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Treatment of postoperative pulmonary embolism

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THE TREATMENT OF POSTOPERATIVE PULMONARY EMBOLISM

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INTRODUCTION

Postoperative pulmonary embolism is an unpredictable catastrophy which, when it occurs, frequently interrupts a convalescence that is otherwise relatively uneventful. Because of its unexpectedness and the suddenness of the fatal type, death is most tragic for all concerned. Robinson(72) claims that every person who is confined to bed with illness, whether operative, medical, obstetrical, or traumatic, is a potential candidate for pulmonary embolism.

In some of Rudolph Virchow's papers, collected by Long(53), he says in description of pulmonary embolism, as early as January, 1848, "The occlusion results from a more or less compact mass which is brought by the circulation to the pulmonary arteries, and there impacted, bringing about an alteration of the lung parenchyma. As often as I have found plugs in the pulmonary artery, I have always been able to demonstrate plugs also in the venous system thereto, and I consider the occurrence of the former a sure sign that old blood clots are to be found in some part of the venous system.

"In a majority of cases the plugs in the lung do not originate in the capillaries, but extend a

certain distance into the pulmonary artery, usually being seated at the dividing point of a large vessel, or riding the bifurcation. The usual site is in the vessels of second or third order."

Thus, as far back as 100 years ago, this entity was recognized, and very adequately described by Virchow. Then, in 1889, Cohnheim(18) felt that Virchow was correct in his opinion, supporting his theory by further pathologic specimens. He called the condition "embolism".

PREDISPOSING FACTORS OF THROMBOEMBOLISM

Ochsner(65) states that from most aspects, it is necessary to distinguish between the two major types of intravenous clotting, thrombophlebitis and phlebothrombosis. The clotting in thrombophlebitis is the result of injury to the vascular endothelium from mechanical trauma, chemical injury, or bacterial invasion, whereas in phlebothrombosis, the intravascular thrombus formation is due to alternations in cellular and fluid constituents of blood, which increase the clotting tendency, and to venous stasis. The prognostic significance of this difference lies in the fact that in thrombophlebitis, unless there is suppuration, which is rare, the clot is firmly attached

to the vein wall, and therefore is not likely to become detached and result in embolism. On the other hand, the coagulum of venous thrombosis is loosely attached to the vein wall, and can be detached easily, resulting in embolism.

Barnes(13) also believes that phlebothrombosis, not thrombophlebitis, is a predisposing factor in pulmonary embolism, for he says that histologic study of the emboli found in the pulmonary artery rarely reveals any evidence of organization such as would be observed if such an embolus had been detached from a thrombophlebitis. Allen, Barker, and Hines(5) support the above concept, in that all evidence points toward the fact that marginal organization of a thrombus takes place quickly, usually within the first twenty-four hours, and this organization is accompanied by a rather firm adherence of the thrombus to the wall of the vein. The histologic examination of a fatal pulmonary embolus fails to reveal any evidence of organization; therefore, it must be assumed that these emboli are detached or recent thrombi.

Snell(77) showed that obesity definitely predisposes an individual to fatal pulmonary embolism. Farr and Spiegel(31) found that the average age of their patients who died of pulmonary embolism was fifty

years; thirty-five years in those with pulmonary embolism clinically diagnosed, who recovered. Henderson(38) has noted that there were a few more females in his series of fatal cases than there were males, and that the average age was 53.2 years, whereas the average age of all patients operated on was 42.8 years. The average age in Lindsay's(50) series was fifty-two years. Apparently, there is also a geographic difference in occurrence, for a survey made by Rosenthal(73) shows there had been a distinct rise in the frequency of pulmonary embolism in central Europe between 1919-1928, whereas reports of the North American clinics failed to show a similar increase. Ochsner(65) concurs with this viewpoint when he says that the average incidence in the northern states of the United States is 1.74 cases per 100,000 population, as contrasted with 0.41 cases per 100,000 population in the southern states. Ochsner also believes that smoking, because of its vasospastic effect, predisposes to intravenous clotting.

According to Priestley and Barker(67), the incidence of fatal pulmonary embolism after exploratory operation alone for malignancy is unusually high, and is virtually the same as that for abdominal hysterectomy or splenectomy, the other proced-

ures which most often are followed by fatal pulmonary embolism.

The incidence of pulmonary embolism varies with statistics of various authors, as indicated by Hosoi(43) who found, after an extensive review of the literature, that it was between 0.10 and 0.67 per cent in post-operative cases. In his own series, Lockhart-Mummery (51) reported it as 0.10 per cent.

TABLE #1

Incidence related to age in Abdominal Hysterectomy
Mayo Clinic--Priestley & Barker(67)

AGE	OPERATIONS	Thromboembolism	
		Number	Per cent
Less than 20	10	0	0
20-29	168	3	1.8
30-39	1449	42	2.9
40-49	2870	126	4.4
50-59	975	48	4.9
Over 60	258	11	4.3
TOTAL	5730	230	4.0

Belt's(15) series of 567 complete autopsies on adults showed an incidence of 10.0 per cent fatal pulmonary embolism, in which medical cases predominated over surgical in the ratio of 40 to 16. In a

TABLE #2

Relative Incidence Thrombophlebitis & Pulmonary Embolism Mayo Clinic--Priestley & Barker(67)							
OPERATIONS	Cases	Clinical thrombo-phlebitis		Pulmonary Embolism			
				Total		Fatal	
		No.	%	No.	%	No.	%
Head & Neck	50844	19	0.04	32	0.06	14	0.03
Extremities & Trunk	18839	19	0.10	22	0.12	14	0.07
Thorax	1779	5	0.28	9	0.51	2	0.11
Breast-Radical	2919	26	0.89	17	0.58	5	0.17
Exploratory for inop. malign.	2427	20	0.82	29	1.19	17	0.70
Resection for Ca. stomach	2246	33	1.47	31	1.38	13	0.58
Benign Gastric operations	10278	112	1.09	112	1.09	35	0.34
Gall Bladder & Ducts	13103	143	1.09	119	0.91	47	0.36
Hysterectomy	5730	163	2.84	87	1.52	42	0.73
Splenectomy	391	10	2.56	13	3.32	3	0.77
Appendix (unruptured)	7975	38	0.48	36	0.45	6	0.08
Appendix (ruptured)	835	7	0.84	12	1.44	3	0.36
Hernia(unilat.)	3852	28	0.73	29	0.75	14	0.36
Hernia(bilat.)	661	13	1.97	10	1.51	4	0.61
Intest. Resection	2571	25	0.97	62	2.41	16	0.62

study of 25,771 autopsy records at the University of Minnesota, McCartney(59) demonstrated that in the 4,070 deaths which were considered as postoperative, there were 216 cases, or 5.3 per cent where it was believed that pulmonary embolism was the cause of death. Henderson(38) found that 6 per cent of the postoperative deaths in the Mayo Clinic between 1917-1927, were due to pulmonary emboli.

Priestley and Barker(67) reviewed a series of 897 cases of pulmonary embolism, both fatal and non-fatal. In approximately a fourth of all cases, the embolism appeared prior to the seventh day, half from the seventh to the fourteenth day, and the remainder after two weeks. Allen, Barker, and Hines(5) place the time of occurrence anywhere between six and twenty-one days after operation.

The most common sites of origin of the emboli which are carried to the lungs are in the deep veins of the legs and of the pelvis. Robertson(71) says that the veins of the pelvis and the legs, usually the left (because of pressure of the right common iliac artery as it passes over the left common iliac vein), are the most common sites of thrombosis which may produce embolism.

Frykholm(33) states that according to early opinion, which has been kept alive since the time of Virchow, and which has been carried on by Aschoff and his school, the femoral vein and its valve pockets are the most frequent points of origin of the deep-lying venous thrombi of the lower extremities. However, Aschoff(6), in 1924, said that the plugs, which occlude the large branches of the pulmonary artery, could only come from the inferior vena cava or the origin of the iliac veins, they are so large; but upon closer examination, they are actually composed of numerous folded thrombi of a finger's breadth, on the average, and therefore are very long. If one carefully unfolds the thrombus, they will be able to substantiate that fact that one is dealing with blood clots 35-45 centimeters in length. This finding shows unequivocably that the fatal embolus can only arise from a very long, medium sized vessel. The only vessel which comes into play as a possible source is the femoral vein. In 1934, Homans(41), supported by clinical and pathologico-anatomical observations, emphasized the great importance of the veins of the calf and plantar veins as areas of origin of an ascending thrombosis. Frykholm(33) cites four main areas of incipient

thrombosis: 1. Plantar veins; 2. veins of the musculature of the calf; 3. veins of the adductor musculature; and 4. the visceral pelvic veins. Evans(27) says that the superficial veins of the legs and the veins of the arms rarely cause pulmonary embolism.

PATHOLOGIC PHYSIOLOGY

According to Martland(55), some form of physical exertion often dislodges a thrombus, and causes embolism. Thus he noted the high incidence on getting out of bed, defecation, and coughing. However, in seventy of one-hundred cases, DeTakats and Jesser(23) could find no obvious precipitating cause.

DeTakats and Jesser(22) wish to emphasize the fact that an embolus is not equivalent to a pulmonary infarct. The obstruction of an artery in the lung will produce hemorrhagic infarcts only in case of secondary venous thrombosis. If an anemic infarct occurs, it can often give the picture of a localized emphysema because of the concomitant bronchial obstruction, which is usually incomplete, so that air is aspirated into the alveoli but cannot be exhaled.

DeTakats, et al(21) divide postoperative emboli into two types: One which plugs the terminal vascular bed and is characterized by cyanosis and dyspnea; and

one which represents an obstruction to the main pulmonary artery and exhibits a syncopal attack, with pallor and shock. Boyd(16) adds one group: Small emboli which give rise to pain in the side and spitting of blood, but no physical signs.

Boyd also says that the bronchial artery supplies blood for nutrition at systemic pressure, whereas the pulmonary artery supplies blood for oxygenation at one-third of that pressure. The bronchial artery serves the important function of filling both circulatory beds with blood beyond an embolus. The collateral circulation is therefore abundant, giving infarcts which are always red. The infarct appears as a wedge-shaped area; the base of the wedge is at the surface and covered by a thin pleural exudate. Pleurisy, if present, is the cause of the characteristic pain in the side and the friction rub. As recovery takes place, the infarct is partly absorbed, partly replaced by a scar which can seldom be detected if the patient dies later. Should the embolus be septic, the element of infarction is obscured by the development of abscesses which are usually multiple, in the lung.

As for mode of death in cases of pulmonary embolism, there are apparently several conditions, or a

combination of conditions, which are precipitating factors.

Allen, Barker, and Hines(5) say that there is some evidence that pulmonary embolism produces reflex constriction of the pulmonary arterioles and also the bronchioles, both of which may seriously embarrass pulmonary function. The secondary effects on the heart may be profound, producing marked right ventricular strain and right ventricular failure--acute cor pulmone. DeTakats, et al(21), do not support the theory of mechanical obstruction as a cause of death when they say that most experiments do not take into consideration that the mechanism of death from a mechanical viewpoint does not explain some of the fatalities in which only parts of the vascular tree are blocked. But, they argue, if death can occur reflexly from the occlusion of one or two lobar branches of the pulmonary artery, why do patients tolerate a lobectomy or a pneumonectomy without any serious disturbance in circulation? This they answer by explaining that there are respiratory and cardio-vascular reflexes originating in the pulmonary plexus of the vagus, which can be abolished by anesthesia. Allen, Barker, and Hines(5) agree with this, for they hold that in twenty

to thirty per cent of fatal cases, the main pulmonary artery is only partly occluded, or only one branch of the pulmonary artery is occluded. There may be reflex constriction of coronary arteries, and sometimes when pulmonary embolism has not been immediately fatal, multiple infarcts have been found in the right ventricle. It is uncertain whether these result from coronary spasm or lowered pressure in the coronary arteries, plus distention of the ventricle and compression of the muscle. Megibow, Katz, and Steinetz(61) think that the theory of reflex coronary vasoconstriction as a cause of sudden death finds little support in their experiments on animals, since mechanical factors are enough to explain possible changes in coronary circulation. They believe the cause of death in pulmonary embolism to be due to a rapid or slow failure of the right heart. Death is often very rapid. Evans and Boller(29) review 52 cases of fatal pulmonary embolism over six years at the Lahey Clinic, 21 of which died before adequate treatment could be instituted.

In the final analysis, Barnes(13) explains death as due to shock, a fall in blood pressure in the coronary and systemic arteries, pulmonary hypertension,

and anoxia, all being cardinal factors. Increased right auricular pressure increases the pressure gradient in the coronary arteries. The coronary blood in the right ventricle is further decreased, since 92 per cent of the venous return from the right ventricle is by way of the thebesian veins. Thus, increase of pressure in the right ventricle decreases the coronary blood flow to this side of the heart. All these factors cause dilatation and failure of the right ventricle.

DIAGNOSIS

Since, according to Priestley and Barker(67), approximately one in four cases of pulmonary embolism is associated with clinical evidence of thrombophlebitis, and similarly, approximately one in four cases of thrombophlebitis is associated with evidence of embolism, it would be well in passing, to mention the symptoms and signs of thrombosis from which emboli arise.

In looking for postoperative thrombophlebitis or phlebothrombosis, Homans(42) emphasizes strongly that the more silent and insidious the deep thrombosis, the more dangerous it is; the more out-spoken, the less liable to cause embolism. In a bilateral disease, for

example, when one leg is tensely swollen and the other seemingly normal, embolism is threatened less by the swollen limb than by the apparently normal one.

Ochsner(65) describes thrombophlebitis briefly as a pyrexia ranging from 101-103 degrees, with pain along the involved vessel, along with swelling of the involved extremity. The patient with phlebothrombosis may have no symptoms. It can be diagnosed definitely only by demonstrating the presence of venous obstruction by means of visualization of the venous system (venography). Ochsner feels that in a suspected case of phlebothrombosis, the diagnosis should be accepted without venography for the sake of time. Evans(25) stresses the importance of watching for Homan's sign (pain in the calf with forcible dorsiflexion of the foot) and an unexplained low-grade septic temperature in any postoperative case where thrombosis is suspected.

As stated previously (p.9-10), pulmonary embolism gives a varied clinical appearance, depending upon the site at which the embolus lodges. Barnes(12) thinks that it has been custom to think that acute pulmonary embolism has, as its cardinal signs, cyanosis and dyspnea. As a commoner picture of pulmonary embol-

ism, he wishes one to regard pallor, sweating, marked fall in blood pressure, vomiting, and sometimes collapse: shock, with or without dyspnea. McGinn and White(58) agree with this picture, and say it is followed rapidly by the reaction of the infarction itself--namely, fever and elevation of the pulse and respiratory rates. Hemoptysis may occur after a few days.

Physical signs also vary with the location and size of the embolus. Allen, Barker, and Hines(5), in description of the small, peripheral infarct, call attention to the frequent elevation of the diaphragm, suppression of breath sounds over the area of the infarct, and a few scattered rales. With a larger embolus which causes shock, these same signs are merely intensified.

They also name two conditions which they believe are the most commonly confused in diagnosis. In the first, pneumonia, the temperature is usually higher, and remains so longer than with pulmonary embolism. There are other evidences of infection; cough is a more prominent symptom, hemoptysis is less severe, the findkings of consolidation are more difinite, there are more rales and the roentgenograms of the thorax show a larger lesion or multiple disseminated

lesions. In the second, coronary thrombosis, the electrocardiogram is of great value in differentiation from pulmonary embolism, since the patterns are different even if the coronary thrombosis is in the posterior descending branch. In coronary thrombosis, the pain is frequently more severe; it is not pleural; it often extends to the arms or shoulders; cyanosis is infrequent; and signs of a localized pulmonary lesion are absent. Averbuck(7) points out that whenever emboli arise, the symptoms caused by a pulmonary embolus in a patient who has proved coronary disease may so simulate a coronary occlusion as to be impossible of differentiation.

Barnes(13) lists the electrocardiographic changes present with acute cor pulmone occurring with pulmonary embolism, but which are not always present in pulmonary embolism. S_1 is constantly present and of considerable amplitude; T_2 is diphasic, iso-electric, and seldom inverted; RS-T_2 is not elevated and often depressed; RS-T_3 is slightly elevated; in leads IVR and IVF the ST segment is unchanged and the T wave may be negative or positive.

Acute cor pulmone associated with pulmonary embolism is described by White(80) as acute dilat-

ation of the right ventricle and pulmonary conus in massive but non-fatal pulmonary embolism, possibly giving rise to certain cardiovascular signs which can be recognized on physical examination. One may observe dilatation and pulsation of the veins of the neck. Increased pulsation may be noted in the second and third interspaces to the left of the sternum. Marked accentuation of the second pulmonic sound may be observed, and a loud systolic murmur in the region of increased pulsation may be present. Gallop rhythm, heard best to the left of the sternum, is present occasionally.

PREVENTION

Most writers agree that the best treatment of any disease is the prevention of its occurrence. In citing thirty deaths from pulmonary embolism at Henry Ford Hospital from 1939-1944, Lam(48) says there were twenty-eight fatal cases which had a sudden embolism and there was no opportunity for treatment. With this he emphasizes the fact that the main problem facing the medical profession is one of prevention rather than treatment. Flynn(32) says that anyone who has had thrombophlebitis or embolism six months prior to approaching surgery may

be considered a candidate for postoperative pulmonary complications of some type, and should definitely be treated prophylactically. Barnes(13), in widening the scope of prevention, concentrates his efforts on patients who, by virtue of age, habitus, cardiac status, and type of operation, constitute a very vulnerable group. He considers the focal point of efforts at prevention center on those procedures that will insure a normal venous return from the lower extremities.

Hines(40) puts forth a regime for general prophylaxis, the various points of which are agreed upon by most contemporary writers:

1. Careful, clean surgical technique.
2. Pre- and postoperative treatment of anemia.
3. Avoidance of abdominal compression by tight binders or dressings.
4. Adequate fluid intake.
5. Prompt treatment of infection.
6. Warm environmental temperature.
7. Early ambulation.

Frykholm(33) advocates elevation of the head of the patient's bed so that maintenance of position forces the patient to push up in bed with his feet, and empty the veins of the legs by muscle contractions.

However, most writers agree with Gray(36), Mayo(57), Barnes(13), and Cogswell(17), that for the first twenty-four hours postoperatively, the foot of the bed should be elevated ten inches off the floor, placing the patient in a modified Trendelenburg position, to facilitate adequate venous drainage from the legs and pelvis. Gray(36) lists the following contra-indications for this procedure as follows:

1. Drainage of any intra-abdominal, suppurative process.
2. When the position would embarrass respiration, as in a weakened myocardium.

Early ambulation, or early movements in bed, such as routine pedalling on a bicycle apparatus every day, are also advocated by Mayo and Cogswell. In Cogswell's (17) series of 403 adult patients who were confined to bed with major surgical operations, a bicycle-pedal apparatus attached to the foot of the bed was used routinely every day. None of these patients developed thrombophlebitis or pulmonary embolism.

In 1930, Walters(78) suggested increasing the rate of metabolism, of blood pressure, and of blood flow with two grains of dessicated thyroid three times a day. He reviewed 4500 major surgical procedures

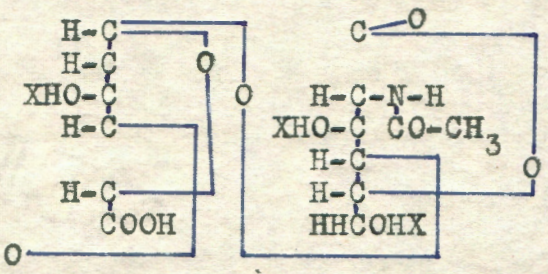
over four years at the Mayo Clinic, and reported that this regimen led to only one-fourth of the number of cases of postoperative embolism as were seen in a comparable period previously. Charles Mayo(57), in 1937, said that thyroid in this dosage had not proved of much assistance in the prevention of embolism. Priestley and Barker(67), also of the Mayo Clinic, show that experimentally, thyroid extract increases the rate of venous blood flow. They point out that as it is employed clinically, however, this may not be the case, since the physiological effects of a given dose vary widely in different cases.

Recognition of venous thromboses and the importance of Homan's sign have been discussed elsewhere (p.14). Once thrombosis has occurred, definite steps must be taken in the prevention of embolism, and the physician must always be on the alert for the possibility of pulmonary embolism.

ANTICOAGULANTS

There are two distinct factions in specific methods of prevention of pulmonary embolism. One group advocates surgical measures involving Thrombectomy and venous ligation, while the others support anticoagulant therapy with heparin and dicumarol.

Heparin was first isolated by McLean(60), in Howell's laboratory in 1916, and first employed in the prevention of experimental thrombosis and embolism by Mason(56), in 1924. Murray(63) gives the suggested formula for heparin:



(X shows where esterification with H_2SO_4 may take place)

Murray says that heparin is an antiprothrombin. Loewe and Hirsch(52), however, list a more complex mechanism of action:

1. Prevents, with the aid of a plasma co-factor, the conversion of prothrombin into thrombin.
2. Forms a strong antithrombin in conjugation with serum albumin.
3. Prevents the formation of thromboplastin from the platelets.

They also give the action of heparin of the thrombus itself:

1. Red cell clots which are not organized and which contain a minute amount of fibrin

(sludge stage) disappear completely under heparin therapy.

2. Heparin therapy prevents propagation of a thrombus and maintains patent adjacent collaterals which ordinarily would become involved in the thrombotic occlusive process.

It is universally recognized that heparin rapidly produces a prolongation of coagulation time of the blood. However, most authors dislike it, in that it is expensive and difficult to administer. As explained by Priestley and Barker(67), there are two methods of administration of heparin: the method employed by the Scandinavian group, of giving repeated single injections; and that used mostly in this country, of continuous intravenous administrations of it in physiological solution of sodium chloride or in a 5 per cent solution of glucose. When divided doses are employed, four doses are given during the course of twenty-four hours, three of fifty milligrams each during the day, and one of one hundred milligrams at bedtime. When heparin is given by means of continued intravenous injection, the physician should endeavor to maintain the venous coagulation time of the blood at a value of 15 to 20 minutes. There is considerable variation in the

amount of heparin necessary to accomplish this purpose in different individuals and also at different times in the same patient. A starting dosage of twenty milligrams per hour usually is satisfactory. This dosage then must be regulated according to the requirements of the individual patient. It is 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 (2-6 times daily), so that it may be certain that the rate of flow and the coagulation time remain within the desired limits. When once started, the administration of heparin should be continued for a minimum of seven to ten days or longer. According to Barker and Priestley(9), "Prompt return of the coagulation time to normal will occur within several hours following discontinuance of the administration of heparin." Schreck(75) says that the only toxic effect to this form of therapy is an occasional case of nausea and vomiting, which are not severe or prolonged.

In 1946, Loewe and Hirsch(52) announced that the objection to the continuous intravenous drip method of heparin administration had been overcome by incorpor-

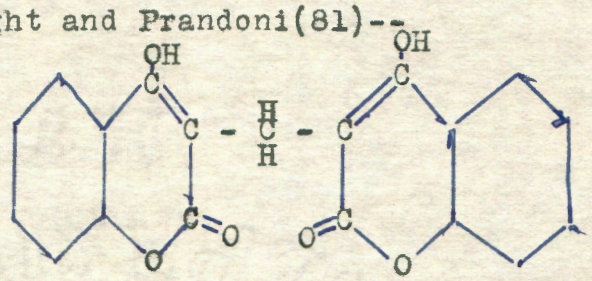
ating the drug with Pitkin menstruum, which was developed to retard the release of water-soluble drugs injected subcutaneously or intramuscularly. A short time later in the same year, Evans and Boller(30) put their stamp of approval on this material when they said that their patients who need heparin, receive repeated injections of heparin/Pitkin. These same two authors(31) describe Pitkin menstruum as composed of 18% gelatin, 8% dextrose, 1 to 1.5% acetic acid, and distilled water sufficient to make 100%. Heparin (100 to 200 milligrams) is added to this menstruum with and without vasoconstrictors, 10milligrams of ephedrine and 1.0 milligram of epinephrine. This mixture is supplied in 1 and 2 cc. ampules. Their experience has led them to the conclusion that the following dosage is most effective: To patients under 150 pounds (68 Kg.) they give a 1 cc. ampule containing 100 milligrams of heparin without vasoconstrictor, and a 1 cc. ampule containing 100 milligrams of heparin with vasoconstrictor. If the patient is over 150 pounds, he is given 100 milligrams of heparin/Pitkin without vasoconstrictor and a 2 cc. ampule containing 200 milligrams of heparin/Pitkin with vasoconstrictor. Daily coagulation time is

determined. They advocate heparin/Pitkin over dicumarol, where liver function is poor, and use it very effectively in the latent period of dicumarol therapy. In evaluating the use of heparin/Pitkin, they found the anticoagulant effect to begin within two hours, the time of maximal effect between twelve and twenty-four hours, and the average duration of effect at forty-one hours. Side effects of local pain, swelling, and tenderness were sometimes encountered, but no active measures to combat this local reaction were necessary. If it is desirable to discontinue the heparin activity as produced by this subcutaneous method, simple application of a tourniquet above, or an ice bag on the site of injection, with or without small transfusions of whole blood, will suffice.

The compound 3,3'methylene-bis(4-hydroxycoumarin), formerly called dicoumarin and now called dicumarol, was first isolated from spoiled sweet clover, and synthesized in 1940, by Link and his associates at the University of Wisconsin(10). Its discovery came about through the efforts of a Canadian veterinarian, Schofield(74), who discussed, in 1924, a new disease in cattle similar to hemorrhagic septicemia and blackleg, characterized by a marked increase in the

clotting time of the blood, followed in a few days by hemorrhage and death, caused by eating sweet clover contaminated by a mould of the aspergillus group.

The dicoumarin--3,3'methylene-bis(4-hydroxycoumarin): from Wright and Prandoni(81)--



In their investigation of dicumarol in 1941-1942, Allen, Barker, and Waugh(4) presented the following data:

1. Dicoumarin, when administered orally prolongs the prothrombin time, impairs clot retraction, and increases the sedimentation rate of the erythrocytes. Large amounts prolong the coagulation time. Hemorrhage may occur when dicoumarin has greatly prolonged the prothrombin time. The drug seems essentially harmless otherwise.
2. Dicoumarin should be administered only when its effect can be determined by repeated calculations of the prothrombin time.
3. A plan of administration--300 milligrams on

the first day, 200 milligrams on the second day and 200 milligrams on each day after the second on which the prothrombin time is less than 35 seconds.

4. After administration of the first dose, from twenty-four to forty-eight hours elapse before an effect on the prothrombin time is noted. After discontinuing administration, prothrombin time may be prolonged from two days to two or three weeks, depending on the dosage given.
5. Heparin and dicoumarin may be administered together when both quick and prolonged action are desired. The use of heparin is discontinued when the prothrombin time has been satisfactorily prolonged by dicoumarin.
6. Synthetic vitamin K has little or no effect on prolongation of prothrombin time resulting from dicoumarin. Transfusions of fresh blood will reduce, for variable periods, the prothrombin time which has been increased by dicoumarin.

These facts have been confirmed numerous times in the literature(2,3,9,10,11,26,30,69).

In additional data, Reich, Yahr, and Eggers(70)

offer the information that dicumarol acts by inhibiting the production of prothrombin at its source, namely, the liver. Quick(69), in 1946, stated that dicumarol itself is not an anticoagulant. When added to blood in a test tube, it exhibits no inhibitory action on coagulation. When ingested, it causes a fall in the prothrombin level of the blood. The effect does not come on immediately, but requires a latent period of from twelve to twenty-four hours. The reason for this is that dicumarol has no action on the circulating prothrombin, but exerts its effect by blocking the mechanism which synthesizes the latter agent. The fall in prothrombin therefore is due to the normal metabolic consumption and the failure of the body to replenish the supply. Since man normally has four to five times more prothrombin than the minimum requirements for coagulation within physiological limits, the prothrombin must be reduced to twenty to thirty per cent of normal before coagulation time is significantly influenced.

In 1943, Barker, Allen, & Waugh(10), and Barker(8) listed the contra-indications for the use of dicumarol:
Absolute Contra-indications--

1. Renal insufficiency.

2. Purpura of any type.

3. Blood dyscrasia with tendency to bleed.

4. Existing prothrombin deficiency, such as may occur in hepatic disease with jaundice, and malnutrition.

5. Subacute bacterial endocarditis.

Relative Contra-indications--

1. Existence of ulcerating lesions, open wounds, potentially bleeding surfaces.

2. Necessity for surgery during the next two weeks.

3. Vomiting due to gastric or intestinal obstruction, or use of continuous gastric drainage.

4. Operations on brain or spinal cord.

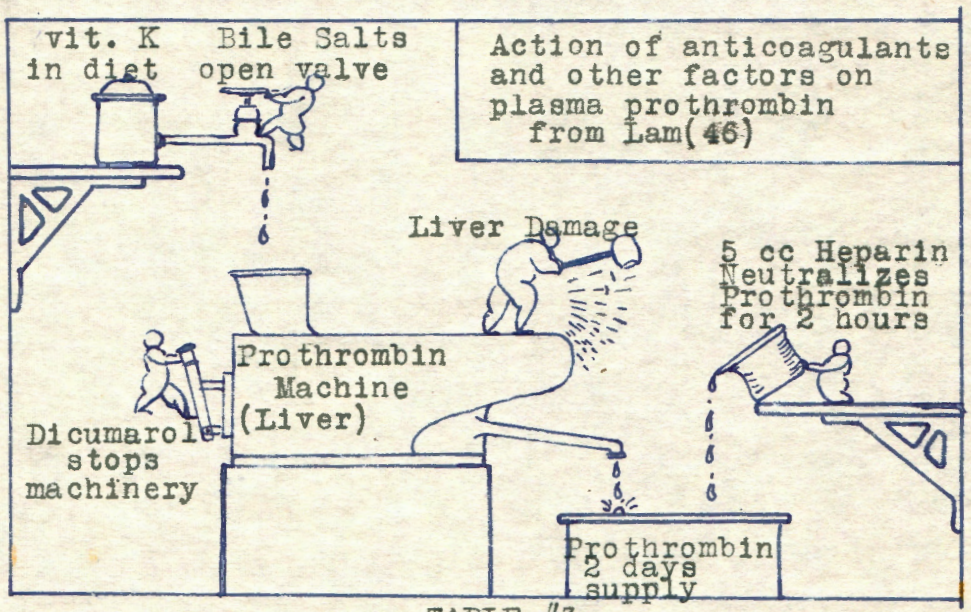


TABLE #3

The contemporary use of these two anticoagulants in prevention is by means of combined therapy. Heparin and dicumarol therapy begin together, the heparin being discontinued after the latent period in the action of dicumarol is past.

Lam(47) lists 637 cases where anticoagulant therapy was instituted, and attributes only two cases of death to dicumarol. Both of these were in cases of subacute bacterial endocarditis, previously listed as an absolute contra-indication to the use of anti-coagulants.

Barker, et al(11) gave dicumarol to 1,000 patients for the purpose of preventing postoperative venous thrombosis, pulmonary embolism, and thrombophlebitis. they found it effective in preventing these complications in cases where there had been non-fatal pulmonary embolism, thrombophlebitis, or a history of a previous thrombosis or embolism, and when the frug had been given prophylactically when no thrombosis or embolism had occurred. They claim there is small risk of bleeding, which can be further minimized by proper administration of the frug and rapid control of excessive prothrombin deficiency. If bleeding occurs as a result of excessive prothrombin deficiency, they

advocate, in addition to the previously suggested blood transfusions, the intravenous administration of menadione bisulfite (synthetic vitamin K) in large doses (60-64 milligrams).

TABLE #4

Non-fatal Postoperative Pulmonary Embolism and Infarction Barker(8)				
	Control Group no Anticoagulant		Dicumarol given	
	No.	%	No.	%
Total Cases	678	100	111	100
Subsequent Thrombosis embolism or Infarct	297	43.8	2	1.8
Subsequent Fatal Pulmonary embolism	124	18.3	0	0

TABLE #5

Postoperative Thrombophlebitis Barker (8)				
	Control Group no Anticoagulant		Dicumarol given	
	No.	%	No.	%
Total Cases	897	100	83	100
Subsequent Episode of Thrombophlebitis	95	10.6	2	2.4
Subsequent Fatal embolus	51	5.7	0	0

As can be seen in tables 4 and 5, when dicumarol was administered following thromboembolic disease, no cases of fatal pulmonary embolism occurred.

Another type of medical management mentioned in the literature in 1933(54), which has not appeared since then, is the use of leeches over the thrombosed areas. While leeches have been used for the purpose of decreasing congestion in thrombosed areas, the authors believe this to be the only review of the literature from the aspect of prevention of pulmonary embolism. Mahorner and Ochsner(54) reviewed the literature from 1922-1931 (mostly European), and drew out the following fact: Out of 216 cases of postoperative thrombosis treated with leeches, 3 cases (1.3%) of fatal pulmonary embolism occurred.

SURGICAL PREVENTIVE MEASURES

Homans(41,42) states that surgical interruption of veins has a most attractive quality in that, if properly performed, it ends all danger of embolism. Pilcher(68) advocates ligation "because of its simplicity, its safety, and the possibility of offering immediately to the patient and his family positive assurance against recurrence or fatality. Welch and Faxon(79) qualify their acceptance of ligation, when they state

that all cases of deep phlebitis should be ligated bilaterally whether associated with a previous infarct or not.

Allen, Linton, and Donaldson(1) classify their indications for bilateral femoral vein ligation:

1. Patients who have developed non-fatal pulmonary embolism, even though no positive signs of venous thrombosis in the legs can be detected.
2. Any patient who develops phlebitis, as evidenced by pain, tenderness, swelling in the lower extremity, dilated superficial veins, or pain in the calf muscle when the foot is forcibly dorsiflexed (Homan's sign).
3. Cases with femoro-iliac thrombosis--the mechanical removal of the thrombus from the vein by aspiration has been demonstrated as a safe procedure. This reduces the pain and swelling in the leg and hastens the recovery, in addition to preventing massive fatal pulmonary embolism.

As for the level at which the femoral vein is sectioned, Homan(42) explains that the common femoral vein, proximal to the profunda must be preferred.

For, if the femoral vein is ligated distal to the great branch entering from among the musculature of the thigh (profunda), thrombosis may, although rarely, to be sure, short-circuit the obstruction with a fatal result. Into this large vessel, a smooth glass tube can be introduced to suck out detachable thrombus. In this way, even the common iliac vein can often be cleared.

There are those who advocate a surgical procedure no less radical than ligation of the inferior vena cava, as a method of prevention of pulmonary embolism. O'Neil(66) thinks it should be done in every case where pulmonary embolism has occurred and its source is not evident. Moses(62) reviews a series of thirty-six such operations and says that thrombophlebitis of the pelvic veins with pulmonary embolism cannot be properly handled with any surgical intervention less than ligation of the inferior vena cava below the renal veins. Gaston and Folsom(34), in their report of two cases, said that in each case, the caval interruption probably forestalled a fatal issue by preventing massive pulmonary embolism. At the time of ligation, both patients had suffered multiple pulmonary infarcts. Adequate collateral circulation around the obstructed cava developed, and the peripheral edema

eventually disappeared.

Evans(29) enumerates the disadvantages of venous section and ligation:

1. An additional operative procedure on a patient who may be very sick.
2. The added risk of a swollen leg at least until collateral venous circulation is accomplished.
3. No chance of recanalization being established.
4. The difficulty of knowing from which leg the embolism has metastasized, and therefore to be consistent, the necessity of ligating both sides unless a venogram has indisputedly established normal deep venous circulation in the supposedly healthy extremity. Venograms have their limitations in this respect.
5. The possibility that embolism has sprung from pelvic or abdominal veins, whether or not both legs are normal.
6. The possibility that thrombosis may proceed above the level of ligation.
7. The necessity and technical difficulty of tying the common iliac vein to get above the thrombus.

Kaplan(44) says that while both methods have their

advantages, there are also disadvantages to both. In addition to the disadvantages of surgery listed on the previous page, anticoagulant therapy requires constant supervision and accurate laboratory work. There is some danger of hemorrhage in postoperative patients. It does not prevent an already formed thrombus from breaking off, so that embolic episodes may occur during administration or after stopping the drug. It should not be used in the presence of renal disease, where there is impaired liver function, or a known tendency toward bleeding.

Evans(27) feels, however, that the use of both anticoagulant therapy and surgical procedures have their place in prevention. He uses anticoagulant therapy in deep pelvic thrombosis and in femoral vein thrombosis if the patient is under fifty. Otherwise he uses ligation and section.

Kirby(45) said, in 1946, "The statistical evidence available at present does not establish a clear-cut superiority of one over the other. Moreover, the use of one or a combination of these measures does not assure protection in all instances."

Lam and Hooker(53) list the results of treatment of non-fatal embolism at Henry Ford Hospital:

Yr.	Number of operations	Nonfatal Embolism	HEPARIN	DICUMAROL	LIGATION	Fatal Emb.	Fatal C & R
'39..	5106	21	7	--	--	4	0
'40..	5835	19	15	--	--	5	1
'41..	6148	30	23	--	--	3	1
'42..	6340	17	5	7	2	5	0
'43..	6175	9	--	7	--	8	0
'44..	7452	6	1	2	3	5	0
	37,056	102	51	16	5	30	2

THE MANAGEMENT OF PULMONARY EMBOLISM

Homans(42) stresses that in proposing any emergency measures in cases of pulmonary embolism, one must recognize that a correct diagnosis is not always made, and only measures should be used which would do no harm even if pulmonary embolism were not present.

Martland(55), in his discussion of immediate treatment, says that when the 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 any treatment. Thus there is no practical treatment for massive embolism. It is his opinion that when smaller emboli occur, temporary or final recovery takes place no matter what treatment is applied. He also believes it debatable whether or not removal of emboli from the pulmonary artery surg-

ically should be undertaken. He says there is too much chance of a mistaken diagnosis.

Shambaugh(76) thinks that the clinical picture in fatal cases will be clear enough so mistakes in diagnosis will be few, and he advocates an attempt at operation. But Mayo(57) points out that the procedure cannot even be attempted in most hospitals. When embolectomy is done on the pulmonary artery, the staff to whom the operative technique is to be entrusted must be at hand at all times, and they must be perfect in every detail of the operation. For the success depends largely on the skill and rapidity with which the operation is carried out.

Pulmonary embolectomy was perfected first by Trendelenburg, in Germany, and carries his name. DeTakats(23) reviewed the 134 operations reported to 1944, of which nine were supposedly successful. Shambaugh(76) says that no successful operation of this kind has ever been reported from the United States. Henry(39) reported three attempts, all of which were unsuccessful. Edwards(24) reported three cases in which there were no recoveries.

In reporting two unsuccessful cases, Griswold(37) describes the modification of the Trendelenburg oper-

ation which is in use today:

"A straight incision is made along the left side of the sternum from the upper border of the second to the lower border of the 4th costal cartilages, dividing the origin of the Pectoralis major. A Doyen raspatory is passed about the 3rd cartilage close to the sternum, and pushed sharply to the left. This strips the soft tissues from the rib and enables one to do a rapid resection without injuring the pleura or the internal mammary artery. The 2nd and 4th cartilages with a bit of rib, are similarly resected and from one-fourth to one-third the width of the sternum is removed with large rongeurs. The forefingers are inserted at the lower angle of the wound and swept cephalad, easily stripping the pleura laterally from the pericardium. The pericardium is picked up and opened with knife or scissors. The opening may be enlarged by the fingers or by cutting. In the latter case there is some chance of injuring the thymus gland. A Trendelenburg sound is passed from left to right through the great transverse sinus behind the aorta and pulmonary artery, a rubber tube with its tip attached to the sound, and drawn back. Gentle traction on the tube lifts these vessels from the depths of the wound. The longitudinal

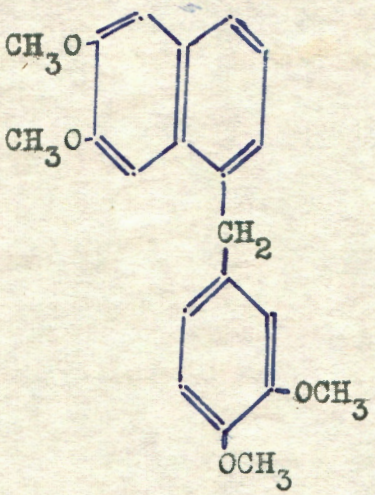
incision should be placed with care, to avoid injury to the orifice of the valve. An incision of 1.5 centimeters is sufficient. The rubber tube is relaxed to allow clots in the heart to be flooded out, then the tube is tightened and blood rapidly removed from the pericardium. Gentle traction is important.

"With the Trendelenburg forceps the pulmonary branches are explored, first on one side and then on the other. The right main branch extends toward the right axilla and the left directly backward, and there is usually little difficulty in finding them. If difficulty and delay are experienced, it is a good idea to close the slit in the artery with the fingers and allow the heart to recover somewhat, before another attempt is made at extraction. If the suction tip has been used, the vessel should be flooded with blood, to drive out the air before closure. The slit in the vessel is held up by thumb forceps and an artery clamp applied, and the lips of the incision closed with continuous fine silk suture. An opening should be left in the pericardium to prevent tamponade from accumulation of fluid. If necessary, the clamp may be left on the vessel while any resuscitating measures are taken, such as cardiac massage, intracardiac adrenalin,

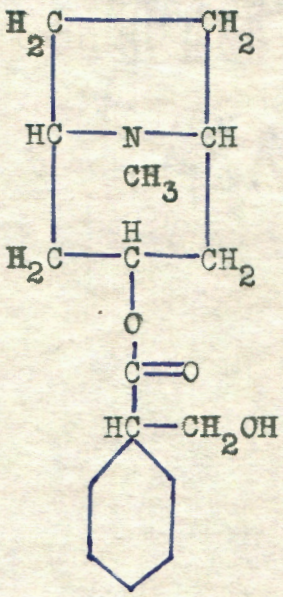
or artificial respiration."

If the attack of pulmonary embolism is recognized, it must be regarded as a medical emergency.

Collins(20) has shown that papaverine hydrochloride in the dose 1/2 grain should be given intravenously. DeTakats and Jesser(22) feel that the addition of atropine, 1/60 to 1/75 grain, intravenously is very important. These should be given every four hours(14). In experimental study, DeTakats, et al(21) found that a large per cent of animals dying from the massive embolism are helped by atropine and papaverine.



PAPAVERINE



ATROPINE

In explaining the action of these drugs, Goodman and Gilman(35) say that papaverine relaxes smooth muscle spasms, especially those of the blood vessels. In pulmonary embolism, the drug acts not on the obstructed vessel, but by increasing collateral circulation in reflexly constricted vascular beds. Atropine relaxes the smooth muscles of the bronchi and bronchioles, resulting in a widening of the airway and a slight increase in the volume of residual air, helping the pulmonary edema, but more important, it acts as a pressor substance on the harmful vagal reflexes.

All authors advocate, in addition, the use of oxygen therapy where cyanosis and/or dyspnea are present. Most prefer a Boothby mask in this administration of oxygen.

Martland(55) suggests that to prevent radiation of autonomic reflexes originating in the lung, injection of the stellate ganglion with procaine hydrochloride may be tried, although variable success results.

DeTakats(23) would like to see the following information in the form of a chart in every hospital ward:

PULMONARY EMBOLISM

Recognition: Sudden onset of shock, with rapid pulse,

restlessness, difficult, rapid breathing, sweating and pallor, pain in chest, fainting, collapse or unconsciousness. Apt to be in a patient who has phlebitis or in convalescence from an operation or delivery or is a known cardiac.

Emergency Treatment:

1. By Nurse
   - -Place in semi-sitting position.
   - -Start oxygen by catheter or mask immediately.
   - -Give 1/75 grain atropine, hypodermically, immediately.
   - -Call intern.
2. By Intern
   - -Give second dose of 1/60 to 1/75 grain atropine intravenously (if previous injection has not caused flushing of face and dilatation of pupil)
   - -Give 1/2 grain papaverine intravenously.
   - -Repeat atropine and papaverine three or four times a day.
   - -Order portable chest film and electrocardiogram.

Murray(63) and Coller & Singleton(19) advocate the immediate intravenous use of anticoagulants, saying that this regime shows rapid clinical improvement of

symptoms within twenty-four hours.

DeTakats(23) says that if the patient survives the initial attack, the second phase of treatment starts by the administration of anticoagulants, for Barnes(13) says that fully one-third of the fatal attacks are preceded by milder premonitory attacks. Therefore, heparin-dicumarol preventive therapy(p.24, p.26-27) is definitely indicated in all patients who have suffered a pulmonary embolus. It may occasionally increase the hemoptysis, but it should also protect the patient from a propagating thrombus at the site of the primary blood clot. A thorough search should now be made for the site of origin of the embolus. Unless it is in the pelvis or the right heart, it is apt to be in the lower leg, and this can be easily excluded from the circulation by section of the femoral vein.

DeTakats(23) describes some patients who made an initial recovery on combined therapy with papaverine, atropine, oxygen, and anticoagulants, yet slowly fail and die on the second to fourth day after the initial attack. He says they unquestionably die of right heart failure, since the combined antispasmodic and anti-coagulant therapy has been unable to decrease the large resistance in the pulmonary arterial bed, and he

speculates that perhaps this type of case might be the kind suited for the Trendelenburg operation.

SUMMARY

1. The history and some of the background of thromboembolism are reviewed.

2. The use of venous ligation and section in the prophylactic treatment of pulmonary embolism are discussed.

3. Anticoagulant therapy by heparin or heparin in Pitkin menstruum in combination with dicumarol as a practical method in prevention is discussed.

4. Treatment of the immediate attack of embolism is reviewed.

COMMENT

From the information covered, it seems to me that the most important phase of pulmonary embolism is its prevention. At present, the preventive measures of apparent value previous to thrombotic episodes are the venous ligation of the femoral system in debilitated persons over fifty years of age, and the general post-operative measures to prevent venous stasis, such as the Trendelenburg position for twenty-four hours, bed exercises, and early ambulation.

The diagnosis of thrombosis is important. In any

unexplained rise in temperature, one should look for Homan's sign, and suspect thrombosis.

The appealing treatment, where thrombosis and/or embolism have occurred, is the use of heparin or heparin/Pitkin in conjunction with dicumarol. Venous ligation has many advocates, but should perhaps be reserved for specially selected cases. The disadvantages of venous ligation and section have been enumerated.

One program of emergency treatment of pulmonary embolism is practically universally accepted. It consists of exygen for cyanosis and dyspnea; immediate intravenous papaverine and atropine; and a regime of anticoagulant therapy for at least seven to ten days to prevent further emboli. Apparently the Trendelenburg operation has little place in treatment generally, for it is an extreme emergency measure, requiring constant attendance by an adequately trained surgical team.

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