1-1-1943

Problem of pulmonary embolism

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THE PROBLEM OF PULMONARY EMBOLISM

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SENIOR THESIS

Presented to the College of Medicine

University of Nebraska, Omaha

1943

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INTRODUCTION

Fatal pulmonary embolism is a major tragedy. It is particularly so when it afflicts patients following surgical operations, for almost all such patients are well on the road of recovery and without this castastrophe would probably be completely restored to a normal state of health. Mayo (1) states there is no complication in surgery which is more difficult to predict than pulmonary embolism. Cases in which this develops are conspicuous by the absence of signs. Embolism is prominent as a complication of the otherwise uneventful convalescence. Because of its unexpectedness and the suddenness of the fatal type, death is most tragic for all concerned.

Interest in pulmonary embolism has been as active in recent years as when the condition was first recognized. It seems justifiable due to the progress that has been made in the prevention and treatment of pulmonary embolism, particulary with the development of anti-coagulant therapy, to review the subject and point out the progress that has been made.

Statistics of various clinics in attempting to determine the frequency of pulmonary embolism show a wide variation. According to Rosenthal (2) this may be explained by the fact that different types of clinical material are reported and that figures from some clinics are more carefully compiled than others. In this author's series of 1000 consecutive posts a 7.6 per cent incidence of pulmonary embolism was found. Belt (3)

found that pulmonary embolism was the cause of death in 6.5 per cent of 567 consecutive cases in which necropsy was performed on adults. He also states that pulmonary emboli are found in 10 per cent of autopsies in adults. McCartney (4) reviewed 14,419 cases in which necropsy was performed on all ages. In 9,615 of these cases, the patients had been treated medically; in the remaining cases the patients died after operation, accident or obstetric delivery. Pulmonary embolism accounted for 2.72 per cent of deaths in this series. Collins (5) reported that pulmonary embolism was responsible for 2.07 per cent of 10,940 consecutive cases in which necropsy was performed. At Los Angeles County Hospital Snell (6) found that pulmonary embolism ranked third among causes of postoperative deaths at at the Mayo Clinic from 1920 to 1925. Barnes (7) states that pulmonary embolism accounted for six per cent of all surgical deaths at the Mayo Clinic from 1917 to 1927 and for 5.8 per cent of all surgical deaths from 1931 to 1937 despite all efforts at prevention.

Estimations of Barnes show approximately 34,000 people die of pulmonary embolism yearly in the United States. He concludes that if such a percentage of deaths from pulmonary embolism is applicable to the general population, and unless this expectancy can be modified by effective treatment, it may be assumed that more than 3,000,000 people now living in this country will eventually die of pulmonary embolism.

ETIOLOGY

Embolism implies thrombosis, and the production of the later is generally conceded to be influenced by certain factors. Virchow (8) in 1846 thought that retardation or standstill of the blood stream was the important factor in causing intravascular clotting. He was the first to describe clearly pulmonary embolism and to correlate the relationship between thrombosis and pulmonary embolism.

The original views of Virchow were maintained and elaborated by Aschoff (9) and his school. And, until recent years, the entire concept of femoral vein thrombosis, prevention, and treatment has been influenced almost entirely by these original concepts. Aschoff attributed thrombus formation chiefly to mechanical stasis in the femoral vein. He was of the opinion that a white thrombus forms owing to the sluggish blood stream and gradually obstructs the lumen of the vein. He considered this to be the origin of the entire thrombus and believed that the red coagulation thrombus is formed afterwards in the blood which is damned up distally to the primary thrombosis.

In the last decade several investigators have critically attacked some of the salient features of the Aschoff theory of thrombosis. Martland (10) cites the work of Denecke in 1929 and Olow in 1930 who found that the earliest clinical symptoms of thrombosis often appeared in the sole of the foot and calf of the leg. This suggested that the thrombosis began in those

locations and was propagated in an upward direction with the blood stream and not in a retrograde direction from the femoral vein.

Furthermore, Homans (11) in 1934 emphasized the importance of the veins of the calf as an important site of origin of thrombosis which gives rise to ascending thrombosis and which he believes carries a high incidence of pulmonary embolism. This was followed, according to Martland (10), by extensive pathological investigations of Roessle in 1937 and Neumann in 1938. These authorities also claimed that the plantar veins and the veins of the calf played the dominant role in thrombosis and were the site of the primary thrombus formation.

Finally, Frykholm (12) in 1940 came to the conclusion that there are four important locations in which venous thrombi might originate. These are: (1) the plantar veins, especially in younger patients; (2) the veins of the musculature of the calf; (3) the branches of the deep femoral vein of the adductor musculature of the thigh; and (4) the visceral pelvic veins. Frykholm was of the opinion that when a patient is confined to bed, the veins in these locations are more or less collapsed. This allows the walls to touch in places. Owing to nutritional disturbances from close contact and the trauma of contact, desquamation and death of intimal cells may occur and as a result a small thrombus forms over the injured area. The thrombosis once started propagates upward in the direction of the venous blood

distending the collapsed vein which again regains its circular contour. As the thrombus propagates upwards it finally protrudes through the opening of the deep femoral into the upper part of the femoral vein. Frykholm (12) believes a white thrombus forms at this point, caused by the platelets and leucocytes sticking to the walls of the vein.

Probably the most important of the factors favoring thrombosis is a slowing of the rate of blood flow. There are many causes that tend to retard the return of venous blood from the legs and pelvis. Murray and MacKenzie (13) believe that when a patient with a weak heart action is put to bed, the massaging action of the muscles of the legs on a venous system, normally well supplied with valves, is lost. Or when such a patient has an inflamatory lesion of the abdominal wall or chest walls or cavities or an incision in the abdominal or chest walls, the normal respiratory excursion is diminished, thereby putting out of action the abdominal muscles and diaphragm whose pumping action take a great part in the return of blood to the right side of the heart especially from the lower extremities.

Murray and MacKenzie and Robertson (14) emphasize that under anesthesia and especially under spinal anesthesia, the heart rate is increased and its force weakened, the blood pressure frequently falls and during the operation the patient may be in cramped and unusual postures, there may be loss of blood and more or less shock, all of which make the circulation

of blood slower throughout the peripheral vascular system. Bellis (15) states that the circulation time of the blood is usually decreased post operatively. He and his co-workers have found the cubital vein-to-carotid body time and ankle vein-to-carotid body time to be shortened after major surgery.

A second factor favoring thrombosis is a physical change or abnormality in the blood itself. According to Murray and MacKenzie (13) there are many elements and properties of blood which are known to exist and which may play the more important roles in thrombosis, but for which there are at present no methods of functional quantitative measurement. With the exception of calcium these authors assign no definite role to the salts in the formation of a thrombus. They believe that prothrombin and fibrinogen variation may help in predicting variations from normal in clotting times and thrombosis. Many investigators have observed that the number of platelets in the blood stream bears some relation to clotting and thrombosis. The relationship between the diminished number of blood platelets and the prolonged bleeding and clotting times in hemophilia is well known. There is considerable evidence by Krumbhaar (16), Evans (17) and others that high platelet counts tend to coincide with shortened clotting times and a tendency to thrombosis.

Of lesser importance, damage to the intima is a factor favoring thrombosis. Murray (18) has shown that sufficient damage to the intima of any vessel will cause thrombosis and occlusion

of its lumen. At every surgical operation many smaller and larger vessels are divided, and during parturition a multitude of vessels are torn across and whether with ligature or without, they are closed with clots, thus setting in action a spreading process. Under normal conditions this is arrested at the next branch of the vessel where active circulation of blood is going on. Under abnormal conditions the spreading thrombosis may extend from pelvic or abdominal wall veins into the iliac or femoral veins, vena cava and practically all return channels and cause them to be occluded by the same process. Murray and MacKenzie (13) further state that a similar occlusion of femoral, iliac, saphenous or other veins may occur without damage to the intima of any of the vessels involved or their branches.

MECHANISM OF DEATH

The actual mechanism by which pulmonary embolism results in death is a subject of much controversy. The two outstanding explanations are neurogenic and mechanical obstruction.

Advocates of the former believe that death is due to reflex cardiac standstill, inhibition of the respiratory center or vasomotor shock. The latter group favors purely mechanical obstruction of the pulmonary artery with resultant reduced cardiac output and its consequences.

The generally accepted theory that pulmonary embolism produces death by acting as a mechanical plug is pointed out by Barnes (19) as being not entirely satisfactory. Correlation between size of the embolus and the fatal issue is lacking since at times a relatively small embolus is sufficient to cause death. The fact that Crafoord performed a successful pulmonary embolectomy after 3 minutes of complete strangulation of the pulmonary artery and aorta should verify such skepticism. Barnes believes that part of the discrepancies may be explained by the demonstration by Mann and his associates (20) that the cross section of the lumen of an artery may be reduced 50 per cent without any change of blood flow, while a reduction of 90 per cent of the lumen will reduce the blood flow only 50 per cent.

Gosset, Bertrand and Patel (21) believe that the embolus is partially held at the site of obstruction by intrinsic spasm of the arterial smooth musculature. Barnes (19) cites the work

of Villaret and his co-workers who produced emboli experimentally in rabbits. They concluded that death was the result of sympathetic inhibition, the stimulus for which arose in terminal pulmonary arterioles. de Takats, Beck, and Fenn (22) presented experimental evidence that atropine and also papaverine protects a large percentage of animals dying from the massive type of embolism. They advocate a combination of atropine and papaverine to counteract the radiation of automomic reflexes, which originate in the effected lung. Jesser and de Takats (23) have found that powerful bronchoconstriction occurs in dogs subjected to pulmonary embolism and that this often is abolished by sufficient doses of atropine and, to a less extent, by papaverine.

The observations of Hall and Ettinger (24) throws doubt on the possibility that stimuli arising in the wall of the pulmonary artery set up a reflex mechanism important in the production of death. They distended the pulmonary artery both with and without occlusion, without demonstrable effect on aortic blood pressure, rate of heart beat or output per beat.

Westdahl (25) believes deaths occurring after five minutes or more form an embolus of large or moderate size are most likely due to something other than cardiac standstill or respiratory inhibition. He states the majority of these can be explained by mechanical obstruction.

Mendelowitz (26) in some recent experiments has carefully studied the course of changes in the circulation

accompanying pulmonary embolism. He concluded that death was probably caused by anoxia of the brain or of the heart with secondary acute heart failure or both. Anoxia was attributable primarily to a decrease in cardiac output and secondarily in some cases to arterial anoxemia.

Barnes (19) is of the opinion that shock, a fall in blood pressure in the coronary and other systemic arteries, pulmonary hypertension and anoxemia are cardinal factors in the cause of death from pulmonary embolism.

Megibow, Katz and Steinitz (27) produced pulmonary embolism in dogs and felt that they were able to account for death by the rise of systolic and diastolic pressures in the pulmonary artery with resultant right ventricular heart failure. They pointed out that cardiac arrhythmias are known to accompany clinical pulmonary embolism or that produced experimentally. They regard these arrhythmias as the end result of failure of the right ventricle. On this basis, sudden death from pulmonary embolism, even though the embolism is relatively small, is best explained according to them by some mechanism of cardiac arrhythmia, probably resulting in ventricular fibrillation.

In the final analysis, due to facts that a controversy exists indicates that a combination of factors are necessary to explain death from pulmonary embolism.

DIAGNOSIS

There are no pathognomonic signs of pulmonary embolism. It may be so insignificant as to produce no symptoms whatsoever, or so massive to result in death in a few minutes or hours. Westdahl (25) states that even the classical case with sudden onset followed by rapid death in a postoperative patient supposedly in good condition may be simulated by coronary occlusion.

The severity of the symptoms depends largely on the size and number of emboli and the resultant degree of embarrassment from pulmonary circulation. Welch (28) describes the symptoms of a large pulmonary embolism as the "sudden appearance of a painful sense of oppression in the chest, rapid respiration, intense dyspnea, pallor followed by cyanosis, turgidity of the cervical veins, exophthalmos, dilatation of the pupils, tumultous or weak and irregular heart action, small empty radial pulse, great restlessness, cold sweat, chills, syncope and convulsion. The intelligence may be preserved or there may be delerium, coma and other cerebral symptoms. Particularly striking is the contract between the violence of the dyspnea and the freedom with which the air enters the lungs and the absence of pulmonary physical signs."

According to Churchhill (29) the most frequent symptoms of massive pulmonary emboli are the suddeness in onset, intensive pallor, loss of pulse and conscousness, oppression, craving for

air and a mild cyanosis with a typical venous pulsation above the clavicles.

White (30) found that acute dilatation of the right ventricle and pulmonary conus in massive but nonfatal pulmonary embolism may give rise to certain cardiovascular signs which can be recognized on physical examination. He states one may observe dilatation and increased pulsations of the veins of the neck may be noted in the second and third interspaces to the left of the sternum. There may be marked accentuation of the second pulmonic sound and a loud systolic murmur in the region of increased pulsation. Gallop rhythm, heard best to the left of the sternum, is present occasionally.

Relatively small pulmonary emboli, according to Martland (10), may cause sudden sharp pain in the chest and marked cyanosis followed by signs of consolidation and pleurisy. The temperature rises and the leucocyte count is usually found to be moderately increased. The respiration is shallow and rapid, due to the pain produced by deep breathing. After a short time a cough may develop with expectoration of blood-streaked sputum. After a few days the symptoms may resolve and the patient completely recover.

Barnes (19) believes in the past too much emphasis has been placed on sudden cyanosis and dyspnea as cardinal signs of pulmonary embolism. He says that a common picture of pulmonary embolism is that of shock, with or without dyspnea, faintness, palor, sweating, a marked fall of blood pressure, tachycardia,

vomiting and sometimes collapse. Barnes also states that not only may the classic symptoms of pulmonary embolism be lacking but the triad of diagnostic observations, that is, bloody sputum, pleural friction rub and signs of pulmonary consolidation, may not be present for 24 hours after the onset and they may never be present in some cases.

According to Barnes roentgenologic evidence of pulmonary embolism may be lacking in the early stages. Jellen (31) pointed out that accentuation of the hilus shadow on the side of occlusion, presumably due to dilatation of the pulmonary vessels on the occluded side, may be an early roentgenographic sign. Later, there appears increased density of the lung shadow owing to infarction and, in some cases, owing to pleural effusion.

Electrocardiographic evidence may play a deciding role in the clinical recognization of pulmonary embolism. In 1935 McGinn and White (32) and shortly afterward Barnes, published their independent observations on electrocardiographic findings, which they consider diagnostic of pulmonary embolism. The following is a list of the changes described by these suthors: 1. Prominent S. 2. Low origin of the T in lead I. 3. Staircase ascent of S T in lead II. 4. Inversion or flattening of T_2 without elevation of S T_2. 5. Presence of Q_3. 6. Inversion of T_3. 7. Inversion of T_4. Barnes (19) emphasizes that precordial leads may be essential in the recognition of pulmonary embolism and that unless the precordial electrode is placed at or near

the left border of the sternum in C_2 or C_3 positions the electrocardiographic changes may be missed.

Coronary occulusion offers the greatest problem in differential diagnosis. Averbuck (33) discusses the differentiation of acute coronary thrombosis from pulmonary embolism. He says that pulmonary embolus may cause a clinical picture indistinquishable from acute coronary thrombosis and names the following points which may help in diffucult cases;

1. Females without hypertension or diabetes are likely to have embolus.
2. Postoperative cases are likely to be embolus.
3. A previous history of coronary disease would suggest coronary thrombosis.
4. Marked cyanosis and dyspnea suggest embolus.
5. In some cases of pulmonary embolus there may be typical right chest pain, pleural rubs and later hemoptysis.

Westdahl (25) concludes that if treatment of pulmonary embolism is to be of value, diagnosis must be immediately considered in any postoperative patient with a sudden onset of symptoms and signs referable to the chest.

An attack of fatal pulmonary embolism frequently is preceded by one or more milder attacks according to Barnes (19). Barker and his associates (34) have presented evidence that, if

all fatal pulmonary embolism that is preceded by nonfatal attacks could be prevented, the number of deaths from pulmonary embolism could be reduced by more than one third. Obviously, the ability to recognize pulmonary embolism is essential.

PREDISPOSING FACTORS

While the cause of pulmonary embolism is unknown, many so-called predisposing factors have been advanced on the basis of clinical study.

Snell (6) showed that obesity definitely predisposes an individual to fatal pulmonary embolism. He advances the possibility that after operation on obese patients, there may be an increased liberation of thromboplastic lipoid substances such as kephalin due to the extensive areas of fat invaded.

Age is a predisposing factor of major importance. Barker (35) found that 93 per cent of patients who died from this cause were more than 40 years of age. McCartney (4) stressed the age factor and was of the opinion that certain operations were attended by a high incidence of pulmonary embolism as much because of the late average age at which the operation was performed as because of the operation. In confirmation of this viewpoint, Barker found that the incidence of fatal pulmonary embolism was five times as high after herniotomy as it was after appendectomy, except in cases in which the latter operation discloses a rupture of the appendix.

The type of operation has an important bearing on the incidence of fatal pulmonary embolism; surgical procedures on the abdominal viscera are major sources of difficulty. Resection of the stomach, exploratory celiotomy for inoperable malignat lesions, colostomy, enterostomy, repair of femoral or

inguinal hernia, resection of the intestine, hysterectomy, operations for ruptured appendix, operations on the prostate gland and bladder, open reduction of fractures, operations on the brain and spinal cord and cholecystectomy were found by Barker (35) to account for fatal pulmonary embolism, the frequency of this complication decreasing in the order in which the operations are named. In constrast, Barker says that death from pulmonary embolism almost never occurs after thyroidectomy.

In some way, unexplained at present, the presence of carcinoma seems to predispose to thrombosis and embolism. Priestley and Barker (36) have found that operations performed on the stomach for malignant conditions are followed by a higher incidence of thrombosis and embolism than are gastric procedures performed for benign lesions. According to them, the incidence of fatal pulmonary embolism after exploration alone for malignancy is unusually high. They consider it possible that the poor general condition of the patient, anemia, loss of weight and strength, inanition and other general changes associated with inoperable carcinoma in this regard are as important as, or even more so than, the actual malignant lesion itself.

Barnes (19) states that heart disease is an outstanding predisposing cause of pulmonary embolism. Priestley and Barker believe that cardiac disease such as chronic valvular lesions, hypertensive heart disease, auricular fibrillation or

coronary disease, predisposes to thrombosis or embolism after operation. It has been observed by Belt (3) of patients who succumb to various medical conditions, with evidence at post-mortem examination or thrombosis or embolism, that cardiac disease is more prevalent than any other condition.

Vance (37) pointed out the occurrence of pulmonary embolism after various forms of trauma to the lower limbs. The degree of trauma varied from mere contusions or abrasions to severe fractures, and in the large majority of instances, the causal thrombosis was found on the side of the injury. McCartney (4) found embolism after trauma occurred more often in females than males and suggested this was due to the higher incidence of varicose veins in females. Homans (11) calls attention to the thrombosis of the deep veins of the lower leg after minor injuries below the knee. He states that the incidence of fatal pulmonary emboli is high in this condition.

PREVENTION

Physical Measures

Pulmonary embolism results as a sequelae from venous thrombosis. The preventive treatment of embolism is directed first toward the prevention of thrombosis and next toward the prevention of embolism if thrombosis occurs. It is generally agreed that the greatest predisposing cause of thrombosis is a retardation of the venous blood flow. Thus it is this factor which is most vigorously attacked. Westdahl (25) believes that physical measures, particlarly active and passive motion of the lower extremities are the most effective means of increasing the blood flow and should therefore be encouraged and even enforced in the group of patients in which emboli are prone to occur. Such a program should be varied according to the condition of the patient. In general, the poorer the patient's condition the greater will be the need for periodic passive exercise and massage. Robertson (14) uses massage motion and heat to the lower limbs as well as encouraging an increased respiratory rate. Frequent change of the patient's position according to Westdahl is more important than all of these methods as a means of overcoming th natural tendency for the blood flow to be slower in the pelvis and lower extremities while the patient is lying quietly on his back. A turn of 90 degrees every hour, alternating from side to back and opposite side should be carried

out. Brief passive and active movement of the extremities may be performed at the same time.

Potts (38) and Cogswell (39) believe that retardation of the venous blood flow is due for the greater part to two factors: lessening of the excursions of the diaphragm thus diminishing the negative intra-thoracic pressure which ordinarily aspirates the blood into the large veins of the thorax; and lack of muscular contractions and tone, which pump the venous blood to the right heart. To substantiate this view Potts measured the changes in the blood volume flow through the inferior vena cava of dogs after elevation of the lower extremities, muscle contractions, and increased depth of respirations. An increase varying from 100 to 150 per cent in the blood volume was noted. From these observations it appears that deep breathing, muscular exercises and elevation of the lower extremities are of value in increasing the venous blood flow, and prevent thrombus formation by "washing out any accumulation of blood elements which might lead to beginning formation of thrombi". The clinical importance of these findings is paramount when it is recalled that the deep veins of the lower leg are regarded as the most common site of origin of venous thrombosis. Potts (40) substantiated his views clinically by observing 728 patients who underwent major surgical procedures and carried out routine breathing and muscular exercise. In none of these did thrombophlebitis or embolism occur. During the same time he followed 112 adult patients with fractures, who

were immobilized in plaster casts. In this series there were five cases of pulmonary embolism. Cogswell (39) for the past few years has made clinical observations similar to those of Pott's and is convinced that postoperative deep breathing and leg exercises have a definite prophylactic value in preventing thrombosis and embolism. However, Cogswell observed that exercises were not being accomplished in any efficient or complete manner; and so a pedaling apparatus was devised which elevated the lower extremities and gave the patient definite, measured, muscular exercise. He studied 403 patients who were confined to bed because of major surgical operations and who used his pedaling apparatus routinely. None of these patients developed thrombophlebitis or pulmonary embolism. Cogswell uses the pedaling apparatus three times a day, beginning on the morning of the first postoperative day on all of the adults who had under gone major surgery. Since the amount of exercise is limited on the day of operation, other measures were taken to prevent stagnation of circulation. On returning from surgery the patients were placed in the Trendelenburg position from four to six hours. Until the patients could move themselves they were turned from side to side every hour. The idea of pedaling in bed is not original with Cogswell as de Takáts and Jesser (41) had previously recommended devices using the same principle and have reported similar prophylactic results.

Barnes (7) suggests the use of CO_2 postoperatively to encourage deep breathing and favor venous return. Bancroft (42) stresses the prevention of increased intra-abdominal tension. He insists that abdominal wounds be so carefully closed that tight strapping and binders are not necessary.

Medical Measures

Among the medical measures in the treatment of prevention of thrombosis is the use of thyroid extract. Walters (43) recommends its use to increase metabolism, the rate of blood flow and blood pressure after operations. He reported the results of using thyroid in 4,500 surgical patients and found no fatal emboli in patients in good general condition with this regime. Kvale, Smith and Allen (44) found that hyperthyroidism, elevation of the extremities and exercise increased the speed of the blood flow. Ayre (45) and Coller (46) advise the administering of thyroid extract postoperatively. Also of value in prophylaxis of embolism according to Ayre is the treating of anemia early and vigorously, the treatment of heart disease and varicosities pre-operatively, and the maintenance of a normal blood sugar level in convalescence.

Anti-coagulants

Another main etiological possibility for the formation of venous thrombosis in addition to retardation of the venous

flow is some abnormality in the blood itself. Priestley and Barker (36) believe that certain abnormal clotting factors which as yet have escaped clinical recognition may be active in certain cases of venous thrombosis. There has been considerable recent work on the mechanism of the clotting of blood and on the value of anti-coagulant therapy in the prevention of venous thrombosis and pulmonary embolism. Heparin and dicoumarin have proved to be the most valuable to the anti-coagulants. Heparin is the older and more established of the two and will be discussed first.

Although heparin was first isolated by McLean in 1916 and later named by Howell and Holt and first employed for the prevention of experimental thrombosis and embolism by Mason in 1924 (47), only during recent years has its clinical use become feasible with isolation of a purified form of heparin which can be administered to patients without the production of toxic manifestations. The action of heparin was demonstrated by Ferguson (48) who found that it inhibits the conversion of prothrombin to thrombin, and by direct anti-thrombic activity.

There are two general methods for the administration of heparin: 1. by the continuous intravenous drip; and 2. by multiple intravenous injections. In the first, advocated by Murray and Best (49) and utilized widely in this country, the appropriate amount of heparin is added to 5 per cent glucose solution, normal saline or Ringer's solution. Should fluid

restriction be imperative, the entire daily dose may be given in as little as 800 or 1000 cc. Prandoni and Wright (50) state the amount of heparin required to secure an arbitrary optimal prolongation of coagulation time, namely 20 to 30 minutes, varies according to the response of the individual patient. 20 to 30 mg. per hour usually suffice to maintain this level according to them. Johnson (51) suggests a doseage of 300 mg. per 1000 cc. on a basis of 2000 cc. per day. Variation in response in different patients and in the same patient from day to day will of necessity modify the dose. Wright and Prandoni (50) believe that coagulation times in excess of 40 minutes are hazardous. They believe in the maintenance of a coagulation time of 20 to 30 minutes determined by repeated estimations of the venous blood clotting time at 4 hour intervals. Priestley and Barker (36) and Murray (52) recommend that the coagulation time of the venous blood should be kept at a level between 15 and 20 minutes. They consider it essential, when heparin is administered by means of continuous intravenous injection, that the rate of flow be watched closely and the coagulation time of the blood be determined as often as necessary (2 to 6 times daily) so that it may be certain that the rate of flow and coagulation time remain within the desired limits.

The second or intermittent intravenous injection method has been used almost exclusively by Crafoord, Jorpes and Lindgren (53) since 1936. They have been using doses from

50 to 75 mg. three times daily at 8 A.M., noon and 4 P.M. with and evening dose of 100 to 125 mg. at 8 P.M. Certain theoretical disadvantages are inherent in this method of heparin administration. Chief among these is the impossibility of maintaining the more or less constant elevation of coagulation time as secured with the continuous intravenous drip. Doseage should be so regulated that the coagulation time never falls below 15 minutes. Secondly, the coagulation time immediately following injection of undiluted heparin attains levels, which may be hazardous, of one hour or more.

There is voluminous available literature concerning the indications for the prophylactic and therapeutic use of heparin. A summary of recent clinical and experimental developments will suffice to prove the value of heparin prophylactically. In a series of 627 patients reported by Crafoord (54) 325 who had received heparin prophylactically during the postoperative periods ahowed a complete absence of thrombo-embolic phenomena. The remaining 302 patients subjected to comparable operative procedures, who had not received the anti-coagulant, showed an incidence of thrombo-embolic complications of approximately .9 per cent. Nine of this latter group died. Diagnosis was confirmed by autopsy. Similar observations supporting the efficacy of heparin as a prophylactic agent against thrombosis and embolism have been reported by Murray and Best (49). Murray (52) observed 440 hospital patients treated with heparin. Thrombosis and embolism

did not occur in any of these patients. Heparin was also used to treat patients with thromphlebitis and their morbidity rate was materially reduced. Priestley and Barker (36) have found heparin to be effective prophylactically in postoperative thrombosis and embolism. Wetterdal and Leissner (55) have reported the efficacy of heparin as a prophylectic agent against thrombosis following obstetric and gynecologic procedures.

There exists some difference of opinions as to how long heparin therapy should be continued. Murray and MacKenzie (13) prefer to continue heparinization postoperatively until the patient is out of bed. Priestley and Barker believe that heparin when once started should be continued for a minimum of 7 to 10 days or longer if conditions indicate. Prompt return of the coagulation time to normal within a matter of several hours follows discontinuance of the administration of heparin. This is greatly hastened by the administration of proamine sulfate, which will cause return of the coagulation time to normal within a few minutes. Priestley and Barker (36) advise the continuation of heparin until the patient has been out of bed for several days. Johnson (51) maintains mobilization of the patient on the 4th or 5th day is important. He does this by having an intravenous needle that is properly and well fixed, and sufficient tubing. Thus the patient will be up walking, if possible, when the heparin is discontinued.

Administration of heparin has been found to be safe for operative patients immediately after or even before operation. (22). Few complications from its use have been reported. In 315 cases reported by Murray and Best (49) four developed hematomata of the wound. Priestly and Barker (36) observed transient hematuria in several of their 45 patients.

Although heparin is a valuable agent in anti-coagulant therapy, it does have certain disadvantages. Chief among these are:

1. Difficulty in administration with its attendant discomfort to the patient.
2. Costliness: 15 to 20 dollars worth of heparin is required daily in the average case.
3. Prolonged administration.
4. Occasional failures.

These factors have tempered the enthusiasm for heparin and have often discouraged its use where it was felt it might be advantageous. For this reason, and inexpensive, orally administered anti-coagulant agent, dicoumarin, has been studied.

Dicoumarin was introduced as a possible substitute for heparin by Bingham, Meyer and Pohle (56), and by Butt, Allen and Bollman (57) in 1941 following studies by Link and his co-workers on hemorrhagic sweet clover disease in cattle. This disease has long been known among cattlemen and veterinarians. It was particularly studied by Roderick (58), who showed that

the hemorrhage in cattle caused by eating spoiled sweet clover depended on a prolonged clotting time, accompanied by a reduction in the prothrombin.

Butt, Allen and Bollman (57) first reported the clinical use of dicoumarin, 3, 3'-Methlylenebis (4-Hydroxycoumarin), in prolonging the prothrombin and clotting times of the blood. Meyer, Bingham and Axelrod (59) found that the administration of dicoumarin either orally, or intravenously, in the form of the di-sodium salt, is succeeded by protracted prolongation of the prothrombin time and coagulation time in dogs and human beings. Allen, Barker and Waugh (60) state the effect of dicoumarin seems to be on prothrombin only. Meyer, Bingham and Axelrod do not know whether or not the coagulation time is prolonged because of the decrease in prothrombin, although there is, in most instances, a parallelism. The manner in which the dicoumarin acts to produce prolongation in the prothrombin time after a latent period of 24 to 48 hours is not known. Allen, Barker and Waugh offer the theory that it acts as a physiologic inhibitor of prothrombin formation by the liver and that during the latent period the prothrombin of the blood is depleted. This possibility of liver inhibition is strengthened by the fact that vitamin K administration in adequate doseage is ineffective in preventing the increase in prothrombin time.

The studies of Bollman (61) on animals, of Bingham, Meyer and Pohle (36) on human beings and Allen, Barker and Waugh

indicate that hepatic function, the composition of urine, the value for blood sugar, the erythrocyte and leukocyte counts, the concentration of bilirubin and calcium in the serum, the value for the nonprotein in the blood, the icteric index and the fragility of the erythrocytes and blood platelets are uninfluenced when dicoumarin is administered. The bleeding time is not influenced by dicoumarin as used clinically. The sedimentation rate of erythrocytes is almost routinely increased. Allen, Barker, and Waugh (60) conclude from all these studies that dicoumarin inhibits the action of prothrombin by destroying it or by inhibiting its production. Secondary effects are interference with normal clot retraction and increased rate of sedimentation of erythrocytes. They state if enough dicoumarin is given, coagulation time is prolonged and bleeding may occur.

Dicoumarin is given orally or the di-sodium salt may be given intravenously. Under both conditions Meyer, Bingham and Axelrod (59) have found that there is similar lag or latent periods between the administration and the appearance of the effect. Allen, Barker and Waugh have found as well as Meyer and his associates that this lag is usually 24 to 48 hours.

The plan of administration of dicoumarin varies somewhat among the authors. The doseage is practically the same however. The variations are due to the response of the prothrombin time of different patients. Allen, Barker and Waugh (60) advise a method where 300 mg. is administered on

each day after the second on which the prothrombin time (Magath's modification of the method devised by Quick and his associates) is less than 35 seconds. They have found that in general larger doses produce greater prolongation of prothrombin time than do smaller ones, and the effect endures longer. After administration of the first dose from 24 to 48 hours elapse before an effect on prothrombin time is noted. After discontinuation of of administration, prothrombin time may be prolonged from 2 days to 2 or 3 weeks, depending on the amount given.

Meyer, Bingham and Axelrod (50) suggest that the minimum effective dose should be employed. They believe the necessary dose for the desired decrease in coagulability of the blood varies with the individual case. They have found that an initial oral dose of 5 mg. per kilo with subsequent daily oral doses of 1.5 mg. per kilo is effective in most cases. Butsch and Stewart (62) suggest the basic dose for the prophylactic oral dose to be 300 mg.

Dicoumarin should be administered only if the prothrombin time can be determined repeatedly. Dicoumarin is a hemorrhagic agent which may produce dangerous hemorrhage unless its administration is controlled rigidly. The amount of drug administered must depend on the prothrombin time. Allen, Barker and Waugh (60) and Meyer, Bingham and Axelrod (59) believe that prothrombin time should be determined daily when dicoumarin is being administered. Meyer, Bingham and Axelrod have found

prolongation in the prothrombin time to between 12.5 and 19 seconds (approximately 50 to 25 per cent if normal) is probabaly reasonably safe. At the 19 second level the percentage of prothrombin in the blood by the Quick method is approximately 25 per cent. Lower levels are not desirable.

Allen, Barker and Waugh (60) and Evans (63) have found it safe and practical to combine the 2 anti-coagulant agents, heparin and dicoumarin. Since there is a latent period after administration of dicoumarin and before impairment of prothrombin time, this drug cannot be used when a quick anti-coagulant effect on the blood is desired. Under these circumstances heparin is given intravenously and dicoumarin orally at the same time. Heparin will raise the clotting time within an hour or two, depending on the rapidity of injection of the first few 100 units of heparin. Allen, Barker and Waugh state that since heparin does not influence the prothrombin time, the effect of dicoumarin can be determined by determining the prothrombin time even when heparin is given at the same time. When the effect of dicoumarin is adequate, as determined by the calculation of prothrombin time, administration of heparin is discontinued. A plan used by Evans (63) of the Lahey Clinic for the combined use of heparin and dicoumarin is as follows:

" 1. Heparin is given I.V. immediately on making the diagnosis of phlebothrombosis, thrombophlebitis or pulmonary embolism.

2. When the clotting time (Lee Method) is raised from 20 to 25 minutes, an initial dose of dicoumarin, 5 mg. per kilo, is given orally.
3. Heparin is discontinued 36 hours after the initial dose of dicoumarin.
4. Dicoumarin, 1.5 to 3 mg. per kilo, is then given daily for 2 to 3 weeks if necessary."

Dicoumarin is contraindicated for patients who are bleeding and those who have ulcerating or granulating lesions. Evans (63) considers the greatest potential danger of dicoumarin lies in its accumulative action, probably due to slow individual absorption. Transfusion offers almost immediate safety from dicoumarin bleeding by replacing absent prothrombin. It may be necessary to repeat the transfusion.

Shapiro, Sherwin and Gordiner (64) have recently proposed and adopted a plan for the prevention of postoperative thromboembolizations. Their procedure is based on studies of the clotting mechanism of the blood. They showed that there is initially a temporary reduction in thrombocytes followed on or about the 6th day by a more or less sharp rise, after which the count gradually recedes to normal on the 10th to the 14th day. Their date also indicates that prothrombin and thromboplastin which take part in the process of coagulation of the blood increase in concentration and/or activity commencing about the 6th day after operation. This is the interval when the incidence.

of postoperative thromboembolizations is greatest. It is believed that there is casual relation between these two events.

The mechanism of blood coagulations involves several reactions. Although these overlap, the process of blood clotting is, nevertheless, continuous and progressive. Hence, inhibition at any one stage stops all succeeding reactions. Thus Shapiro, Sherwin and Gordiner (64) believe there is an indication for a therapy which is capable of limiting the coagulation of the blood. They advocate dicoumarin since it prevents or inactivates prothrombin in man. Their procedure for the prevention of postoperative thromboembolizations is as follows: "Prothrombin estimations are made daily after surgery. In those instances in which the difference between whole and 25 per cent plasma prothrombin time becomes progressively shortened to below 6 seconds for two successive days, the dicoumarin is given."

The question arises in the prevention of thrombosis and pulmonary embolism as to whether it is justified to give dicoumarin and heparin to all patients. Obviously, it cannot be done with heparin because it is too expensive and difficult to administer. Oschner (65) believes it not necessary to give dicoumarin to every patient. He states that if a patient gives a history of previous thrombosis or thrombosis in members of his family, it is desirable to give dicoumarin or heparin

prophylactically. Barker and Priestly (36) agree with Oschner in the prophalactic use of an anti-coagulant in any person who, because of previous phlebitic or embolic phenomena or other reasons, is expected to experience further difficulties in this regard.

As previously stated, the preventive treatment of embolism is directed first toward the prevention of thrombosis. Therefore it is important to recognize premonitory symptoms which may later be followed by the manifest thrombosis or remain latent abortive types of phlebitides. de Takats (66) suggests that a small rise in the evening temperature, a persistently elevated pulse rate without any detectable cause should cause one to look around after the 4th day to 5th postoperative day for other signs and symptoms of latent thrombosis. These signs are: "1. An elevation of skin temperature of the sole of the foot on the affected side. 2. Pain on pressure in the sole of the foot, in the calf muscles, in the popliteal space on dorsi flexion of the foot, or in the groin. 3. A slight edema of the groin or suprapubic region. 4. Frequent urination or mucous stools. 5. Pain in the small of the back."

Martland (10) stresses the importance of early diagnosis of thrombosis to prevent pulmonary embolism. He believes frequent questioning of the patient as to localized pain over the calf and femoral veins and careful palpation of the leg and thigh in the relaxed postion is important in the early diagnosis of

thrombosis. For if thrombosis is present, preventive measures against embolism must be taken.

Venous Ligation

Recently it has been advocated that ligation of the femoral vein should be done in cases of thrombosis of the veins of the lower extremities. The advocates of ligation are basing their work on the pathological studies of Neumann, Hunter and Frykholm that in fatal cases of pulmonary emboli, the thrombosis, almost necessarily the quiet phlebothrombosis, originated in the venous plexuses among the muscles, particularly in those of the calf, but sometimes in those of the foot or thigh. Frykholm's work (12) has been previously discussed in the chapter on etiology. The statistical figures of Barker, Nygaard, Walters and Priestley (34) indicate that about one person in 20 in whom thrombosis is recognized will suffer an embolism whether or not fatal.

Coller (46) advocates that ligation of the femoral vein above or below the profunda should be done in cases of venous thrombosis of the lower legs. He states that ligation of the femoral vein is more important in patients over 50 years of age as the initial infarct is more apt to be fatal. Coller uses venography in doubtful cases of thrombosis or to search for thrombosis if a pulmonary embolus occurs without clinical evidence of trouble in the legs. Bauer (67) has introduced a

new technic of venography where, by injecting diodrast into the short saphenous vein of the leg, he can demonstrate X-ray changes diagnostic of thrombosis in early cases before the true clinical picture has appeared.

As a result of their clinical experience, Fine and Sears (68) recommend, as a routine procedure, exploring the femoral vein to head off the embolism, remove the clot and ligate whenever a diagnosis is made. Homans (69) prefers conservative treatment in early cases, but opens and divides the femoral or one of the iliac veins when embolism or recurrence of symptoms (after nonoperative treatment) indicates that healing without further accident is unlikely. Welch, Faxon and McGahey (70) by combining the routine use of venography with special clinical observations, have determined to their satisfaction the indications for femoral vein exploration and the management of thrombosis at various levels and stages.

TREATMENT

Martland (10) believes that when embolism is massive, obstructive death takes place so rapidly and the shock is so great that there is no therapeutic response to the use of oxygen, sympatathomimetic or antispasmodic drugs. Even the heroic but dangerous emergency embolectomy is almost useless. Thus there is no practical treatment for massive embolism.

Barnes (19) states that once an attack of pulmonary embolism is recognized it must be regarded as a medical emergency. He and Coller (46) advocate a syringe containing 1/2 grains of papaverin hydrochloride to be available for intravenous administration on the shortest notice. In view of the work of de Takats, Beck and Fenn (22), the intravenous injection of atropine is indicated. Coller gives 1/6 grain of atropine and advises the administration of 100 per cent oxygen, preferably by the Boothby mask to combat anoxia. According to Barnes if close observation discloses significant cardiac arrhythmia, it is justifiable to give 3 grains of quinidine sulfate four times daily in the hope that it will forestall the onset of ventricular fibrillation. To prevent radiation of autonomic reflexes originating in the lung, injection of the stellate ganglions with procaine hydrochloride has been advocated by numerous authors.

Embolectomy of the pulmonary artery has a limited field of usefulness. de Takats (71) believes if the patient is alive five or ten minutes after the embolism has formed and if,

instead of improving, the pulse rate, respiration rate and cyanosis become progressively worse and the patient has lost consciousness, an attempt to extract the embolus should be considered. This is only feasible according to Griswold (72) if a surgical team of resident physicians is systematically trained for such an operation on cadavers and if the necessary set of instruments has been previously packed and sterilized and is ready for immediate use. The heroic nature and extreme danger of such an operation is best appreciated by summarizing the procedure as carried out by Edwards (73). He believes since the patient usually dies within 10 to 15 minutes after the attack, the operation should be done in bed after consciousness is lost or even before. There is not time for anesthetic block. The surgeon removes the second rib and cartilage; the pulmonary artery is differentiated from the aorta by feeling its main division into left and right branches through the pericardium; the clots are removed through a small incision by the use of Trendelenburg forceps. The operation takes about two minutes. Edwards performed this operation 3 times but none of the patients survived.

Martland (10) argues against the operation of embolectomy by stating that if this operation becomes popularized, many of the patients suffering from small emboli who recover without special treatment would have an operation. He believes it would be difficult to find whether the embolus or the operation had a

higher mortality. Westdahl (25) states that operative removal of the embolus has not been generally accepted as a feasible and practical procedure.

Fortunately, many attacks of pulmonary embolism are mild and do not threaten the patient's life immediately. The problem raised in such an event is the prevention of a subsequent and possibly fatal attack. Barker, Nygaard, Walters and Priestley (34) have presented evidence that fully 1/3 of the fatal attacks of pulmonary embolism are preceded by milder premonitory attacks. If these premonitory attacks could be recognized invariably and if measures were available to prevent the occurrence of subsequent fatal attacks in all cases, the mortality of the disease, according to Barnes (19), would be reduced at least 1/3. To date, two drugs, heparin and dicoumarin, have been used to accomplish this purpose, and in both instances very encouraging results have been obtained. Priestley, Essex and Barker (74) and Murray (50) have administered heparin intranvenously and continuously until the patient is able to be up and about. This method is rather expensive and the procedure is a very tedious one for the patient. However, Priestley, Essex and Barker found that when heparin was given to patients who had had mild premonitory attacks of pulmonary embolism it was extremely effective in preventing subsequent embolism. Murray states heparin has served well in the management of patients with nonfatal pulmonary embolism. Priestley and Barker (36) have administered

heparin to 63 patients who had experienced nonfatal pulmonary embolism and only two of these, or 3.2 per cent, subsequently succumbed to another episode of embolism. Both of these deaths occurred early in their experience and heparin had been administered for only two days. Both deaths occurred after the administration of heparin had been discontinued and the coagulation time had returned to normal. Even so, the authors conclude this figure of 3.2 per cent of embolic deaths due to embolism among patients treated with heparin compares most favorably with a death rate from embolism of 18.3 per cent in members of an untreated group of patients, who had anything other than an originally fatal single embolus.

Recently, Allen, Barker and Waugh (60) have administered dicoumarin to a series of 70 patients who had premonitory attacks of pulmonary embolism. Statistical study (34) has shown that a patient who has a mild attack of pulmonary embolism has slightly less than one chance in five of having a subsequent fatal pulmonary embolism. On this basis, 14 of the 70 patients should have died of subsequent fatal attacks. Actually only two patients in this series died. One death resulted from uremia and the other from the effects of a large embolism which occurred before the prothrombin time was elevated. Although the group is too small from which to draw any far reaching conclusions, it gives an extremely promising outlook.

Allen, Barker and Waugh (60) and Evans (63) have found it safe and practical to combine the two anti-coagulant agents, heparin and dicoumarin in the treatment of nonfatal embolism. The methods of administration of heparin and dicoumarin individually and together have been discussed in detail in the section on prevention.

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