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Pathogenesis and prophylaxis of venous thrombosis and pulmonary embolism

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PATHOGENESIS AND PROPHYLAXIS OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM

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TABLE OF CONTENTS

INTRODUCTION

The problem of venous thrombosis and its most serious complication, pulmonary embolism, rightly commands the continued interest of all physicians. Pulmonary embolism is a problem troublesome to surgeon and medical practicioner alike and is not too infrequently a cause of sudden death in persons forced to bed for any longer than a very few days.

Textbooks in all of the specialties of medicine have almost universally chosen to repeat shopworn phrases concerning venous thrombosis and embolism, many of which are no longer in keeping with newer and well-documented information. For this reason, certain fundamental and now well-authenticated facts need emphasizing.

It is still common for all venous thrombosis to be referred to as "thrombophlebitis." However, when the mechanism and prognosis of venous intravascular clotting is considered, two types are found. These are; 1) phlebothrombosis, defined as venous occlusion unassociated with inflammation, the clot being loosely attached to the vein wall, and 2) thrombophlebitis, clotting associated with and dependent upon inflammation of the vein wall, with the result that such clots are usually firmly attached.

Also, there is a woeful lack of appreciation as to which veins serve as the commonest sources of thrombotic emboli, a vital feature of the problem from the point of view of prevention and treatment. It is still generally assumed that pulmonary emboli usually arise from clots in the femoral, iliac, or the pelvic veins or from the right side of the heart, disregarding the now ample data to the contrary.

Another fallacy is that only the surgical patient is in danger of sustaining a pulmonary embolus. Statistics show however, that patients suffering from medical diseases are fully as susceptible and just as frequently die from pulmonary embolism. Nevertheless, the worst mistakes probably have to do with neglect of prophylactic treatment.

Approximately 34,000 people die of pulmonary embolism yearly in the United States. Unless this expectancy can be modified by effective treatment, it may be assumed that more then 3,000,000 people now living in this country eventually will die of pulmonary embolism. (5)

PATHOGENESIS

The causative factors leading up to venous thrombosis and pulmonary embolism are many. So as to discuss this topic systematically, it will be devided into four parts; namely, (1) physiology, (2) predisposing factors, (3) precipitating factors, and (4) source of emboli.

PHYSIOLOGY

By thrombosis is meant the intravital partial or complete obstruction of a vessel by a clot due to changes in preëxistent constituents of the blood. These changes may affect either cellular elements or plasma or both. The clot itself is termed a thrombus. Morphologically, three types of thrombi can be distinguished: 1) red thrombus; 2) white thrombus; and 3) mixed thrombus. The latter type is the most frequent and represents a combination of the first two types. As to origin, two types of thrombi may be distinguished, namely; agglutination thrombi and coagulation or fibrin thrombi. The agglutination process is the first stage in thrombosis and is followed by a coagulation process. The mechanism of these two processes will be described and discussed in turn.

Three theories have been advanced to explain the mechanism underlying agglutination of cells and, in particular, the cellular elements of the blood.

(1) The first theory assumes that agglutination is due to changes in the ectoplasmic layer of the cells, which makes them sticky. (2) According to the second theory, agglutination is due to changes in the electric charge of the surface of the cells which prevent the mutual repulsion of particles carrying the same electric charges. (3) The third theory assumes that a protein substance, which is deposited on the surface of the cells, makes the cells sticky and leads to their agglutination. This increased agglutination tendency causes clumping and is probably responsible for the initiation of a thrombus. (34) The blood current however, has to be maintained to a certain extent to bring about agglutination and also coagulation. (47)

According to the first theory of agglutination of the cellular elements of the blood, physical changes and changes in the surrounding medium must be considered. Physical changes, such as those induced by contact with rough surfaces, suffice to make thrombocytes send out pseudopods and to become sticky. Also, there are cations and anions that tend to cause a swelling of gelatin, soften the ectoplasmic layer of thrombocytes, and favor their agglutination and amoeboid movement. Loeb (29) concluded that agglutina-

tion thus depends upon alterations which occur in the ectoplasmic layer of the cells, as reactions to certain environmental stimuli or under the influence of changes in the medium.

In 1942, Wright (56) made serial observations on the platelet count, platelet stickiness, red cell sedimentation rate, red cell count and hemoglobin percentage of thirteen obstetrical and eleven general surgery cases following delivery or operation. The correspondence between the rise in the platelet count and the occurrence of thrombosis was not found to be complete. To account for these divergencies, MacKay (30) suggested the possibility that changes in the agglutinability of the platelets might also be a contributary factor in thrombus formation.

The rise in the platelet count is believed to be a contributory cause however, affecting the onset of thrombosis following surgical operations and delivery. After a preliminary fall immediately after operation, a rise in the number of platelets begins about the fourth day and attains its peak on or about the tenth day, subsequently falling back to the initial level between the fourteenth and twenty-first days. (56) Maynard and Hollinger (31) found that the number of thrombocytes in the circulating blood is diminished

in regions of the extremities where there is peripheral vascular disease.

The present work has shown that there is an increase in the stickiness on or about the same day as the peak in the number of the cells. There appear to be two possible explanations for the increase in this stickiness of the platelets. It may be due either to an essential alteration in the cells themselves or to some change in the plasma which cause them to agglutinate and adhere more readily. In an attempt to decide this point, the sedimentation rate of red cells on the days after delivery or operation has been determined in all cases under observation. The parallel observations on the sedimentation rate and stickiness show however, that no single change in the plasma will account for the alteration in the agglutinability of both red cells and platelets. An increase in platelet stickiness, as well as in platelet number, was observed on the forth day and was maximal on the tenth day. The red cell sedimentation rate was maximal on the forth to fifth day, and declined considerably by the tenth day. Key (28) found that the greatest stickiness of the platelets coincides with the peak in their number on about the tenth day, so it may therefore be due to a progressive re-

duction in the average age of these cells in the circulating blood between the first and tenth days. It is now recognized that young blood cells tend to be more adhesive than maturer forms.

According to the second theory of agglutination, it was found that under normal conditions, the red corpuscles and the thrombocytes have a negative charge and therefore repel each other, remaining in suspension. It is assumed that agglutination is induced by a loss of the electric surface charge. Such a discharge is supposed to occur as a result of adsorption of globulin and fibrinogen by the surface of the cells, which takes place the more readily, the closer the isoelectric point of the particular protein approaches the neutral point. An increase of the globulin-fibrinogen fraction, as is found in certain diseases, is supposed, therefore, to lead more readily to agglutination. Red corpuscles are less agglutinable than the thrombocytes, because they have normally a higher electric charge. The change in the electrical charge of the formed elements is the result of the disturbance in the albumin-globulin ratio. There is an increase in globulin and a decrease in albumin. (34, 47)

Finally, in accordance to the third theory of

agglutination, Shinoya (46) thought that the stickiness of platelets was due to the formation of a thin film of fibrin on their surfaces. Wright (56) surmised that, if this should be the case, it would explain the variations observed with the different concentrations of anti-coagulant. Thus, in blood samples having a high concentration of anticoagulant, any thrombokinase liberated from the platelet surface is relatively ineffective in forming fibrin, either because of the chlorazol dyes or of the absence of calcium ions in the presence of oxalate.

As a rule, the coagulation process furnishes the greater quantity of the thrombus. It is of great significance because of its complications and sequelae. Its dominant role in thrombus formation consequently is associated with pulmonary embolism. To get to the bottom of the problem of pulmonary embolism then, an understanding of intravascular clotting must be obtained.

The function of intravascular blood clotting is a normal defence mechanism against prolonged bleeding and is normally initiated under certain circumstances. Prothrombin, thrombin, thrombokinase, ionized calcium, and fibrinogen take part in the mechanism of blood

clotting. When blood is shed, thrombokinase is liberated from the injured tissues or from the fragmentation of platelets and the clotting mechanism is initiated. Heparin, an anticoagulant, is present in the liver, lung, muscle, intestinal wall, spleen, heart, and thymus. It is an anticoagulant mainly by its property to inactivate thrombin. It acts locally, is present only in minute amounts in the circulation, and is not responsible for the maintenance of the fluidity of the blood in the living body. The blood remains as a fluid in the vessels normally because; 1) there is insufficient thrombokinase in the blood to convert the prothrombin to thrombin, and 2) there is an antithrombin other than heparin in the circulating blood. It is the opinion of Harrison and Mason (18) that intravascular and extravascular coagulation are identical except for the streaming action of circulating blood.

Concerning thrombosis, several factors leading to coagulation must be considered. These are; 1) an increase of the globulin-fibrinogen fraction within the blood. This process goes hand in hand with a decrease of blood albumin. 2) extraction of blood coagulins from disintegrated agglutinated thrombocytes or from fibrin. 3) extraction of tissue coagulins from

disintegrated red corpuscles, from injured vessel walls or from the surrounding muscle tissue. (29, 40) If red corpuscles solely are injured, thrombosis may not occur, although the coagulability of the blood may be increased. But thrombosis is effected if substances are set free from the damaged vessel wall and from the surrounding tissues. In this way more active tissue coagulins are liberated. 4) parenteral administration of proteins, intravenous injection of other colloid substances, and also microorganisms or substances set free by their disintegration, may cause intravascular coagulation. and 5) foreign bodies. These probably determine the place where coagulation first takes place by causing a slight primary agglutination process. Harrison and Mason (18) believe that tissue extract should be considered the primary cause of intravascular clot formation.

Injury to tissue, as a result of an operation, an accidental trauma, a delivery, or invasion by infection or malignant disease, results in increased coagulability of the blood because of absorption into the blood stream of noxious substances derived from the traumatized cells. The increased blood coagulability is the result of changes in the plasma and the formed elements of the blood.

The changes in the plasma consist of increased viscosity, hypoproteinemia, hyperglobulinemia, increased fibrinogen content, increased antitryptic power, increased peptidase, increased calcium content, and decreased carbon dioxide combining power. The peptidase content of the plasma is an indication of the cell destruction, and the aseptic destruction of the cells produces a decreased blood stability and a decrease in antithrombin with an increased tendency toward clotting. Associated with this is a disturbance in the ratio of calcium and potassium ions and also a disturbance in the A/G ratio, in that the globulin is increased and the albumin decreased as in agglutination.

Whereas the changes in the blood and blood constituents resulting from tissue injury and associated circulatory retardation are responsible for the intravenous clotting in phlebothrombosis, in those cases in which there is an inflammatory process of the vein wall (thrombophlebitis) the clotting is due principally to injury of the endothelium by the inflammatory process. In the latter instance the inflammation of the vein wall is usually the result of bacterial invasion, as in puerperal thrombophlebitis and in many cases of postoperative thrombophlebitis associated with febrile

reaction. The microörganisms generally gain entrance to the venous system through the medium of the perivenous lymphatics.

Relatively rarely the vein intima may be involved by bacteria present in the blood stream which has been designated secondary phlebitis in contradistinction to the primary form in which the venous involvement begins in the wall and extends to the lumen. The former occurs relatively infrequent and is seen only in those cases in which there is an actual pyemia.

There are several ways of preventing or retarding coagulation. Briefly, these are; 1) lowering the temperature, 2) preventing injury to the platelets and preventing contact with the tissues, and 3) adding oxalate; fluoride; isotonic sodium citrate; neutral salts, such as magnesium and sodium sulphate solution; zinc sulphate; sodium thiosulphate; germanin; azo dyes; and substances of a biological nature such as hirudin, snake venoms, heparin, peptone solution, cysteine, and dicoumarin.

The mechanism of thrombus formation was first studied by Zahn (57) in 1875. More recently, Aschoff (4) described the white and red thrombi, the white usually being associated with thrombophlebitis and the red with phlebothrombosis.

In white thrombus formation there is a maximum change in the wall of the vessel resulting in a deposition and agglutination of the platelets on the vessel wall. There also becomes adhered to the vessel wall in this area leukocytes and fibrin, resulting in a white thrombus. The blood flows sluggishly through the sponge-like texture of the developing white thrombus, whereas in the formation of a red thrombus the local circulation is brought to a standstill. When the vein becomes completely obstructed, the thrombus has a white portion or head which is directed proximally and a dark red portion or tail. If the flow of blood is not completely blocked, the thrombus consists of the white portion alone.

A minute examination reveals a framework of ribs or beams extending from the wall of the vein and traversing the entire substance of the white thrombus. These ribs are made up chiefly of massed platelets covered with a layer of leukocytes. There is little or no sign of fibrin or of red cells so that this white plug is not a clot in the ordinary sense. The longer red portion, or tail of the thrombus, extends distally for a variable distance along the vessel and is made up of all the elements of the blood in their normal proportions. Fibrin threads are

plentiful and this portion is evidently formed by the coagulation of the blood en masse, as it is finally brought to a standstill by the obstruction of the vessel by the white thrombus. The arrangement of the platelets to form the framework of the head of the thrombus is explained simply by the slowing of the blood current. The ribs or beams formed of accumulated platelets commence as low ridges upon the inner surface of the vein wall. Owing to their lower specific gravity, the platelets leave the axis, or core of the stream, and separate from the other blood elements and come to occupy the more slowly moving zone next to the vessel wall. Finally, it is the reduction of the velocity in this outer zone of the current to a certain critical level that causes the platelets to settle upon the vascular walls. The ribs or ridges increase in height by the aggregation of fresh platelet masses, and secondary ridges later are formed upon the primary ones until at last the fabric extends like a coral growth into the axis of the stream. The leukocytes, also on account of having a lower specific gravity than the red cells, separate from these and move in the outer currents of the many streams into which the original blood column has been now divided. They cling to, and finally come to rest

upon the walls of the new-formed channels, and ultimately filling them, cause complete blockage of the vessel.

A white thrombus, either with or without a covering of clotted blood, is likely to form as a result of platelet deposition: 1) in the auricles during a auricular fibrillation, 2) in the slowing of the blood stream caused by a local dilatation of the blood channels, such as in an aneurysm or varicose vein, and 3) whereever eddies are produced. This mechanical formation of such a thrombus in the femoral vein would perhaps be of little consequence if there were no danger of the plug of blood becoming detached , since the circulation would be carried on through collateral channels or the thrombus itself would probably in time undergo canalization with consequent re-establishment of the current in the vessel. Emboli found in pulmonary artery branches after death however frequently have the structure of a thrombus as described above, and are of a size which can be accounted for only by their formation in a vessel such as the femoral vein.

Aschoff(4) pointed out that the white thrombus is associated with thrombophlebitis in which there is maximum change in the wall of the vessel resulting

in a deposition and agglutination of the platelets on the vessel wall. There also becomes adhered to the vessel wall in this area, leukocytes and fibrin. In those cases of thrombophlebitis in which there is suppuration resulting in liquefaction of the coagulum, portions of the thrombus may become detached resulting in septic emboli. In phlebothrombosis however, the thrombus is similar in many, if not all, respects to an extravascular clot. This is designated as a red thrombus or coagulation thrombus. It has much the same relative proportions of blood elements as are found in the circulating blood. The red thrombus is attached only loosely to the vein wall and it is this type of thrombotic process that is particularly likely to give rise to pulmonary embolism.

Circulatory retardation is probably the principal reason why clotting usually occurs in the lower extremities because in these areas the greatest amount of vascular stasis occurs. As is well known, movement of venous blood is dependent upon a number of factors, the chief of which are the vis a tergo through the capillaries, the negative pressure within the thorax, and the contraction of the skeletal muscles. As a result of an operative procedure, any illness, or cardiovascular disease the vis a tergo

is definitely diminished. In the first instance this is due partly to decreased cardiac function, and also to vasoconstriction. (38) In the other two instances it is due mostly to the decrease in cardiac function. The negative pressure within the thorax is definitely less marked following a laparotomy or in severe illness than is found normally, because hypopnea is the rule. This favors circulatory retardation in the venous system of the lower extremities. Increased intra-abdominal tension tends to compress the abdominal veins and therefore produce venous stasis in the lower extremities. (34)

Frykholm (17) states that when a patient is confined to bed, the veins of the visceral pelvis and legs are collapsed or pressed together to a certain degree so that two intimal layers come into close contact. The vitality of the endothelial cells depends, to a great extent, on their contact with flowing blood, and when the cells are deprived of this source of nutrition, disturbances arise in nutrition and a thrombosing process is begun.

Ochsner and deBakey (38) emphasize the fact that a localized area of thrombophlebitis initiates a state of vasospasm throughout the involved extremity. The flow of blood is therefore reduced and metabolites

then collect in the tissues and edema develops.

Ochsner (34) states that although slowing of the venous flow is probably the most important factor in the production of postoperative thrombosis, alteration in the blood itself following tissue injury no doubt encourages the formation of the white thrombus. Increase in the number of platelets and their tendency to clump together, the rise in fibrinogen concentration, and the effect of this upon the sinking rate of the cells are alterations refered to. Anhydremia, by increasing the viscosity of the blood, also favors its occurrence. Mercurial diuretics also favor intravascular clotting by the hemoconcentration they produce.

Frykholm (17) however, thinks injury to the intima is the most important factor in the pathogenesis of thrombosis. However, injury to the interior of a vessel per se, such as observed in the suture of a vessel alone, will not produce thrombosis. There must be coexisting a slowing of the circulation or a change in the composition of the blood.

Pulmonary embolism has been the subject of study for about one hundred years, when as far back as 1846 Virchows (52) epoch making observations laid down the principles of blockage of vessels and these prin-

ciples were applied to sudden changes in the pulmonary artery.

The shortening of the clot retraction time has been shown by Hirschboeck and Coffey (21) to coincide with the occurrence of pulmonary embolism. It was thought that strong and rapid clot retraction would favor dislodgement of a thrombus from the wall of a vessel if one were formed. Increase in the blood platelets and in plasma fibrinogen, both known to occur postoperatively, and anemia, are other factors which favor rapid clot retraction.

Hunter, Sneeden, Robertson, and Snyder (25) found repeated embolic episodes more frequent than a single massive attack. Multiple small fragments were found to do harm by placing an added burden on an already embarrassed circulatory system. The explanation for the release of mural thrombi, that so often lie in the leg veins, is in the observed facts that venous pressure and volume in the legs rise sharply during a Valsalva experiment (expiration with the glottis closed.) Associated with this rise in venous pressure is the finding that the return of blood to the heart is temporarily impeded, so that the peripheral veins become distended with blood, which may loosen an insecurely attached mural throm-

bus. With the drop of venous pressure in the next inspiration, the dammed venous blood rapidly empties from the peripheral veins, washing with it any loosely attached thrombus. (8)

deTakats (11) states that, when patients die from a comparatively small embolus obstructing only one lobe or part of one lobe, the cause of death must be a reflex effect on the heart. deTakats, Beck, and Fenn (14) found that a widespread radiation of autonomic reflexes occurs during embolism which affects the heart, the pulmonary vascular tree, the bronchi, and the gastrointestinal tract.

PREDISPOSING FACTORS:

Burke (6) emphasizes the importance of the increase in thrombosis and embolism, particularly since the first World War, and believes that it is due to a number of factors which are; 1) lengthening of the average life expectancy; 2) consequent increase in number and longer survival of cardiac patients: 3) increase, in the hospital, of patients; and in general, earlier and more widespread resort to recumbency; to the practice of going to bed with less provocation than in hardier days: 4) larger volume of surgery on aged and handicapped patients; and 5) greater use of

intravenous therapy and diuretics.

As a result of any trauma, changes may occur in the blood constituents which favor clotting. Unfortunately in many instances, the increased coagulability of the blood is undesirable and is the predisposing factor in the production of intravenous clotting. The trauma may be accidental, the result of an operation or delivery, or may follow the invasion of tissue by microörganisms or neoplastic tumors. Cardiovascular disease, advancing age, seasonal variation, constitutional diathesis, obesity, debility, varicosities, excessive smoking, anemia, and foci of infection are other predisposing factors.

Ophüls and Dobson (39) found cardiac disease to be present in fifty-two percent of their cases of thrombosis and embolism, and Burke (6) states that of a total of 648 cases of intravascular clotting, 444 were associated with cardiac disease. White (54) observed patients suffering from, or thought to be suffering from, cardiac or pulmonary disease and found that quiet thrombosis may take place not only in persons already incapacitated by a cardiac disorder of some sort but in others apparently leading an active and sufficiently normal life. Such persons may even be young, that is in their teens, although pulmonary

embolism in the first four or five decades is unusual. (22, 53) McCartney (31) divided his 25,771 cases according to anatomically normal and abnormal hearts. This analysis showed that in persons with heart disease, thrombosis and embolism occured approximately three times as often as it did in persons with normal hearts. Further subdivision of these two groups by age revealed that in persons with anatomically normal hearts there was a slight but gradual increase of thrombosis and embolism as age advanced, whereas in persons with diseased hearts thrombo-embolism occurred fairly uniformly in all decades of life, excepting the first. When the liver showed chronic passive congestion, venous thrombosis was five to six times as common as it was when the liver appeared normal.

Generally, intravenous clotting occurs more frequently during the spring and winter months than during the summer months, and the incidence is definitely higher in the northern clinics than in the southern ones. (36) Probably these seasonal and geographical variations are due to the vasospastic effect of cold and its effect on the blood flow. The vasospastic effect of smoking also accounts for its predisposing factor in intravenous clotting.

Intravenous clotting frequently occurs in certain families, so a constitutional diathesis to this con-

dition cannot be denied. Ochsner (34) states that the type of individual who is likely to develop an intravenous clot is fat, pale skinned, asthenic, and weak muscled. This tendency is inherited. Henderson (19) found that the average weight of patients with thrombo embolism was thirteen pounds greater than normal.

Debility and anemia are predisposing factors in intravenous thrombosis because of increased coagulability of the blood and decreased cardiac tone. Polycythemia also predisposed because of increased blood viscosity, leading to easier coagulation. Malignancy greatly increases the clotting tendency and is intimately associated with thrombosis. Sproul (49) and Kenny (27) have emphasized the high incidence of venous thrombosis as a complication of carcinoma of the body or tail of the pancreas. Immobility of the lower extremities of patients following operation or who are otherwise ill, is a very important factor in producing vascular stasis and thus leading to thrombosis. Even in lobar pneumonia, thrombo-embolism occurs in about 2% of cases. (24)

The clotting tendency is also increased by 1) hemoconcentration resulting from vomiting, inability to take liquids by mouth, diarrhea, operations, burns, nephrosis, peritonitis, large fibrinous exudate in the

pleural cavity, and polycythemia, 2) slowing of the venous return from a fall in arterial pressure, decreased diaphragmatic excursions which greatly influence the emptying of the vena cava, increased intra-abdominal pressure owing to distention and tight dressings,and Fowler's position which creates a venous pool in the pelvis, and 3) meterologic factors. (11)

Ochsner (37) pointed out that inhalation anesthesia, particularly ether, has been blamed for the relatively high incidence of thrombosis, whereas local analgesia is attended with a relatively low incidence. deTakats (12) stressed two causes of thrombo-embolism which are; 1) injury to the intima,and 2) increased coagulability of the blood. Injury to the intima may result from ankle sprains; fractures of the lower leg and knee; pelvic injuries; infections such as bacterial endocarditis, typhoid fever, pneumonia, scarlet fever, and virus pneumonia. The vessels may also be sensitized to allergens, according to Rich (43), thus producing damage. Ulceration of an atheromatous plaque in the aorta produces thrombosis and aneurysms invariably harbor thrombi. Any trauma which liberates thrombokinase from the tissues will increase blood coagulability.

In the 351 cases that Hunter, Sneeden, Robertson, and Snyder (25) studied, it was found that there was

little difference in the incidence of thrombosis between medical (53.2%) and surgical (46.9%) patients, or between men (52.2%) and women (53.5%). Phlebitis, either as a cause or as a complication of thrombosis, had a monor role in their cases (8.1%). They were of the opinion that the greatest single factor favoring thrombus formation in the lower extremities is sudden confinement to bed of a previous ambulatory older person without the benefit of exercise or the aid of gravity in the maintenance of an efficient venous circulation.

Conditions predisposing to pulmonary embolism are; thrombophlebitis and phlebothrombosis, recent surgical operations, severe trauma, the formation of mural thrombi in bacterial endocarditis, auricular fibrillation and myocardial infarction. Of these, phlebothrombosis is the principal offender because of its tendency to form a large easily detachable clot. BeBakey (10) and Homans (22) assert that thrombophlebitis, which is easy to recognize, rarely causes pulmonary embolism because of the adhesiveness of the clot. However, the thrombus of thrombophlebitis may suddenly grow proximally and form a loosely attached propagating clot which serves as the source of a pulmonary embolus. The distinction be-

tween thrombophlebitis and phlebothrombosis is not always well defined. There are many gradations between these two extremes and pulmonary embolism may occur with all. The important point to bear in mind is that all types of intravenous thrombosis may extend proximally and are therefore potential sources of pulmonary emboli. (26)

It has been known for a long time that many of the mild pulmonary complications following illnesses or operations were due to parts of a thrombus from the veins of the leg breaking off and lodging in the lung. Only in recent years have we appreciated the significance of these so-called attacks of pleurisy. Life in bed, the reclining position, abdominal distention, enfeeblement of the circulation, and elevation of venous pressure in the lower limbs, perhaps combined with muscular relaxation and atrophy of the legs, are to be considered as of first importance. (22)

De Takats, Mayne and Peterson (15) correlated the occurrence of 100 cases of pulmonary embolism with meterologic charts and with fluctuations ofenviromental temperatures and found the weather factor to be one which readily lends itself to registration. During the spring and fall periods, which showed marked barometric and thermal fluctuations, actually more emboli occurred and the summer months were comparatively exempt. The

effect of marked deviations from the mean temperatures for any particular period also seemed to bear influence on the mobilization of blood clots. (11)

Operative procedures on the extremities, trunk, head, and neck are less often followed by thrombembolic phenomena than are abdominal operations. (42) Spleenectomy has the highest postoperative rate of pulmonary embolism of all operative procedures. The number of deaths from pulmonary embolism following operation for malignant lesions is also high. (25) It is also a common observation in patients with malignant lesions on whom no surgery has been done, since inanition and dehydration predispose the patient to pulmonary embolism. On the other hand, obesity also definitely subjects a patient to the danger of pulmonary embolism. (42) Other factors which are significant in the development of postoperative pulmonary embolism, in particular are infection, blood dyscrasias (especially polycythemia rubra vera), leukemia, and severe anemia.

Heart disease deserves special prominence in any discussion of the etiology of pulmonary embolism. The reason for the frequency of pulmonary embolism lies in the occurrence of venous thrombosis, mural thrombi, and valvular endocarditis in patients with heart disease.

Pelvic thrombophlebitis is an important clinical

entity seen most often as a manifestation of post-partal or postabortal infection.. Pulmonary embolism from this source is frequent and the resultant emboli are infected, giving rise to septic infarcts, often with abscess formation. (26)

PRECIPITATING FACTORS

There is no pulmonary embolism without a preëxisting thrombosis. However, in the majority of cases the primary source of the embolus is unknown at the time of its occurrence. The thrombus which is most apt to break loose comes from large tributaries of the femoral or iliac vein, but produces hardly any clinical symptoms, as it does not occlude the main vessel. However, when these thrombi from the periprostatic, perivesical, uterine veins, or from the muscle veins of the calf and popliteal space, extend into the main swift current and propagate centrally, the loose, red thrombus, the tail of the clot, which is hardly fixed to the wall, breaks loose very rapidly. In tabulating the factors responsible for the mobilization of the clot, deTakats and Jesser (13) reported that in thirty percent of their cases some definite immediate cause such as bowel movement, active or passive physical exertion, the milking action of a large enema,

sitting up out of bed for the first time, and reverse gastro-intestinal peristalsis seemed to have precipitated the embolism. In seventy out of 100 cases however, no obvious precipitating factor could be found. (13) Chapman and Linton (8) found sudden pulmonary embolism more common from acts of defecation, parturition, coition, and lifting by those confined to bed by illness or operation , than deaths due to heart failure from sudden changes in venous pressure and total hemodynamics. These deaths are frequently referred to as "bedpan" deaths.

SOURCE

As early as 1934, Homans (23) in this country, supported by clinical and pathologico-anatomic observations, emphasized the great importance of the veins of the calf as areas of origin of ascending thrombi.

A very thorough study of thrombosis of the pelvic and leg veins was published by Frykholm (17) in 1940. The following list gives the location and number of instances in which he found clots: iliac, 2; hypogastric, 3; visceral pelvic, 5; femoral (above profunda), 4; deep femoral, 9; adductor muscle, 16; femoral (below profunda), 5; popliteal, 23; calf muscle, 39; anterior tibial, 0; posterior tibial and peroneal, 25;

malleolar and plantar, 2. He also searched the veins of the gluteal region and the extensor musculature of the thigh with negative results. Thus, he concluded that the areas of origin of incipient thrombosis was four, namely; 1) the plantar veins, 2) the veins of the musculature of the calf, 3) the veins of the adductor musculature, and 4) the visceral pelvic veins. DeTakats and Fowler (12) also stressed four groups of venous thromboses as being the primary sources of clotting. They speak of them as being the superficial venous thrombosis, the ascending plantar vein thrombosis, the calf muscle thrombosis, and the pelvic vein thrombosis.

On the basis of the findings in 351 cases, Hunter, Sneeden, Robertson and Snyder (25) found that; 1) bilateral involvement was found 110 times and unilateral, seventy-five times. The right side alone was affected a little more often than was the left. Thrombi formed in the veins accompanying the larger arteries far more frequently than in other veins and were present in the soleus muscle more often than in the gastrocnemius. (2) Fatal pulmonary embolism was responsible for 3.13 % of all deaths. In 45.4% of the cases of death from such embolism the most probable source was thrombosed leg veins. There is good author-

ity for the belief that, although fulminating emboli often spring from the femoral vessels, thrombosis here represent an extension from older clots in the legs and feet. (3) Lesser emboli frequently originate from the veins of the calf. Showers of these, even though of small diameter, may consist of long clots, which, by buckling or coiling, are capable of occluding even the major pulmonary arteries.

Castleman (7) found in a series of autopsies that ninty-five percent of all fatal pulmonary emboli arose in the deep veins of the leg; the other 5% arose in the heart. Of emboli arising in the heart, acute bacterial endocarditis of the pulmonary or tricuspid valves cause infected pulmonary infarcts. The vegetations are luxuriant and friable here whereas in subacute bacterial endocarditis the vegetations are firmer so embolism is less frequent.

EARLY RECOGNITION OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Aside from the clinical syndrome of thrombophlebitis, many physicians have believed that venous thrombosis cannot be recognized ordinarily. However, there is increasing evidence that blood venous thrombosis produces signs and symptoms which may be recognized easily by the experienced physician.(2)

Rose(44) states that signs and symptoms of phlebothrombosis are few and difficult to recognize. There is an increased pulse rate, tenderness over the vein, and pain in the calf when the foot is passively dorsiflexed. The superficial veins may be dilated and non-fatal pulmonary embolism heralds a terminal event.

In the cases of Veal(51) et all, all of the small infarcts presented the signs and symptoms of pneumonia, physical signs, constitutional symptoms, and x-ray appearance. In practically none were the infarcts recognized.

Munnaghan, McGinn and White(13) have demonstrated a typical electrocardiographic pattern of acute cor pulmonale in one third of 92 cases of pulmonary embolism. This may serve as an aid to the diagnosis of the small preliminary infarct.

DeTakats(16) emphasized the symptoms of pain in the groin, marked livid and later pallid swelling of the limb with a rise in temperature and pulse rate. He considered the early premonitory symptoms more important. These may later be followed by the manifest thrombosis or remain latent abortive types of phlebitis. This group of patients is more endangered by embolism than those in which a large "milk leg" has appeared. It is the opinion of

most authors that once a milk leg has appeared the danger of embolism is slight. Experience has shown 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 fourth to fifth postoperative day for other signs and symptoms of latent thrombosis. These 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 dorsiflexion of the foot, or in the groin, 3) a slight edema of the groin or suprapubic region, 4) frequent urination or mucous stools, and 5) pain in the small of the back. The last three symptoms are suggestive of pelvic thrombosis, while the location of pressure pain often denotes the site of the original thrombus which, if it remains localized, may not progress to a manifest thrombosis. There are, however, postoperative blood clots in which even these premonitory signs and symptoms are missing. The patient may show a smooth postoperative course with no rise in pulse and temperature, no pain or swelling. Most of the fatal pulmonary emboli originate from just such thrombi. Their location is either in the muscle veins of the calf or in the large pelvic plexuses.

Many small emboli go unnoticed. Proof of this is frequent finding of emboli in the lung in patients whose clinical symptoms were not suggestive. A small stitch in the side followed by a mild dry or exudative pleurisy, a short retrosternal attack of pain, or a few minutes of dyspnea followed by a feeling of lassi-

tude should make the surgeon suspicious of embolism. Further showers of greater magnitude and importance may follow. Three leading symptoms were found to be dyspnea, cyanosis and chest pain. The fall in blood pressure, which was not recorded except in the last few years, is suggested by notes such as "weak pulse," "rapid pulse," and "restlessness" by nurses. Abdominal symptoms of pain in the epigastrium, right upper quadrant, or shoulder, often suggest intra-abdominal lesions, notably a gall bladder colic. This syndrome usually signifies an infarct in the right lower lobe with diaphragmatic irritation. Cerebral anemia due to the fall in blood pressure and the loss of oxygen from the blood is signified by "convulsions" or "dizziness." (11) The number of the intermuscular and intramuscular veins, their abundant anastomoses and collateral circulation, cause the thrombosis to present few or no external signs when the leg is not in use.(23)

It has been found that the process of thrombosis may be almost entirely silent due to the fact that it causes little venous obstruction. However, careful examination may reveal slight calf tenderness, or tenderness of the plantar aspect of the foot, slight increase in the girth of the affected leg, and calf pain in dorsiflexion of the foot (Homans' sign) (26).

Priestly and Barker(41) found clinical evidence of venous thrombosis or thrombophlebitis in only 25% of 897 cases of postoperative pulmonary embolism.

DeTakats and Fowler(12) stressed sudden onset of shock with rapid weak pulse, restlessness, difficult rapid breathing, sweating and pallor, pain in chest, fainting, collapse, or unconsciousness. These symptoms were found more apt to be in a patient who has phlebitis, is convalescing from an operation or delivery, or is a known cardiac.

PREVENTIVE PROCEDURES AND EARLY TREATMENT

The therapy of thrombophlebitis is classified into prophylactic, conservative and radical measures. The prophylactic measures consist of hydration, mobilization, respiratory stimulation, prevention of increased abdominal tention, application of heat, administration of sodium thiosulfate, hirudinization and heparinization. The conservative measures consist of immobilization and elevation of the involved extremity, application of heat, hirudinization, use of compression bandages and production of vasodilation. The radical procedures consist of ligation, excision and drainage and thrombectomy or embolectomy.

Greatest effort at prevention should be centered on the group of patients who have factors which make them liable to pulmonary embolism. Therapy aimed at increasing the rate of venous return from the lower extremities will prevent many instances of pulmonary embolism. The use of the Trendelenburg position for twenty-four hours postoperative, passive and active leg exercises, frequent leg massage for the first forty-eight hours, and two to three times daily thereafter until the patient is out of bed, application of heat to the legs, deep inhalation several times daily, and early postoperative movement, have been advocated. (26)

Many efforts have been made to establish some method of detecting which individuals are susceptible to thrombosis and therefore are candidates for anticoagulant therapy. Prothrombin time, measured postoperatively, has been found reliable and in the in-

stances in which a state of relative hyperprothrombinemia exists, dicumarol is administered, (46) Shortening of the clot retraction time had been used by Hirschboeck and Coffey (20) as an indication for anticoagulant therapy. DeTakats (11) has devised a heparin tolerance test to select those patients who are susceptible to thrombosis. The determination of the clotting index is also capable of detecting potential "clotters" preoperatively.

Frykholm (11) states that injury to the intima is the most important factor in the pathogenesis of thrombosis as can be counteracted by raising the head of the bed so that the patient begins to slide downward in bed. Then the venous pressure in the extremities will rise, so that the veins become distended with blood, and the patient will be forced to make active movements with her legs to maintain her position. Thus, the veins which are especially threatened by thrombosis will be rhythmically emptied and distended.

Evans (16) says that the best prophylactic measures are exercises of the feet in bed, heat and postoperative protection by dicumarol of the patient who has already had a venous thrombosis. Paravertebral procaine sympathetic block is reserved for patients with thrombophlebitis. Also, sulfonamide drugs are a useful adjunct in the treatment of thrombophlebitis and papaverine is used to relax arterial reflex spasm.

The value of increasing the rate of the static venous

circulation has been demonstrated recently by Potts (36) who employed the routine of having the patients take fifteen deep breaths with active flexing of the legs with each breath, twice a day, starting on the eve of the operation. In 837 patients who followed this routine there was no phlebothrombosis or pulmonary embolism. In 124 patients who were immobilized because of fractures, there were five phlebothromboses and four infarctions. In 150 postoperative cases in which this prophylactic method was not used, there were four instances of phlebothrombosis.

Crafoord,(9) in Europe, gave heparin in 325 postoperative cases. Of these, only three patients developed thrombo-embolic phenomena as compared to a group of 302 similar patients who had no heparin and in which 17.5 % had thrombo-embolic phenomena. Priestly and Barker (42) at the Mayo Clinic gave heparin to sixty-three patients in whom non-fatal embolism had already occurred. Only two of these succumed to another episode of embolism. However, it is difficult and costly to give and occasionally complications result. This drug is given intravenously every four hours. Average dosage is sixty milligrams.

Allen, Barker and Waugh (3) have obtained good results with the use of dicumarol in postoperative patients predisposed to pulmonary embolism and give the drug orally. 300 milligrams are given the first day, 200 milligrams are given the second day, and 100 milligrams are given the third day. 100 milligram capsules are given thereafter if the daily prothrombin

time remains between twenty-seven and sixty. If the prothrombin level is below sixty seconds, bleeding does not have to be feared. If it is kept above twenty-seven seconds, a thrombotic process does not have to be feared. The optimum value is thirty-five seconds and the dosage is prescribed every day so as to keep close to this optimum. It is of the utmost importance that satisfactory cooperation be obtained from the laboratory in giving this drug. The prothrombin time is based upon Quick's method. In 374 postoperative cases, only three patients had thromboses during the administration of this drug. However, dicumarol has a latent period of action, and heparin must be given during that time.. The prophylactic procedure at present consists of giving heparin intravenously every four hours for a day or two. Dicoumarol also is started at the same time that the heparin is and is continued for weeks if need be.

As long as the edema is marked and the patient is febrile, bedrest in the Trendelenburg position is maintained. Patients with saphenous phlebitis need not be immobilized for any length of time but may get up early with adequate longer rest. It has been customary for deTakets (11) to keep these patients in bed for ten days after the evening pulse has returned to its level which is normal for the individual. Then the patient is allowed to sit up, hang his feet over the bed, and perform a few flat-foot exercises for five minutes three times a day. This sometimes results in an elevation of temperature or pulse on the night of the exercise, which suggests further immobilization.

However, if no reaction ensures, a Unna's glycerine-gelatine cast is applied form the toes to the groin, which is worn for three weeks and then reapplied for another three weeks. Thus, many of the late sequelae of deep thrombophlebitis may be avoided.

According to Hunter, Krygier, Kennedy and Sneeden, (24) another step that must be taken if progress is to be made is that of education of medical students, interns, physicians in practice, and nurses. Hereafter the teaching must be that all adults confined to bed are potential subjects of phlebothrombosis and pulmonary embolism. Nursing supervisors, out of training long enough not to have been taught the newer facts, must be so informed. These women stand in a crucial position, for upon their wholehearted cooperation largely depends the success or failure of any regime of treatment. Periodically in every hospital someone should give lectures and demonstrations both to the nurses and to the interns so that with changes in personnel the matter is not forgotten or allowed to lapse.

A simple means of making the hospital "embolism conscious" and of serving as a constant reminder that something is being done to prevent embolism, is to hand stamp in large letters on the order sheet of every chart the words leg exercises: Yes....or no.....Hunter, Krygier, Kennedy and Sneeden (24) state that they do not know just how many times each day a patient in bed should flex and extend the feet, knees, and thighs, but one thing is certain and that is that some of the periods of exercise should be made in the presence

of the nurse or physician. A convenient time for both is when the temperature is being taken, or at mealtimes. In this way the nurse can observe whether the patient is putting any effort into the exercise or merely playing at moving. Likewise, the intern and the resident should ask the patient to demonstrate his ability to exercise every time rounds are made. Pillows under the knees for more that a very few minutes at a time should be an absolutely forbidden practice in all hospitals. At best, the popliteal space is an anatomic bottleneck and to increase it by flexion and elevation of the knee is wholly unjustifiable.

During Blood transfusions, Zurerman (58) emphasizes careful venepucture technic; immediate discontinuance of the bleeding if hematoma develops on the donor complains of the needle causing discomfort; preventing the donor from flexing acutely his forearm after venepuncture; and the importance of leaving a circular dressing bandage off.

The emergency treatment of pulmonary embolism is carried out as follows: as soon as the nurses observe any of the cardinal symptoms discussed above, oxygen is started with the emergency mask and the permanent equipment is called for. Atropine gr. 1/60th. to 1/75th. is given subcutaneously and the intern staff is notified. On the arrival of the intern, papaverine gr. 1/2 is given intravenously and the atropine gr. 1/75th. may be repeated intravenously if no marked flushing and dilatation of the pupil exists. Both atropine and papaverine should be on the surgical floor, the former in tablets and the latter in powder form. They are dissolved in

sterile water or salt solution, boiled over the flame in a spoon and injected. Ampules are not always reliable in regard to their potency. (9)

The modern practice of early rising after operation and the shortening of confinement to bed of medical patients brought about by chemotherapy are undoubtedly doing something to prevent phlebothrombosis, but we must never forget that the process can begin within a very few days so that early rising alone will not insure against thrombosis. (24)

DeBakey (10) states that there are simpler, safer and more economical prophylactic agents than anticoagulants and their use have given better results than have been obtained with anticoagulant therapy. He cites a series of 4,410 consecutive major surgical operations performed at Charity Hospital of New Orleans with only three instances of postoperative thrombophlebitis. In another series of 6,000 operations, not a single pulmonary embolism occurred.

Some authors rely upon phlebography to detect thrombi early. Then, either the removal of the clot or the ligation of the vein above the clot is imperative. In suppurative thrombophlebitis, ligation of the involved vein above the thrombophlebitic segment or the extirpation of the involved vein and thrombus is necessary to prevent pneumonitis, sepsis, and death. (35)

Welch and Faxon (53) say that the best treatment of thrombophlebitis is overcoming vasospasm with procaine block of the regional sympathetic ganglions. Careful attention must be paid to

correct any abnormalities such as cardiac failure, electrolyte imbalance and anemia. Varicose veins should be ligated preoperative or controlled by compression bandages therafter. Postoperative stasis of blood stream must be avoided. This is promoted by frequent active movements of the legs in bed. It is not sufficient to have the patient get out of bed at an early post operative date for too frequently he will merely stand still, produce a static column of blood in the leg and increases chances of thrombosis.

When phlebothrombosis is present, Rose (44) advocates doing bilateral ligation at one sitting. Veal (50) by doing routine high femoral ligations in 80 amputations had only one pulmonary complication compared to his previous high percentage.

SUMMARY AND CONCLUSIONS

The only real hope of lessening the toll of deaths from pulmonary embolism lies in the widespread acceptance of the newer and well-proved facts as to the causes, the nature, and the anatomic location of most instances of venous thrombosis.

As a rule, thrombosis consists of a combination of two processes which may also occur independently of each other, namely: 1) an agglutination of the various cellular blood elements, in particular the thrombocytes and red cells, and 2) a coagulation of the plasma. A third type of thrombosis is concerned solely with the intravascular coagulation. Thus, there are three kinds of thrombi; agglutination, combination, and coagulation or fibrin thrombi. The close relationship between the agglutination and coagulation processes is due to the fact that mechanical factors may affect both in the same direction and, futhermore, that agglutinated cell material may liberate coagulins.

Thrombosis occurs where the equilibrium of the factors on which the preservation of the ectoplasmic layer of the blood cells or the liquid state of the blood plasma depends, is seriously interfered with. These factors may be localized in the blood itself, in the vascular endothelium or in the the perivascular tissues. They may be of a mechanical,

chemical or physico-chemical nature. They may be of bacterial origin and may be accompanied by inflammatory phenomena. Intravascular clotting is therefore favored by; 1) slowing of the circulation, 2) changes in the composition of the blood, and 3) changes in the wall of the vessel. The factors influencing the stickiness of the platelets are not the same as those affecting the agglutinability of the red cells.

It will be noted that there is considerable overlapping of etiologic factors in venous thrombosis and pulmonary embolism. This fact serves to emphasize that the problem of pulmonary embolism is in reality the problem of venous thrombosis and that when the nature of intravascular clotting has been solved, pulmonary embolism will cease to be an important problem.

Phlebothrombosis of the lower extremities begins in the deep vessels of the calf and tends to propagate toward the heart. The calf and femoral veins both are most frequently involved and therefore are the most important source of pulmonary emboli. Phlebothrombosis of the deep veins of the leg is a frequent event in all classes of middle-aged and older patients who for any reason whatsoever must go to bed for longer than a very few days. The onset is insidious and without prominent symptoms. Thrombophlebitis, as a cause or as a complication of deep extremity vein thrombosis is very uncommon.

The logical approach to the problem of phlebothrombosis and pulmonary embolism is prophylactic. Re-education of physicians and nurses with respect to the source and causes of thrombosis of the legs is urgently needed. Pillows under knees are absolutely forbidden except for a very few minutes. Bed patients should avoid forced expiration with the glottis closed, especially in the sitting position in bed. The most important prophylactic measures are exercises of the feet in bed, heat and postoperative protection by dicumarol of the patient who has already had a venous thrombosis. The modern practice of early rising after operation and the shortening of confinement to bed of medical patients, brought about by chemotherapy are undoubtedly doing something to prevent phlebothrombosis. However the thrombotic process can begin within a very few days so that early rising alone will not insure against thrombosis.

At present, there are two competitive programs of treatment to prevent pulmonary embolism: 1) ligation of femoral and iliac veins and 2) the use of anticoagulants, heparin and dicoumarol. Neither program of treatment is generally considered superior to the other, although each has its proponents who see little virtue in the other. The treatment of thrombosis should vary according to the primary site, the extent

and the age of the thrombosis. Anticoagulant therapy, paravertebral sympathetic block, proximal venous ligation, and roentgen-ray therapy all have their indications but should be used selectively. Visualization of the venous system by opaque substances may be used occasionally but its routine use does not seem necessary. Pulmonary embolism is still often the earliest manifestation of an unrecognized thrombus in the periphery. Its appearance calls for emergency measures and following the recovery of the patient, for a thorough investigation of the source of the embolus, since recurrent emboli are increasingly dangerous. A warning benign pulmonary embolism in a patient over fifty years of age is an indication for venous separation when the source of the embolism is recognized.

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