PULMONARY EMBOLISM:

Recent Advances in Diagnosis and Treatment

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During recent years clinicians have become increasingly aware that in the past many cases of pulmonary embolism and of pulmonary infarction have been missed. The diagnosis has been overlooked because the early signs were not appreciated.

P. D. White,¹ writing in 1940 on 20 years' experience of 75 cases of pulmonary embolism, stated that during the first 16 years he diagnosed 29, but during the last 4 years he diagnosed 46. He² is also of the opinion that medical cases are much more frequent than surgical ones, and in particular does this apply to patients with congestive heart failure. This has been strikingly borne out in a recent paper by Carloti *et al.*³ who found that medical cases were more than twice as common as surgical over the past 10 years, the incidence of medical cases being 0.6 per cent., and of surgical only 0.24 per cent. Of the medical cases in the last five years of their series over 70 per cent. suffered from heart disease. The early recognition of the condition has recently assumed increasing importance as with the advent of antocoagulants such as heparin and dicoumarin, and the employment of femoral vein ligation, the incidence can be reduced and the prognosis in an established lesion strikingly improved. From a careful analysis of Swedish figures, Bauer⁴ has shown that prior to modern therapy the mortality from thrombosis of the deep veins and consequent pulmonary embolism remained stationary for many decades.

The purpose of this article is to present, from a survey of the literature and in particular the study of some of the more recent papers, a concise account of the diagnosis and modern treatment of that condition.

Frequency

White⁵ puts the incidence of pulmonary embolism as high as 8 to 12 per cent. of routine autopsies, and states that nearly 50 per cent. of congestive heart failure patients will show evidence of pulmonary embolism post-mortem. Bauer⁴ analysed 178,252 operations and concluded that thrombosis after operation occurs in about every 60th patient, and of these, 1 in 6 die of pulmonary

embolism, that is to say that 1 of every 400 patients operated on dies from pulmonary embolism. From consideration of 382,508 deliveries he was able to state that among all puerperal women every 80th gets thrombosis and of these almost 1 in 25 dies. It is seen that the mortality rate is only one quarter or one fifth that of post-operation embolism. When we come to medical cases figures are less easily obtained as the literature is deficient. Bauer's figures collected from Swedish clinics since 1939, showed that 56 per cent. of 804 examples of pulmonary embolism came from medical wards. Pilcher's authoritative report of 1937, collected from 12 London hospitals, and quoted by Gibbon⁶ put the frequency of fatal pulmonary embolism from surgical wards as 0.105 per cent., but from medical wards as only 0.064 per cent.

It is important to differentiate clearly cases of pulmonary embolism from those showing pulmonary infarcts. The two may be associated of course, but as will be shown later, it is very much the exception to find evidence of both at post-mortem, and this may have an important bearing on the pathogenesis of those conditions.

Pathogenesis

1. By far the majority, probably 90 per cent. at least, of cases of pulmonary embolism arise from detachment of a thrombus in one or both legs. It has long been believed that the clot usually forms in the large pelvic veins or upper part of the femoral veins, but this view is now known to be erroneous. Nearly a quarter of a century ago, although Aschoff⁷ thought the majority of emboli lodging in the pulmonary arteries arose from the femoral veins, he described clearly the morphology of the clot. He stated that it was commonly 35-45 cm. long and that three parts could be distinguished—the first part (Kopfteil) chiefly white, the middle part (Halsteil) being mixed, and the distal portion (Schwanzteil) red. He emphasized that in all human autochthonous thrombi the white part, consisting mainly of platelets, was the essential thing and required flowing blood for its deposition, whereas the much larger red portion was found when the

blood flow had ceased. Bauer⁴ states that only 3 per cent. of cases arise in the femoral vein, and he has shown by clinical and phlebographic studies of 150 cases that the thrombus begins in a muscle vein in the calf, extends into a larger venous trunk and occludes its lumen, and then grows up the femoral vein forming an eel-like clot, dark red, with a slippery surface and anchored only far down in the lower leg and freely waving in the blood stream. It may extend to the pelvic veins or even the renal or hepatic veins. It frequently becomes bilateral, and thrombosis of the second leg begins in the lower part always. He studied 100 normals by injecting 20 c.c. of 35 per cent. Perabrodil into the vein just behind the lateral malleolus, and demonstrated that the double fibular vein is by far the most important blood channel from muscles of the lower leg. One of the earliest radiological signs of thrombosis is the disappearance of this double channel. Occasionally the occluded vein can be seen obstructed. (Fig. 1.) According to Homans⁸ the plantar veins themselves may also be the site of formation of the original thrombus.

Once deep veins have thrombosed recanalization hardly ever occurs, and venous blood from the lower leg is drained by an accessory system of subcutaneous veins usually with the great saphenous vein as a direct channel of return. A mild state of venous stasis is then always present, and leads to chronic oedema of the lower leg which may later become indurated and break down to form the common so-called 'varicose ulcer' which should properly be called the 'post-thrombotic' ulcer.

A physiological explanation of the sudden detachment of the massive embolus has been suggested by Chapman and Linton⁹ as a result of experiments on themselves. They point out that Valsalva's experiment (holding the breath in inspiration and making an expiratory effort with the glottis closed) raises the venous pressure, and that when physical effort is made, such as the act of defaecation, parturition or straining of any sort, that is exactly what occurs. What is more, they found that the venous pressure in the legs whilst sitting up in the 'bed-pan' position, was more than twice as great as that obtained while recumbent. They suggest the rise of venous pressure distends the peripheral veins and during the next normal breath the dammed venous blood rapidly empties from them and washes with it any loosely attached thrombus. Although the use of the bed-pan, getting up for the first time after prolonged bed rest, and the use of enemata are well recognized precipitating causes of detachment, it must be admitted that in most cases no such factor is evident.

2. The right heart itself may give rise to emboli, especially from thrombus within the auricular appendix. It was pointed out by Bernheim¹⁰ nearly 40 years ago that this can result from left-sided failure, the hypertrophied left ventricle displacing the interventricular septum to the right to encroach on the lower part of the cavity of the right ventricle with resultant right auricular appendix dilatation. Four of Bernheim's original 10 cases had pulmonary infarcts.

3. It has long been realized, and recently emphasized by de Takats and Jesser,¹¹ that pulmonary embolism can occur without infarction and vice versa. Laennec himself failed to recognize the relationship between embolism and infarction and called the latter 'pulmonary apoplexy,' and it must be admitted that at most autopsies at which infarcts are found in medical cases no embolus is discovered. Unfortunately it may be difficult or impossible at autopsy to tell whether a lung infarct is of embolic or thrombotic origin, or a resultant of both. Belt¹² has emphasized the points that distinguish an embolus from a thrombus in the pulmonary artery, namely, that the former may be loose-lying, coiled, jumbled, twisted, impacted or riding a bifurcation; it may have a branching conformity that does not correspond with that of the vessel in which it lies; it may have freshly broken ends; it is usually a red clot; finally, the source of its origin may be discoverable in the peripheral veins. Microscopy is also disappointing, and may even be misleading as it is now recognized that what in the past were taken as changes in the wall of the pulmonary artery branches leading to thrombosis are now known to be involutional changes in the vessel wall distal to the obstruction. This endarteritis with intimal proliferation in the defunct vessel is analogous to changes which occur in the umbilical artery at birth. Perhaps with the recognition of the calf veins as the likely source of clot more infarcts will be accounted for in future, but it is likely that, in cardiac patients in particular, venous stasis in the lungs may result in infarction *in situ*. It is probable that infarction only results if occlusion is large, or the apex of one of the lobes is involved, or some obstruction to the pulmonary blood flow is present already, for example, mitral stenosis or failure of the left ventricle.

I recently went through 500 King's College Hospital autopsy records, and, although the number is small, the results were so definite that they are worth mentioning. The percentage of autopsies at which pulmonary embolism was present was 2.6, and at which pulmonary infarction was found was 2.8, but that at which *both* were present was only 0.4. Of the embolism cases

surgical conditions were more than twice as common as heart cases (1.8 and 0.8 respectively) but with the infarct cases the position was reversed (0.8 and 2.0 respectively). This predominance of heart disease as a cause of infarction and its rather rare association with embolism is brought out even more strikingly by Hines and Hunt¹³ who, in 101 cases of pulmonary infarction, found heart disease responsible for 81. Similarly in de Takat's series¹¹ of 25 medical cases 18 had heart disease. These figures would seem to indicate either that in heart cases infarction *in situ* is almost the rule or that in most cases the source of embolus is never discovered. Surely if the leg veins in life had been under suspicion they would have been opened post-mortem in at least a proportion of cases.

Predisposing Factors

The clinical conditions giving rise to embolism or infarction fall naturally into four groups—post-operative, due to fractures, following child-birth, and medical. As we have seen, of the medical cases heart disease accounts for the majority. Whatever the group, the thrombus is nearly always bland and is rarely the result of inflammation or infection. The term 'phlebo-thrombosis' is preferable to the more usual 'thrombophlebitis.' When one side only is affected the left is slightly more common, and Best and Taylor¹⁴ think this is due to the fact that the left common iliac vein offers greater resistance to the blood flow because it is longer and more oblique than the right, passes beneath the right common iliac artery, is liable to pressure from a distended rectum or sigmoid flexure, and in some cases an adhesion passes between the anterior and posterior walls of the left vein.

Age is an important predisposing factor, pulmonary embolism being rare under 35. Only 3 of 11 of Homan's cases⁸ were under 50, and although White's cases¹ ranged from 15 to 87 the majority was in the fifties and sixties. The most recent paper from Boston³ states that 83.8 per cent of patients were over 40 years of age. Flabby musculature is commonly present too. Pressure on the legs from either a pillow across the mattress to prevent the patient slipping down or during anaesthesia, prolonged immobilization or a long-sustained Trendelenburg position, and excessive manipulation of abdominal or pelvic viscera at operation or excessive blood loss, all favour thrombosis.

The type of operation is important in the surgical cases, pelvic operations being notoriously prone, but recently Atkins (15) has pointed out that when the age factor is considered the opera-

tion is relatively unimportant and the incidence of thrombotic complications is as high after operations upon the stomach, duodenum and gall-bladder as upon the uterus.

Symptomatology

It is instructive, I think, to separate the signs and symptoms into three groups which are in the following order of importance—those found from inspection of the bed-chart, those from examination of the legs, and those from examination of the chest and the rest of the patient.

The bed-chart. This often gives the first clue that anything untoward is occurring or is about to occur. A slight rise of temperature, especially if associated with a little quickening of the pulse and respiratory rate in a cardiac patient who is apparently well controlled on digitalis, should immediately suggest that pulmonary embolism or infarction is occurring. An unaccountable feeling of uneasiness or restlessness may possess the patient. The commonest cause of a rise of temperature of more than one degree in a patient suffering from congestive heart failure is pulmonary infarction⁵ and the majority of cases diagnosed as bronchopneumonia following operation or child-birth are due to pulmonary infarction.⁴

The legs. By the time the usually described picture of swelling up to the thigh, discoloration, and a tender hard vein, presents itself that leg is almost certainly of no further danger as a source of emboli. The thrombus has become adherent to the veins and obstructed them. The innocent-looking leg is the dangerous one. For early signs the calf must be examined with the knee flexed and the sole of the foot resting on the bed to relax the calf muscles. Slight swelling of the lower leg, increased glossiness or tension of the skin, faint cyanotic discoloration compared with the other leg, or the fact that the superficial veins are a little more easily seen are all significant. The examiner's fingers are gradually moved up from the Achilles tendon to the popliteal fossa and local tenderness is searched for, and if found the muscles should be pressed together from side to side at that level. If no pain results the diagnosis is strengthened. Dorsiflexion of the foot with the leg extended also causes pain at the same spot as the local tenderness—Homans' sign.⁸ Tenderness should also be sought for in the sole of the foot and around the external malleolus.

The chest signs. It is important to realize that these may be completely absent or obscured, and this is strikingly so in cardiac cases. As recently as 1941 Hines and Hunt¹³ recorded a series of 81 post-mortems on heart failure patients in which

FIG. 1.—Phlebogram showing obstruction of a deep calf vein.

gross pulmonary infarction was present and yet only two cases were diagnosed prior to death. This prompted them to make a very careful comparison of the symptoms occurring in patients dying of heart disease with pulmonary infarction with those with heart disease without pulmonary infarction, and at once it was seen that there is no characteristic clinical syndrome of pulmonary infarction if heart disease is present. In addition, to add to the difficulty of eliciting typical lung signs one or more of the following may be present—passive hyperaemia, brown induration, pulmonary oedema, pleural effusion, bronchopneumonia and emphysema. Comparing symptoms of those with infarct with those without, their percentages were: Haemoptysis 35, 8; pleural pain 16, 9; precordial pain 46, 42; cough 41, 54; shock or sudden death 12, 19; dyspnoea 96, 95; asthmatic attacks 7, 6. It is seen that with the exception of haemoptysis there were only minor differences in the frequency of symptoms. Although blood spitting in pulmonary

infarction occurs in only about a third of cases it is characteristically of a fair quantity and is repeated. They conclude that infarction must be considered if any of the following occur—persistent or recurrent haemoptysis, persistent deep cyanosis, unexplained jaundice, unexplained fever, or sudden onset of heart failure not explained by over-exertion or infection.

In only about 10 per cent. of cases of pulmonary embolism are the physical signs in the heart at all typical⁵ as there must be sudden blocking of at least 60 per cent. of the pulmonary artery circulation before the normal right ventricle dilates appreciably, and that implies the presence of either a larger rider embolus at the bifurcation of the pulmonary artery or at least two large emboli, one in each lung. In 1935 McGinn and White¹⁶ suggested the term 'acute cor pulmonale' for the symptom-complex which may result from sudden occlusion of a large part of the pulmonary circulation, and pointed out how difficult it may be to distinguish it from coronary occlusion. When

present it consists of signs of dilatation and failure of the right ventricle, such as distension of the neck veins and liver and sometimes protodiastolic triple rhythm most distinctly heard near the pulmonary area, and signs of dilatation of the pulmonary artery, such as forceful pulsation, both visible and palpable, accentuation of the pulmonary second sound and sometimes a loud pulmonary systolic murmur or a to and fro friction rub over the pulmonary artery.

Special Investigations

Only two need be considered, namely electrocardiography and radiology. The electrocardiogram is almost a pathognomic but, unfortunately, only the 10 per cent. or so which present the acute cor pulmonale picture show that change. Radiological evidence is often absent, too, and it must be remembered that infarction shadows take at least 24 hours to appear.

Electrocardiogram. In lead I an S wave develops or is increased; in lead II the T wave is low or inverted; in lead III a Q wave develops or is increased, T is quite deeply inverted, and rarely, the ST segment may be elevated; in lead IV (R or F) T is flat or inverted (Fig. 2). White² recommends CF₂ as the precordial lead most likely to register changes, whereas Wood¹⁷ prefers CR₁ in which T inversion commonly persists for several weeks unlike in other precordial leads.

FIG. 2—The above three records illustrate how the electrocardiogram of pulmonary embolism can closely simulate that of cardiac infarction. In A a posterior infarct has occurred; in B a posterior infarct has followed an anterior one; and C is the result of pulmonary embolism. It will be seen that lead III shows the Q 3 T 3 type of curve in all three records, and even the precordial lead IVF in record B resembles that in C. However, in C in lead I a deep S wave is present and is absent in the other two records.

It is seen that the appearances in lead III simulate those of posterior cardiac infarction, although in pulmonary embolism Q is inconstant and the ST segment rarely elevated and never markedly so. Barnes¹⁸ tabulates the points of difference, but at times both clinically and from study of the limb leads alone, a fourth lead is essential. Wood and Selzer¹⁹ state that T is never inverted in any chest lead as a result of posterior cardiac infarction, but Evans²⁰ states that T is often inverted in posterior cardiac infarction in his CR₇ lead and, as it is upright in pulmonary embolism in CR₇, this point may be helpful in differentiating them.

It will be appreciated that chest lead appearances are not quite pathognomonic of pulmonary embolism, and are only evidence of acute transient distention of the right ventricle. At times the identical appearance can be given by rheumatic carditis, diphtheria and pneumonia. Also, cardiac infarction and pulmonary infarction are commonly present together, as will be seen later.

Radiology. Of recent years shadows typical both of recent infarcts and of old linear scars have been recognized, but it has been pointed out by Homans⁸ that a clear lung field is consistent with serious and repeated embolism. An early and important sign is elevation of the diaphragm on the affected side. If an infarct causes a shadow it may be hidden behind a large heart, or if situated in the costophrenic angle may be mistaken for fluid. Hampton and Castleman²¹ from study of X-rays of the vertical cadaver, and the use of a Kaiserling solution pulmonary injection-inflation technique, concluded that an infarct is always peripheral with one or more pleural surfaces invariably involved. But although in the postero-anterior view the shadow may appear as roughly

triangular with its apex towards the heart, if the infarct is dissected out or a plaster of Paris model is made of it, the apex is seen to be directed away from the heart and the cardiac margin is always convex or 'hump-shaped.' The shadow may also appear as a completely rounded one and simulate carcinoma of the lung.

Complications and Prognosis

Shock, recurrence of embolism or infarct, cardiac infarction due to myocardial strain and anoxaemia secondary to pulmonary embolism, and heart failure may be presented singly or in combination. de Takats and Jesser¹¹ have drawn attention to the fact that pulmonary embolism does not kill instantaneously. Of their 100 fatal cases only 8.5 per cent. died in less than 10 minutes, nearly 60 per cent. lived for more than an hour, and 34 per cent. lived from one to several days. Many of their cases had recurrent embolism—39 per cent. had two attacks, 12 per cent. had three attacks, 5 per cent. had four attacks, 3 per cent. had five attacks, and 1 per cent. had six attacks. They bring out a point concerning the cause of death, which has an important bearing on treatment, namely, that a very small infarct can sometimes be responsible for death. Although it is the 'last straw' often, it cannot act by causing asphyxia, failure of the right heart or insufficient venous return to the left heart, and the authors are of the opinion that death in those cases is due to widespread radiation of autonomic reflexes via the vagus and sympathetic. This results in constriction of the coronaries and vagal inhibition of the heart and they therefore recommend early intravenous atropine and papaverine.

TABLE I
CLINICAL DIFFERENTIATION BETWEEN OCCLUSION OF THE PULMONARY AND CORONARY ARTERIES

	Pulmonary Artery Occlusion	Coronary Artery Occlusion
1. History of recent operation or childbirth	Present in about 50 per cent. of cases.	No relationship.
2. Type of pain	Often substernal, but may be lateral and pleural in type.	Substernal, not pleural.
3. Haemoptysis	Fairly common, and characteristically brisk and repeated.	Rare.
4. Cyanosis and cervical vein engorgement	Common and severe.	Less common and less severe.
5. Presence of râles	More apt to be unilateral.	Commonly bilateral.
6. Triple rhythm	Commonly protodiastolic. Best heard near pulmonary area (right ventricular failure).	Commonly presystolic. Best heard near apex (left ventricular failure).
7. Size of left ventricle	Commonly normal.	Commonly large.
8. Frequency of attacks	Several may occur at short intervals.	Rarely more than two rapidly.
9. Family history	Rare.	Common.
10. Cardiogram	Almost pathognomonic, but present only in at most 20 per cent.	Pathognomonic and probably always present.

Differential Diagnosis

As pointed out above, pulmonary infarction is commonly mistaken for pneumonia, often of atypical type. Massive pulmonary embolism is easily confused clinically with coronary occlusion and, indeed, the two conditions commonly co-exist. Without a cardiogram it may be impossible to be certain which condition one is dealing with. Common to both are chest pain or a sensation of substernal pressure, an increase in the temperature, pulse-rate, respiratory rate and white cell count, collapse, sweating and pallor and a fall in blood pressure. Cyanosis, engorgement of neck veins, accentuation of the pulmonary second sound, triple rhythm, and a pericardial friction rub can be found in either condition. Even so, some findings tend to occur more commonly in one condition than the other. (Table 1.)

Treatment

The treatment of pulmonary embolism and infarction is still far from satisfactory, and the problem really resolves itself into an attempt to answer three questions, namely:

How can these cases of pulmonary embolism and infarction be best prevented from occurring? This may be considered under the heading of prophylactic treatment.

If there is clinical evidence that pulmonary embolism threatens to occur, how can a major catastrophe be best averted? This may be described as abortive treatment.

If the patient is already seriously ill with massive pulmonary embolism, what is the best method of coping with this urgent case and avoiding a fatal issue? This constitutes emergency treatment.

Prophylactic Treatment

From consideration of the previously mentioned predisposing factors, it follows that measures likely to reduce the frequency of embolism and infarction are mostly applicable to surgical cases. As pointed out by Barnes,¹⁸ the three most important predisposing factors are the age of the patient, the type of operation, and the reduced venous flow, particularly from the legs. That age is of conspicuous importance is seen from the fact that in his series 93 per cent. of cases were over the age of 40 and only 1 per cent. were under 30. This corresponds closely to the experience of Carlotti *et al.*³ It suggests that the rise in the platelet count following operation, which coincides with the period of anticipated embolism, cannot be of much importance as a contributory cause because, according to Dawbarn *et al.*²² it occurs in young and old alike. The operations notoriously prone to complication by pulmonary embolism are

hysterectomy, prostatectomy and bladder operations, and resection of the stomach for malignancy. In spite of severe cardiac failure often, embolism, following such an operation as thyroidectomy, is almost unknown. Even so, if due allowances be made for age, the type of operation is relatively unimportant.¹⁵

The maintenance of an adequate venous flow depends on the *vis a tergo* of the systemic arterial circulation, active contraction of skeletal muscle, and the negative intrathoracic pressure which, in turn, depends on the normal descent of the diaphragm. The plunger-like action of the liver, secondary to respiratory movements, tends to squeeze blood out of the intra-abdominal veins. From this it is seen that possible preventive measures comprise the following: (1) Deep breathing exercises prior to, and as soon after operation as the wound permits. (2) Carbon dioxide inhalations several times day and night for the first 48 hours. (3) The encouragement of attempts at early coughing. (4) Massage and leg exercises both before and immediately after operation. (5) The avoidance of a bolster across the bed which keeps the hips in a flexed position and thus may hinder the venous return from lower down. (6) The correction of anaemia prior to operation, and the prevention of post-operative dehydration with haemoconcentration. (7) In the theatre excessive tissue trauma should be avoided. It is well worth while using a small pad to raise the heels a few inches from the operation table so that the flaccid calves are not compressed. (8) Straining at defaecation must at all costs be avoided as the patient is then involuntarily performing Valsava's experiment with its attendant dangers. (9) It has been suggested by Walters²³ that the venous return from the legs can be increased by thyroid gland by mouth, but apparently pulmonary embolism can occur in spite of this.

Although the employment of the above measures for every case operated on is too burdensome for practical purposes, they can be confined to likely candidates for embolism such as fat elderly patients, perhaps with known circulatory defects, about to undergo one of the operations known to be liable to be complicated by embolism. Bauer⁴ suggests that heparin should be used in all such patients as a routine measure, but this practice is, I think, unlikely to become general.

Sodium citrate has been given both as a preventative and as treatment of an established case, but there is no evidence that it influences blood coagulation when given by mouth.

Abortive Treatment

By this is meant the treatment of a case which

shows early evidence of thrombosis or infarction but which is not as yet acutely ill. The signs may be limited to the calves or groins, or perhaps a small haemoptysis has occurred with or without scanty physical signs in the lungs. The objects of treatment in this type of case are twofold, namely, to prevent further formation of thrombus and to prevent emboli reaching the lungs. The former can be achieved by the use of anticoagulants such as heparin and dicoumarin, and the latter may be prevented by ligation of the femoral vein or, rarely, of the inferior vena cava itself. Neither method of treatment is altogether ideal. Unfortunately, neither heparin nor dicoumarin can 'dissolve' clot once it has formed, and once the anticoagulant therapy is stopped its effect wears off in a few days and the patient is then once more just as liable to thrombosis as he was before the course was commenced. With vein ligation, cases are already on record of clot being formed proximal to the ligature. Even so, provided their limitations are recognized, both these methods of treatment are at times quite definitely life-saving.

(1) *Anticoagulant therapy.* It is necessary briefly to consider the theories concerning the mechanism of blood clotting. Even to-day the whole story is by no means fully understood, and according to Best and Taylor²⁴ there are two main schools of thought.

(a) *Howell's theory.* Insoluble fibrin (clot) is formed from soluble fibrinogen by the action of an enzyme called thrombin. Thrombin is formed in the plasma of shed blood by the action of calcium ions upon prothrombin. To prevent in the body the interaction of calcium with prothrombin to form thrombin, anti-prothrombin or heparin is present. When blood is shed, thromboplastin (thrombokinase) liberated from injured tissue, or from platelets, neutralizes the heparin. Diagrammatically this can be represented as :

Circulating blood :

Ca + prothrombin + heparin → No clotting.

Shed blood :

Ca + prothrombin +

heparin + thrombokinase
cancel out → thrombin.

thrombin
then, Fibrinogen → Fibrin.

(b) *Mellanby's theory.* This worker maintains that heparin is not normally present in circulating blood, or if it is so it is only in minute quantities and is not responsible for the maintenance of the fluidity of normal blood. He considers that the action of heparin is to inactivate thrombin *after* it has been formed, but to prevent it being formed

there is an antithrombin substance in circulating blood other than heparin. That substance is believed by Quick to be serum albumen.

Prothrombin is a protein and occurs in the plasma as 40 mgm. per cent. It is synthesized in the liver in the presence of vitamin K. Thrombokinase (thromboplastin) is a lipo-protein and occurs in all tissues, especially platelets. It affects the velocity of conversion of prothrombin to thrombin, but not the quantity. Thrombin converts 2,000 times its weight of fibrinogen to fibrin. Fibrinogen is produced by the liver.

Apart from the production of thrombokinase by platelets, it has been shown by Wright²⁵ that the latter not only increase in number following operation or childbirth, but their adhesiveness increases too.

Dicoumarin. It was discovered by Allen *et al.*²⁶ that cattle feeding on spoiled sweet clover (*Melilotus albus*) developed haemorrhages, mainly in the skin, and in 1940 Link and his co-workers²⁷ at Wisconsin isolated the factor in the clover which was responsible, identified it and then synthesized it. It is 3,3'-methylene-bis-(4 hydroxycoumarin) :

and is generally referred to as dicoumarin or dicoumarol.

It has the specific, reversible effect of inhibiting the formation of prothrombin and hence preventing clot formation. It is very important to bear in mind that when given by mouth dicoumarin has a lag of 24-72 hours before any effect occurs. This effect is antagonized by vitamin K, if sufficient is given, and a fresh blood transfusion will, of course, elevate the prothrombin temporarily.

When dicoumarin is employed the plasma prothrombin must be estimated daily, as whenever it falls too low serious toxic effects occur. The earliest toxic signs according to Wright and Prandoni²⁸ are lassitude and general malaise with aching in the costo-vertebral angles. Then generalized bleeding occurs and may be accompanied by pyrexia. Purpura, bleeding from the gums, haematuria, sublingual ecchymoses, subconjunctival haemorrhage, haematemeses, haemarthrosis, visceral and brain haemorrhage, and spontaneous bleeding from wound sites have all been recorded. The capillary fragility is not increased, and the bleeding time is not influenced. There is a definite retardation of clot retraction, but this is inconstant. The treatment of such

bleeding is immediate transfusion of fresh blood or, if that is not available, stored blood up to 96 hours old may be used. The transfusion is continued until the bleeding stops. If fresh blood is not available vitamin K may be used. First reports suggested that substance was ineffective but Cromer and Barker²⁹ have shown that the original dose recommended was too small. Using 64 mgm. of menadione bisulphite (synthetic vitamin K) intravenously they stopped bleeding in 35 of 37 cases.

Estimation of prothrombin time. The prothrombin is not measured quantitatively but indirectly by measuring the prothrombin time. At King's College Hospital Dr. S. Newstead uses a modification of Quick's method³⁰ in which venom replaces brain extract. 'Stypven' is Russell viper venom and this is a thromboplastin-like substance capable of converting prothrombin to thrombin in the presence of calcium. It is issued as a dried powder and when the ampoule of sterile distilled water provided is added to it this makes a 1:10,000 solution. The technique is to mix 4.5 c.c. of blood with 10 mgm. of potassium oxalate and centrifuge. 0.2 c.c. of the separated plasma is pipetted off and added to a small test tube held in a water-bath at 37° C. 0.2 c.c. of 'Stypven' solution is next added. Then with stop-watch ready 0.2 c.c. of M/40 calcium chloride is added and at the same time the stop-watch is started. The tube is agitated in the bath gently and the end-point (prothrombin time) is the sudden appearance of white fibrin particles. As a check a duplicate is run. Though, as pointed out by Wintrobe³¹ there are several variables which this method does not control, such as variations in the prothrombin conversion rate, differences in the time required for the reaction of thrombin with fibrinogen, and delayed coagulation due to deficiency of fibrinogen or excess antithrombin, the method is quite adequate for clinical purposes. Witts and Hobson³² claim a sharper end-point by using a mixture of Russell viper venom and crude lecithin as thromboplastins.

The normal plasma prothrombin time is 10-25 seconds. Bleeding does not occur until the values are as high as 60 seconds or longer. Recently Allen³³ has made an important plea for the discontinuation of reporting the prothrombin time since thromboplastins vary in potency. He suggests the prothrombin should be recorded as a percentage of normal. In his experience intravascular thrombosis rarely occurs when the percentage of prothrombin time in the blood is less than 30, and bleeding rarely occurs when the percentage prothrombin is 10 or more.

Contraindications to dicoumarin. So far the

following are considered by Lehmann³⁴ to be contraindications—kidney disease, heart disease, especially of the coronary arteries, hypertension, liver disease, and bleeding in pregnancy and in the puerperium and due to other causes. Butsch and Stewart³⁵ concluded that although the haemoptysis of pulmonary embolism was not aggravated, in cases with ulcerating or granulating lesions great caution should be exercised or the drug should not be given. In addition Allen, Linton and Donaldson³⁶ list as contraindications thyrotoxicosis, diabetes, arthritic patients taking acetylsalicylic acid, and disease requiring chest surgery. Allen³³ also includes as contraindications blood dyscrasias with impairment of the normal mechanisms for the prevention of bleeding, and recent operations on the brain and spinal cord because here small bleeding may be disastrous. It is seen that if these contraindications were rigidly observed dicoumarin would not be used in cases of coronary occlusion, in which already good results are being claimed, and it would have to be eschewed in most post-operative cases. Other contraindications are conditions where the prothrombin time is already prolonged, for example obstructive jaundice. High fever is also a contraindication as it increases the susceptibility to dicoumarin. As Christie³⁷ has shown, subacute bacterial endocarditis, because of the already strong tendency to bleed and to renal damage, should not be treated with it. According to Barnes and Ervin³⁸ the vaginal blood loss of patients receiving dicoumarin or heparin in the early puerperium is the same as those of controls. No correlation between the blood loss and prothrombin time was noted. Allen³³ has used dicoumarin in 1,686 post-operative cases. He found the frequency of minor haemorrhages (epistaxis, haematuria, petechiae and ecchymoses) was 3.1 per cent., and major bleeding (mainly from operation wounds) occurred in 1.9 per cent. Two patients of the series died as a result of haemorrhage, but one was obviously not caused by the anti-coagulant. On the credit side, he estimated that from consideration of 'expected' deaths 73 lives were saved.

Dosage. The method of Allen *et al.*²⁶ is usually employed. On the first day 300 mgm. is given by mouth, and on the second day 200 mgm. is given. On the morning of the third day the prothrombin time is estimated, and if it is more than 35 seconds the dicoumarin is omitted for that day, and if it is less than 35 seconds, 200 mgm. is given. From then on the prothrombin time is estimated each morning and a decision whether to give 200 mgm. or none that day is made. The object is to keep the prothrombin time somewhere between 35 and 60 seconds. The drug is continued for as long as the

effect is desired, or for about 10 days in cases of pulmonary embolism. If the prothrombin time has not risen very much by the end of 72 hours the temptation to increase the dose must be resisted. Also, this latent period is followed by a prolonged action after the drug is withdrawn, the effect continuing often for two to ten days, generally three to seven. Thus a close watch must be kept on the prothrombin time for at least a week after administration has ceased. Crawford and Nassim³⁹ give details of a case where the prothrombin time increased disappointingly slowly, reaching only 30 seconds after 30 days. The dose was therefore increased but the patient rapidly developed pain in the abdomen and back, with vomiting, heavy albuminuria with casts, a rise in blood pressure, and later gross haematuria which continued for 11 days. Five pints of blood were needed to control the haemorrhage, and the prothrombin time increased again after the drug had been withdrawn and in spite of transfusion. Wright and Prandoni²⁸ noted that bleeding from a venipuncture site was an ominous sign and should be a signal for transfusion. *Either the appearance of spontaneous haemorrhage from any site, and however small, or the occurrence of backache, is, in the author's opinion, an indication for immediate cessation of dicoumarin therapy, notwithstanding a normal prothrombin time.* Atkins¹⁵ reported two post-operative cases who, although treated with comparatively small doses of dicoumarin and adequately controlled by daily prothrombin time estimations, both bled severely and almost died. Although I have never seen such serious haemorrhages in the presence of a normal prothrombin time I have seen two cases in which, both with a normal prothrombin time, haemorrhage occurred—one was following partial gastrectomy and the other was a post-partum case which developed backache, then bleeding from the gums, followed by a small epistaxis, slight bleeding from one ear and, finally, gross haematuria.

Heparin. This was originally obtained from dog liver by McLean in 1916. It is now obtained from the liver, lung and skeletal muscle of the ox. It is formed, and stored in, the mast cells throughout the body, and the liver capsule and lungs are rich in it. It is now obtainable as a pure powder which is closely related to chondroitin-sulphuric acid. Benzidine-heparin is manufactured and has a prolonged action due to its slow absorption. Heparin does not influence the prothrombin time. It increases the coagulation time.

The use of heparin has not been very popular for several reasons, among which are that, until recently, it could only be given either by continuous intravenous drip or at least six-hourly

intravenous injections, it is expensive, samples vary in activity and several disasters have occurred. Its great advantage is that it acts immediately, unlike dicoumarin. Recently, Loewe and Hirsch⁴¹ have described an improved method of heparinization and adduce histological evidence to show that heparin causes to disappear completely red blood cell clots which have not yet organized (sludge stage) and this maintains patent collaterals which without heparin would become thrombosed. They give the heparin, either deeply subcutaneously or intramuscularly, in Pitkin menstruum. This consists of gelatine, dextrose and glacial acetic acid, and adrenaline or ephedrine can be added to prolong the effect. An injection is needed only every two or three days. They also use papaverine concomitantly in liberal dosage—one to one and a half grains, 4-hourly, intramuscularly or intravenously at first, then later orally.

Dosage. The method of Crafoord and Jorpes⁴² is usually employed. The heparin is given *together with dicoumarin*. Both heparin and dicoumarin are given from the beginning, and as soon as the dicoumarin effect on the prothrombin time is noted the heparin is stopped and the dicoumarin alone is given.

The amount of heparin, if obtainable pure, is 50-100 mgm. intravenously six-hourly, and it is generally needed for some 36-72 hours. The heparin preparation used at King's at present is Roche's 'Liquemin.' One c.c. of this corresponds to 1,000 Toronto units and the dosage recommended by the manufacturers is 4,000 Toronto units (4 c.c.) intravenously every 6-12 hours for several days. If necessary the dose may be increased and the interval between the injections shortened. It is issued in 5 c.c. phials.

Bauer⁴ claims that heparin is surprisingly effective in acute massive pulmonary embolism and recommends beginning with rather heavier dosage, namely, 150 mgm. intravenously four-hourly for the first 24 hours. Probably the embolus does not at the start entirely obstruct the lumen of the pulmonary artery, and complete blockage is caused by deposition of fresh thrombus which is prevented by heparin. Dicoumarin alone is valueless here owing to its long latent period. Bauer also makes the point that it is of the utmost importance to get the patient up before the heparinization is terminated, provided the main disease permits it. He⁴³ also emphasizes the importance in heparin treatment of early mobilization—leg movements are carried out from the beginning of heparin therapy and the patient move about freely during the entire treatment. He is got out of bed the moment the acute thrombotic symptoms disappear, and he is able to leave bed

TABLE 2

HEPARIN AND DICOUMARIN COMPARED AND CONTRASTED CLINICALLY.

	HEPARIN	DICOUMARIN	
Advantages.	<p>Immediate action. Action lasts for a few hours only. Constant response.</p> <p>Laboratory facilities not needed.</p> <p>Haemorrhages during treatment extremely rare.</p>	<p>Latent period of some 48 hours. Effect persists for several days. Response may be variable, even same dose on same patient. Daily prothrombin-time estimations essential. Minor haemorrhages not uncommon.</p>	Disadvantages.
Disadvantages.	<p>Cannot be given by mouth. Expensive. Purity and potency vary.</p>	<p>Oral administration. Inexpensive. Synthetic product.</p>	Advantages.

in less than a week as a rule. The patient is provided with an elastic bandage or Unna's paste stocking, and after wearing this for two or three weeks he resumes work.

Table 2 lists the main differences between the two anticoagulants.

(2) *Vein ligation.* The indications for interrupting the femoral vein are still not decided. (1) Allen, Linton and Donaldson⁴⁴ state that they do not believe femoral vein interruption has any place in the treatment of true thrombo-phlebitis after the seventh day of the disease unless infarcts have occurred, as massive pulmonary embolism is comparatively rare, unlike in the bland clot formation of phlebothrombosis. (2) In the cardiac group they are asked to do femoral vein interruption if infarction occurs or if there are any signs of thrombosis in the leg veins. As they have had no fatalities yet in 464 cases, cardiologists feel that operation is indicated on slight provocation. (3) Paul White in a recent address in London stated that it was the practice at Boston to do *prophylactic* bilateral femoral vein ligation on cardiac patients prior to such operations as pericardial resection for constrictive pericarditis. (4) de Takats and Jesser¹¹ are of the opinion that ligation should be performed in cases with recurrent embolism—two clear-cut infarcts from a well localizable source, and in slowly fatal cases. (5) White⁵ states bilateral deep femoral vein ligation should be carried out if pulmonary embolism occurs or recurs during anticoagulant therapy.

The choice of which vein to tie, and on which side, is not always easy. A transverse incision must be avoided. Homans⁸ is of the opinion that in the usual case it is sufficient to divide the superficial femoral vein. This disturbs the venous return very little, whereas if the common femoral vein is divided, proximal to the profunda, serious congestion and swelling often follow. Lym-

phorrhoea is an occasional complication. If embolism is still taking place when the first leg is already considerably swollen, this really exonerates the swollen leg as embolism seldom occurs from an obstructive thrombosis. In a recent paper by Carloti *et al.*³ comparison is made between conservative treatment over a five-year period and bilateral interruption of the femoral veins over a similar period, and although the mortality rate was somewhat higher in the group ligated (48 per cent as compared with 42.6 per cent.) the mortality in the first month was considerably less (28.3 per cent. as compared with 50.7 per cent.). They are of the opinion that vein interruption must always be distal to the sapheno-femoral junction, and should be proximal to the profunda femoris. Bilateral block of the first four lumbar sympathetic ganglia using procaine hydrochloride and monobromosaligenin has been used in conjunction with femoral vein ligation by Aycock and Hendrick⁴⁵. They claim that it gives a better circulation to the legs for the first few days after ligation, and usually only one block is necessary.

The inferior vena cava has been ligated in 10 cases by Linton⁴⁴ for iliac thrombosis.

Emergency Treatment

In acute massive pulmonary embolism it is important to have a clear plan of action as sometimes death can occur in a matter of minutes. As first pointed out by Belt⁴⁶ some warning of such an emergency may be obtained as pulmonary embolism is not a single event but a recurrent one as a rule, with milder attacks first. Before treatment it may be difficult to decide whether the case is one of acute pulmonary embolism or acute coronary thrombosis. Some points of importance in the clinical differentiation of these two conditions are given in Table 1.

To detect the pleurisy overlying a pulmonary infarct, Sir Charlton Briscoe⁴⁷ has drawn attention

to the great value of running the fingers along the intercostal spaces, when tonic intercostals will be found and often pain on pressure over the contracted muscle. The patients prefer this method to the reiterated 'take another deep breath.'

The actual cause of death is not clear, and, as Barnes¹⁸ has pointed out, there are many objections to explaining it on a basis of arterial obliteration. Such objections are that the patients have died after Trendelenburg's pulmonary embolectomy, in pulmonary surgery it is possible to ligate one pulmonary artery, and there is no correlation between the size of embolus and its fatal issue. Patients may die from a small embolus obstructing an insignificant area of lung, and death here is probably due to widespread radiation of autonomic reflexes, perhaps causing coronary artery constriction and vagal inhibition. Villaret⁴⁸ in experimentally produced pulmonary embolism in rabbits, showed that section of the vagi increased by seven-fold the quantity of embolic particles necessary to produce sudden death. Gosset⁴⁹ submitted evidence that the embolus is fixed in the pulmonary artery by its spasm, and de Takats⁵⁰ showed how papaverine might release this spasm in acute arterial occlusion elsewhere. Available lines of treatment are therefore as follows: (1) Anticoagulant therapy immediately, giving both heparin intravenously and dicoumarin orally as described above. (2) Papaverine hydrochloride in solution, giving one grain (0.064 gm.) immediately intravenously. (3) Atropine sulphate

gr. 1/60 should also be given intravenously as soon as the patient is seen in order to paralyse the vagi. (4) If much pain or restlessness is present morphia must be given. (5) Venous congestion as judged by distension of the cervical veins, and cyanosis, is generally considered an indication for venesection and if this is performed a pint should be removed rapidly. At the same time oxygen should be given. But Gibbon⁶ is of the opinion that there is little justification for venesection as failure of the right heart is not due to high venous pressure but to obstruction to the flow of blood from the right ventricle. For similar reasons digitalization is probably of little or no value. (6) Pulmonary embolectomy has not proved feasible. If the evidence is clearly in favour of a massive pulmonary embolus, and all other methods have failed, it might be attempted *faute de mieux*. Gibbon⁶ quotes Kiser in 1935 as being able to collect reports of 142 Trendelenburg operations and only nine survived. Such an operation may tip the balance the wrong way, and in any case offending emboli may be out of reach in both lungs.

To sum up, it is suggested that all acute cases should be given three drugs intravenously immediately—heparin, papaverine and atropine. The remaining treatment will then be decided on the patient's progress.

I wish to thank Dr. Terence East for many helpful suggestions regarding the subject matter of this paper. I am indebted to Mr. A. W. Kendall and Mr. W. Waugh for the phlebogram.

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