assess, and is different from that in femoro-popliteal artery vein grafts, where tension must be high (Dale, 1959). A greater tendency to graft thrombosis must be anticipated in patients with a predisposition to deep vein thrombosis than in normal dogs, and may compromise results. However, these problems will only be resolved when venous reconstruction is undertaken in patients with chronic venous insufficiency.

Before such surgery is carried out a prolonged period probably in the
region of 2-3 years should be allowed to elapse from the time of the initial thrombosis to allow full development of the collateral venous circulation and to ensure that patients with the severe progressive type of thrombophlebitis discussed on page 49 are excluded. Venographic studies must be complete and both iliofemoral segments and the inferior vena cava must be assessed by direct femoral puncture on the asymptomatic side and the per-trochanteric route on the involved side. The peripheral segment on the latter will have to be visualised by ascending venography to determine what vein is most suitable to attach the graft to, namely superficial femoral or profunda femoris vein or the dilated venae comitantes of the femoral artery. Without adequate pre-operative venographic assessment venous reconstruction will be unrewarding. However, with proper pre-operative selection of cases, meticulous operative technique and careful postoperative care, veno-venous by-pass grafts can be expected to have long term patency and relieve the distressing symptomatology of severe chronic venous insufficiency.

We lack an objective means of assessing improvement in leg blood flow resulting from venous reconstruction. The plethysmographic technique utilised by Ludbrook and Westcott (1968) to evaluate outflow obstruction is a possible solution, but a more direct estimate of venous blood flow such as the leg transit time measured with radioactive isotopes (Payling Wright and Osborne, 1952) has advantages.

**Summary**

Meticulous operative technique with minimal trauma to the graft, is required in experimental veno-venous by-pass grafting in the dog. Once this technique has been mastered good results can be obtained in almost all
instances. Anticoagulants or antiplatelet agents such as Dextran are not required. Recanalisation of occluded veno-venous grafts may not be as common as has been suggested. Late thrombosis is not a problem, and long term patency may confidently be anticipated in clinical cases. Venous reconstruction will only be required in extensive iliofemoral venous thrombosis with severe venous insufficiency. In limited thrombosis, particularly where direct collateral channels such as the ascending lumbar vein are available, it will not normally be indicated. Difficulties exist in finding an objective means of assessing the improvement in venous drainage produced by venous reconstruction. Measurements of leg blood flow such as transit time with radioactive isotopes or by plethysmography are possible methods which are worthy of further study.
SUMMARY AND CONCLUSIONS

A segmental concept of the deep venous system of the lower limb is fundamental in appreciating the problems of venous thrombosis and formulating a rational approach to the management of this disease. There are two segments, the high and iliofemoral segment and the low or peripheral segment, the profunda femoris termination being the line of division, where the functional anatomical reserves of the collateral circulation and the pathological and clinical effects of thrombosis are vastly different.

In the lower segment the potential bypasses provided by the profunda-popliteal connections, the saphenous concomitants of the popliteal and femoral arteries, and the long saphenous vein are direct. In the presence of obstruction these veins enlarge and in time become more linear. Valvular function is frequently retained even when there is marked dilatation and this collateral circulation begins with acute and chronic venous insufficiency never results, and the only sequela is from perforating vein incompetence, which although distressing is effectively managed by subfascial ligation of these vessels.

In the upper segment in contrast the collateral circulation depending on areas communications between the two internal iliac and two saphenous systems, is provided by poorly supported tortuous channels, and vessels not valved as venous circuits. It is functionally poor and even when fully developed venous insufficiency results. In acute obstruction this may be so severe as to produce death in hypotension from sequestration of fluid or progression from closure of small arteries when the tissue tension reduces the transmural pressure below the critical closing level.

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In the lower segment the potential bypasses provided by the profunda-popliteal connections, the venae comitantes of the popliteal and femoral arteries, and the long saphenous vein are direct. In the presence of obstruction these veins enlarge and in time become more linear. Valvular function is frequently retained even when there is marked dilatation. This collateral circulation is always adequate so that acute and chronic venous insufficiency never results, and the only sequelae result from perforating vein incompetence, which although distressing is effectively managed by subfascial ligation of these vessels.

In the upper segment in contrast the collateral circulation depending on cross communications between the two internal iliac and two saphenous systems, is provided by poorly supported tortuous channels, and vessels valved as venous circles. It is functionally poor and even when fully developed venous insufficiency results. In acute obstruction this may be so severe as to produce death in hypotension from sequestration of fluid or gangrene from closure of small arteries when the tissue tension reduces the transmural pressure below the critical closing level.

This segmental concept is basic in considering the pathology of venous
Thrombosis. Iliofemoral venous thrombosis is not only the important form of the disease in regard to leg morbidity but is the source of 2/3 of all serious pulmonary emboli, and the source of all massive fatal embolism.

Thrombosis of the iliofemoral segment is primary in 90-95% of cases and not, as is popularly believed, secondary to extension from the peripheral segment. Thrombosis in the iliofemoral segment is frequently slow and insidious in onset, and is for a time, varying from days to months, non-occlusive. This is an important stage in the natural history of the disease for this non-occlusive thrombus is a source of pulmonary embolism. In many instances this thrombus is large and yet non-occlusive, and can give rise to massive and fatal pulmonary embolism before leg signs develop.

Treatment by thrombectomy at this non-occlusive stage is uniformly successful both in preventing further embolism and averting occlusion and consequent acute and chronic venous insufficiency. Therefore in the management of pulmonary embolism, which is, after all, the life-threatening aspect of the disease in all but a few instances, the impetus must be towards early diagnosis before leg signs develop. Diagnosed at this stage death from further embolism can be prevented.

Bilateral femoral venography is the spearhead of the diagnostic attack. If the iliofemoral segments are clear on venography then the patient is not at risk from major pulmonary embolism and the only danger is recurrent small embolism, resulting in pulmonary hypertension and death from right heart failure. If embolism is oft repeated as judged by recurring symptoms, persistent fever, raised E.S.R., deteriorating chest X-rays, pulmonary scanning or electrocardiographic evidence of right heart strain, then bilateral superficial femoral vein ligation will arrest the process without producing
venous insufficiency. If the iliofemoral segment contains non-occlusive thrombus, venous thrombectomy will cure the patient.

There remains the patients who develop an occlusive iliofemoral venous thrombosis without previous pulmonary embolism. This is a different problem. This is a less serious form of the disease for such patients, in our experience, are not at risk from fatal embolism. If diagnosed early thrombectomy will rapidly relieve leg symptoms and chronic venous insufficiency will result in only a small proportion of cases. Where the process is ultra acute and life is threatened from fluid sequestration or the development of venous gangrene, thrombectomy is the logical approach, and must be undertaken as an emergency. Unless clearance is complete, as judged by operative venography, then the vena cava must be exposed and all thrombus eliminated from the iliofemoral segment. In our experience rethrombosis has never occurred following caval thrombectomy, so that a successful outcome can be confidently expected.

Where the diagnosis of iliofemoral occlusion is delayed the results of thrombectomy are less satisfactory, and other approaches must be considered. Early experience with topical streptokinase in a dose sufficient to produce a systemic fibrinolytic state is encouraging. By this means thrombus at least 30 days old has been lysed, and earlier fears that occlusive thrombus could not be removed are not confirmed when the drug is administered in this way. This is our current preference in the management of late occlusive iliofemoral thrombosis and provided the problems of the change over from streptokinase to anticoagulant drugs can be resolved then this will have a lasting place in the therapeutic armamentarium.

However, this must not produce a false sense of security, and the aim must be early diagnosis in the occluded case just as in the pre-occlusive
case for thrombectomy is, at present at least, more sure and fraught with fewer dangers. High signs particularly groin and suprainguinal tenderness must be sought, and if doubt exists it must be resolved by bilateral femoral venography. The absence of ankle oedema and normal calf and thigh measurements do not exclude iliofemoral venous occlusion and must not delay a definite diagnosis, which only femoral venography can provide.

With improvement in the early diagnosis and treatment of iliofemoral venous thrombosis, occlusive and non-occlusive, the incidence of chronic venous insufficiency of the poor collateral circulation type will decrease. However, the problem will remain for many years to come. Experimental experience in this study confirms that venous reconstruction, by venovenous bypass grafting will be attended by a high technical success rate, provided meticulous attention to operative detail is observed. Case selection remains a problem, and clinical and venographic findings do not provide sufficient information to ensure that a good clinical result will necessarily follow successful venous grafting. Venous flow studies will give valuable information in this regard. Before venous reconstruction is undertaken the position must be more clear and evidence of impaired venous flow established in the individual case. Direct measurement of venous flow by means of radioactive isotopes seems preferrable to indirect study by plethysmography.

This, then, is the sum of our knowledge of this dread disease. The iliofemoral segment is the important site of involvement in venous thromboembolic disease. When the diagnosis is made early, especially in the pre-occlusive phase, thrombectomy affords a good prospect of cure. Nothing more is certain. However, the situation is clearer than that described by
DeBakey 15 years ago. Clinical diagnosis is on a rational basis and is related to the underlying pathological process. Venography is an accurate tool not only for diagnosis but for assessment of the immediate and late results of therapy.

What of the future? Our experience of thrombolytic therapy is encouraging and this may become the treatment of choice. It is essential, however, that the assessment of its value is objective to prevent exaggerated early claims which may lead it into unwarranted disrepute. Thus, while we await safe and effective prophylaxis, advances in treatment of established thromboembolism will be achieved only if diagnosis and management are based on the segmental concept and controlled by venography.
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Changes in rate of flow of venous blood in the leg during pregnancy, measured with radioactive sodium.

Problems in the diagnosis and treatment of thrombophlebitis.