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Pathologic physiology of pulmonary embolism

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THE PATHOLOGIC PHYSIOLOGY OF PULMONARY EMBOLISM

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Much controversy has centered about the pathologic physiology of pulmonary embolism for many years. In particular, the controversy has centered about the possible vascular reactions to such emboli and the mechanisms by which such reactions may take place.

It is the purpose of this paper to present a brief resume of experimental and clinical observations concerning these vascular reactions, and to present a short discussion of the more popular theories concerning such physiologic mechanisms.

I. THE FUNCTIONAL ANATOMY OF THE PULMONARY VASCULAR BED

A brief general consideration of the anatomy and physiology of the normal pulmonary vascular bed is essential to any discussion of pulmonary vascular pathology.

The dual blood supply of the lungs, in which the two components differ vastly from each other to the point of being direct opposites in many aspects is rather unique. Although it has frequently been referred to as the "lesser circulation" the pulmonary circuit actually comprises half of the double circuit which makes up the mammalian blood vascular system and blood volume flow through the pulmonary circuit is essentially equal to that flowing through the "greater" or systemic circuit. The right ventricular output is propelled into the lungs under relatively low pressure (mean 10 to 15 mm. Hg) and with pressure representing a product of flow and resistance, it is obvious that the resistance must be relatively lower in the pulmonary circuit. As in the systemic circuit, the arterioles of the pulmonary vascular bed probably account for the major portion of the resistance.

It has been noted that a single branch of the pulmonary artery closely follows each division of the

bronchial tree but yields no branches until the first alveoli appear in the walls of the respiratory bronchioles. The pulmonary veins, in contrast, are as far removed as possible from the broncho-arterial ray. The pulmonary arteries are end arteries; there are no vessels that traverse the lobule to connect adjacent branches and there is no confluence of their separate streams except in the capillary beds at the periphery of the lobule.[47]

In contrast to the pulmonary arteries, the bronchial arteries are part of the high pressure, high resistance system that comprises the systemic circut. They also contrast in that, characteristically, even though there be but one major trunk arising from an intercostal artery or from the aorta, a plexus is soon formed with at least two major branches, joined by many collaterals, distributed within the wall of each bronchus. Thus, the bronchial artery is the direct antithesis of an end artery.[47] Normally, communication with the pulmonary artery is only by means of a capillary bed in the walls of the respiratory bronchioles. How much of the blood from the bronchial arteries, if any, normally reaches the walls of the alveoli themselves is not known.

Normally, blood brought to the lung via the bronchial arteries may follow one of two courses in returning to the heart: In the proximal thirds of the major bronchi, some of this blood is brought via the azygous veins to the right auricle; more distally in the bronchial tree, drainage is into the pulmonary veins which thus come to carry small amounts of unoxygenated blood.[47] Some authors have observed that in certain lungs, even proximally, drainage may be into the pulmonary venous system and that branches of the pulmonary veins may actually extend far out into the mediastinal tissues in company with bronchial arteries, presumably draining tissues supplied by these vessels. In these cases apparently most of the bronchial drainage is into the pulmonary veins.[47]

Anastomoses between the pulmonary and systemic systems of vessels occur in the walls of the respiratory bronchioles. Such anastomoses are more numerous in certain inflammatory pulmonary conditions, and it has been thought possible that an abnormal increase in the amount of blood entering the pulmonary vascular bed through such channels might raise the pressure in the capillaries sufficiently to overbalance the colloid osmotic pressure of the plasma and lead to

pulmonary edema. It has been suggested that certain types of paroxysmal pulmonary edema may be produced in this manner, as a result of reflex vasodilitation of the anastomosing channels of the bronchial arteries.[5] However, the greatest quantity of blood which enters the pulmonary circut from the bronchial system in normal lungs has been calculated to be not more than 1 per-cent of the total pulmonary circulation volume, even with maximal vasodilitation.[5] It appears unlikely that this would be sufficient to seriously alter the hydrostatic-osmotic balance in the pulmonary capillaries of normal lungs.[5] In the passively congested lung, however, this 1 per-cent may be of more significance.[48]

The pulmonary vessels are able to accommodate the blood representing the resting cardiac output with only a portion of the total lung vascular bed.[92,95] Experimental observation has also shown that many arterioles may open and become widely patent under the impetus of an increased circulatory load, and then close again to prevent flow as circulatory demands subside. This regulation of flow is mediated largely by the "critical closing pressure" of these vessels.[7,11] For example; at a pressure of 5 mm. Hg, one group of arterioles may be open to blood flow; at a pressure

of 6 mm. Hg, a second group of arterioles may open; and at 7 mm. Hg a third group opens, and so on. Similarly, when arterial pressure falls below the "critical closing pressure," the vessels collapse and blood flow through them ceases. This mechanism thereby acts to stabilize pressure in the face of changing flow volumes. With increases in flow and slight resultant changes in pressure, auxillary channels open, permitting runoff of the excess flow.[63] This could be considered a pressure "buffering" mechanism.

All the determinants of pulmonary critical closing pressure are not known. It is probable that variable and changing vasomotor tone of the arterioles is directly concerned,[29,46,99] and it has been established that pulmonary hypertension may result from pulmonary vasomotor responses.[2,61,77] The rise in resistance is probably related to arteriolar constriction by contraction of a small helical band of smooth muscle wound around the arteriole.[71,72] Sympathetic stimulation, epinephrine, and norepinephrine have been shown to increase the critical closing pressure,[64] whereas sympathetic denervation, tetraethyl ammonium chloride, and hexamethonium compounds diminish it.[46] The pulmonary

venous pressure seems unimportant in influencing critical closing pressure when the venous pressure is low.[29] However, there is evidence indicating that critical closing pressure may be dominantly influenced by venous pressure at higher levels.[99] In addition, the surface tensions of blood in the arterioles, as well as airway and transpulmonary pressures are of importance in determining the patency or closure of the pulmonary arterioles.[29]

It is well known that the pulmonary vasculature is possessed of a relatively enormous reserve capacity.[63] This vascular reserve has been demonstrated in several ways: (1) Physical exertion can provoke an elevation of right ventricular output of 250 to 300 per-cent without inducing significant changes in the pulmonary arterial pressures.[15,46] Apparently the increased volume flow is accommodated by enlargement of the available vascular space by overcoming critical closing pressures of arterioles and, possibly, by additional arteriolar dilitation.[15] (2) With constant cardiac output, more than half of the vascular area of the lungs can be excluded without a significant rise in pulmonary arterial tension.[27,62,87] In fact, Steinberg and Mundy, in 1936, were able to demonstrate in experimental animals

that 79 per-cent of the pulmonary vascular bed could be blocked before persistent elevation of the pulmonary arterial tension occurred. More recently, Marshall and his co-workers,[51] demonstrated that in dogs with one radical of the pulmonary artery ligated, increase in cardiac output with exercise was not significantly reduced and pulmonary vascular resistance increased less than 35 per-cent after ligation of the left pulmonary artery. Aramanda and his co-workers,[1] using a gas dilution principle, measured the blood volume of the intact lung in a series of dogs in which the left branch of the pulmonary artery was ligated. They found very little change in the total pulmonary blood volume before and after ligation of the artery and concluded that there was, therefore, a real increase in the blood volume of the lung with intact circulation.

An exception to this great vascular reserve capacity occurs in the passively congested lung where a greater portion of the vascular bed is already patent and engorged because of impaired venous outflow. The reserve being less, occlusion of a portion of the vasculature need be of less magnitude to provoke a marked elevation in resistance. This, perhaps, explains the higher mortality from minor pulmonary embolism in persons in congestive heart failure.

II. PULMONARY VASCULAR REACTIONS TO LARGE OR MASSIVE EMBOLISM

When the right or left main pulmonary artery of an experimental animal is externally occluded, as with a clamp, there is little effect upon pulmonary arterial pressures. However, when one of the pulmonary arterial branches is closed by a large thrombotic embolus, pulmonary hypertension often ensues, the systemic blood pressure declines, and the right heart dilates and fails.[63] It has been noted that in patients during an operation, ligation of the right or left branch of the pulmonary artery usually produces no sudden, dramatic, or prolonged elevation of pulmonary artery pressure while approximately 15 per-cent of patients dying of massive pulmonary embolism with clinical signs of severe pulmonary hypertension and right ventricular failure are found at autopsy to have only a single right or left branch of the pulmonary artery occluded by the thromboembolus.[31]

At this point it is interesting to consider some experimental data concerning how much limitation of pulmonary arterial flow is necessary to produce severe pulmonary hypertension and right heart failure. Haggert and Walker,[34] in 1923, reported that, by gradual

occlusion of the main pulmonary artery in anesthetized cats, from 52 to 66 per-cent of the cross sectional area of the pulmonary artery had to be cut off before there was significant variation in the general circulation. At this rather precise end-point they observed right heart dilitation, decreased cardiac output, and a fall in systemic arterial pressure. Hall and Ettinger,[35] in 1933, performed similar experiments and found 75 per-cent occlusion necessary to initiate circulatory collapse in dogs.

With the preceding observations and data in mind, the question arises, "Why does a patient with embolic occlusion of a lobar or single right or left main branch of the pulmonary artery suddenly show signs of acute pulmonary hypertension and right heart failure, and go on to die?" This apparently did occur in 15 per-cent of Gorham's[30] series of 110 cases of fatal massive pulmonary embolism and in 18 per-cent of Evoy's[22] 110 cases. One of the most controversial explanations for death in these patients is a postulated arterial constriction in the pulmonary bed producing still further impedance to blood flow.

Some authors[30] feel that all the physiologic responses to massive pulmonary embolism may be accounted

for on a purely mechanical basis; others[36] feel that, on the basis of experimental work and clinical experience, mechanical obstruction of localized areas of the pulmonary circulation does not, in itself, account for all the physiologic responses.

Because of the rapidity with which vascular derangement may occur following experimentally produced large pulmonary embolism, it is not surprising that some investigators have attributed these effects to noxious reflexes.[63] Both "pulmono-pulmonary" and "pulmono-coronary" reflexes have been postulated, the former supposedly producing constriction of the arterioles in the pulmonary bed and the latter producing constriction of the coronary vessels.[18,88] In addition, the existence of reflex systemic vasoconstriction[55] has been postulated but never definitely proven.

A number of other theories have been brought forth to explain the postulated pulmonary arterial vasoconstriction occurring with pulmonary embolism. Among these are the effect of sudden hypoxia, the influence of epinephrine and norepinephrine, and the possible effects of other humoral agents such as histamine, acetylcholine, and particularly serotonin.

Hall and Ettinger[35] noted the apparently marked

discrepancy between their experiments, which supported the mechanical theory, and reports that sudden pallor, shock, cerebral and cardiac ischemia, and death may occur in patients when only a single major branch of the pulmonary artery or even a lobar artery is occluded by an embolus. As an explanation they suggested that the discrepancy rested perhaps in the fact that their experiments were done on young, healthy dogs with presumably healthy hearts, while most pulmonary emboli occur in elderly persons in whom the right ventricular myocardium is perhaps "degenerate" and unable to tolerate the sudden increase in work load occasioned by a pulmonary embolus. They proposed that experiments similar to their own be performed after inflicting some sort of damage to the myocardium of healthy animals but these have apparently never been carried out.

In Gorham's[30] 15 cases of death from single major branch occlusion the average age was 65.8 years. Gorham apparently feels that this may suggest senile degenerative changes in the heart played some part in the production of death in such patients. He states, "It may be stated . . . with considerable assurance . . . that rarely, if ever, do patients

under 50 years of age die from the obstruction of a single major branch of the pulmonary artery." There were three patients under 50 years of age in Gorham's series who died with single major branch occlusions but all of these were noted to have severe and extensive underlying disease; in one, atelectasis of the opposite lung, in another, pre-existing severe chronic cor pulmonale, and in the third, severe coronary artery sclerosis.[30]

According to Gorham, also, the post-mortem diagnosis of single major branch occlusion is open to at least two sources of error and the actual incidence of death from single major branch occlusion may be less than the quoted 15 per-cent. These possible sources of error are: (1) Accidental displacement of the thrombo-embolus from the main stem of the pulmonary artery or the right ventricle while the autopsy is being performed. Gorham feels that such an accident is prone to occur unless the examiner is most careful when opening the heart and pulmonary artery, and is definitely looking for an embolus. (2) Occasionally an ante-mortem embolus is disguised in a cloak of post-mortem clot. Gorham feels that such masses should be critically examined and subjected

to microscopic examination or a second source of error is present.

Experimental evidence favoring the existence of pulmono-pulmonary and pulmono-coronary reflexes was published in 1939 by de Takets, Beck, and Fenn.[18] These investigators produced massive pulmonary embolism in dogs by the following technique: The femoral vein of the dog was exposed at Poupart's ligament for a length of one centimeter. The vein was then compressed proximally while an emulsion of iron perchlorate, barium sulfate, and normal saline was injected just distal to the compression site. Compression was maintained for a short time and then released. This produced an embolus the size and shape of the exposed segment of vein and in small dogs this was found to correspond closely to the size of the pulmonary artery and its major branches. At autopsy the emboli were found in the main pulmonary artery or its primary branches in every case.

In a series of normal, untreated dogs this embolus produced death within a few seconds to less than five minutes in all. In a second series of dogs embolized in the same manner but recieving one-fifth grain of atropine intravenously a few minutes prior to the

procedure, over half of the dogs survived more than ten minutes and a few of them lived from two to twenty-four hours. From this point on, the publication of de Takets, Beck, and Fenn is rather confusing. From the text it is clear that some animals pre-treated with an unstated dose of papaverine and other animals vagotomized prior to embolization, survived longer than untreated ones and, although the survival times were not given, it appears from the text that all the animals died. However, in the tabulated results, there appears the term "percentage of fatality." This figure apparently represents an assumed protection of the animals and is apparently based upon the unstated survival times. Because this necessary data is not given, it is not possible to completely evaluate the author's discussion and conclusions.

During and shortly after the period of embolization these dogs were continuously monitored electrocardiographically. A great number of electrocardiographic changes were described following passage of the embolus and these were apparently somewhat less marked in those animals pre-treated with atropine, papaverine, or vagotomy. De Takets and his co-workers took the

apparently protective effects of papaverine, atropine, and vagotomy to suggest the presence of pulmono-pulmonary reflexes causing pulmonary vasoconstriction and pulmono-coronary reflexes producing coronary artery constriction. These reflexes were thought to travel by way of the vagus nerves.

In considering the work of de Takets with papaverine, it is interesting to note some other observations on this drug. Macht[49] studied the in vitro effect of papaverine on arterial rings or strips and found that it markedly relaxed the smooth muscle of the carotid and other systemic arteries but had little effect upon muscle from pulmonary arteries. Bradshaw and Chodoff[9] measured the pulmonary artery pressures in cats before and after administration of eupaverine (considered pharmacologically identical to papaverine), mineral oil embolism, and mineral oil embolism followed by eupaverine. In all animals, alone, eupaverine was found to cause a rise in pulmonary artery pressures and this effect was much more marked when it was given after the mineral oil embolism. Friedberg, Katz, and Steinitz[25] observed that papaverine consistently raised pulmonary artery pressure and lowered systemic pressure in normal, unanesthetized dogs. Jesser and de Takets[42]

studied the size of the pulmonary arteries radiographically in normal and embolized dogs before and after administration of papaverine. These authors stated that their films demonstrated an increase in pulmonary vascularity following the administration of papaverine but they did not know whether this was due to a rise in pulmonary arterial pressure or to a relaxation of the smooth muscle of the large pulmonary arteries.

It is also interesting to consider the experimental results of de Takets and his co-workers in the light of some more recent findings.[63] Nelson and Smith state that the friable proximal end of a large embolus may fragment in the turbulent blood stream created by a partial obstruction and the fragments may disseminate to other lobes as miliary emboli.[60] Moore has shown that relaxation of pulmonary arterioles prior to miliary embolization may allow small particles to pass through the arterioles into the capillary bed where the total cross sectional area is greater and the effect of a given volume of micro-emboli is much less. One wonders whether perhaps the massive emboli produced by de Takets and his co-workers were very friable and did produce miliary embolization as well as massive embolism. If this were the case, a

reflex theory might not be needed to explain the demonstrated protective effects of the drugs administered and vagotomy.

A number of authors have experimentally produced large pulmonary emboli without demonstrating any reflex activities. Mendlowitz,[56] in 1938, embolized dogs with segments of Penrose tubing filled with barium-sulfate. These emboli lodged in the main stem of the pulmonary artery and its two main branches. Mendlowitz was unable to demonstrate any evidence of reflex vasoconstriction with this procedure. It is interesting to note the impossibility of accidental miliary embolization with this procedure.

Megibow, Katz, and Steinitz,[55] in 1942, were the first to perform a pulmonary embolism experiment with direct measurement of pulmonary artery pressures. They embolized dogs with three different sizes of particles. A barium-sulfate filled segment of Penrose tubing was used to simulate massive pulmonary embolism. For emboli of moderate size they used pea seeds in numbers of from thirty-five to fifty, and for very small emboli they used intravenous injections of a 1:20 emulsion of starch in water.

They successfully induced massive pulmonary embolism

in four lightly anesthetized dogs. In two of these animals a riding embolus of the main pulmonary artery was found and in the other two dogs a complete occlusion of the right branch of the pulmonary artery was found at necropsy. The passage of the embolus was followed in all cases by an abrupt increase in both systolic and diastolic pulmonary artery pressures. Dyspnea and moderate tachypnea were noted coincidentally with the rise in pulmonary arterial pressure. A relatively small rise in systemic systolic and diastolic blood pressures was noted in two of these dogs. After a variable period, however, the systemic arterial pressure fell, the venous pressure increased, marked dyspnea became evident, and the animals died. Tachycardia followed embolism in two animals and in one of these it was suspected but not electrocardiographically confirmed that ventricular fibrillation was the terminal event.

Multiple pea seed emboli were introduced in four unanesthetized dogs. The characteristic response to a single dose of these emboli was an abrupt rise in systolic and diastolic pulmonary artery pressures and once this pulmonary hypertension appeared, it became progressively more marked until terminally when

the pressure fell rapidly to zero. This progressive rise in pulmonary artery pressure following a single dose of emboli was explained on a purely mechanical basis when at necropsy the seeds were found covered with fibrin and ante-mortem clot and appeared to have completely occluded the medium sized branches of the pulmonary artery. In three of these dogs the systemic arterial pressure was observed to rise slightly a short time following embolization. It then tended to fall to the control levels where it was maintained until terminally when simultaneously with the pulmonary artery pressure, it fell rapidly. Progressive tachypnea and dyspnea with an apparent increase in the respiratory amplitude appeared soon after the appearance of pulmonary hypertension and persisted until terminally when respirations slowed coincident with the fall in pulmonary and systemic arterial pressures. In two dogs, progressive tachycardia developed, with suspected but not confirmed terminal ventricular fibrillation in one dog. In the other two dogs a terminal bradycardia was observed but the mechanism was never defined.

Four dogs were embolized with the suspension of starch granules in controlled doses. Both systolic and

diastolic pulmonary artery pressures increased abruptly following the injections. There was no progressive rise in pulmonary artery pressure in three dogs and repeated doses of the suspension were required to produce further increments of pressure elevation in them. In one dog, however, a further rise was noted without additional injections. Megibow and his coworkers believed that this could have been explained either by a gradual dispersion of the granules to previously non-occluded arterioles or by a reflex pulmonary arteriolar constriction. Terminally in three of the dogs the pulmonary artery pressure showed a moderate decline. Systemic arterial pressure changes were not striking in this group of animals. In this group of animals tachypnea developed coincident with the pulmonary hypertension and, once present, progressively increased until death. Progressive tachycardia accompanied the development of pulmonary hypertension and tachypnea.

The work of Megibow, Katz, and Steinitz is interesting for several reasons other than their failure to demonstrate evidence of a pulmono-pulmonary reflex. First, they demonstrated some differences in behavior of the animals following different sizes of emboli.

Terminal bradycardia was seen in two animals with pea seed emboli but not in others; tachypnea without increase in amplitude was seen with starch granules but not with the others; venous pressure changes were not striking with pea seed emboli but were with the others, etc. Second, they demonstrated an initial rise in systemic arterial blood pressure following embolization with large and medium sized particles. Since it has been shown that following pulmonary embolism there is a fall in the minute volume output of the left ventricle[56] the relative stability of the systemic arterial tension in this series might indicate that there is a "buffer nerve mechanism" operating to maintain systemic pressure through vasoconstriction.[55] Third, they clearly demonstrated that multiple medium-sized emboli lodged in the pulmonary arteries may enlarge by deposition of fibrin and ante-mortem clot on their surface to produce increasing mechanical obstruction to pulmonary blood flow. Fourth, it is interesting that two apparently normal, healthy dogs with intact hearts died with embolic occlusion of a single main branch of the pulmonary artery. This is in contrast to what some other authors[30,35] have suggested might happen.

Direct efforts have been made to implicate the vagus nerves in pulmono-pulmonary and pulmono-coronary reflexes.[44] [91] Walsh isolated individual vagal fibers which were dramatically affected during pulmonary embolization and which he thought originated from the wall of the pulmonary artery.[70] Paintal, however, later showed that these fibers arose from the right or left atrium of the heart rather than the pulmonary artery.

Experimental evidence for the existence of a pulmono-coronary reflex in massive pulmonary embolism is rather meager.[18] De Takets and his co-workers cited a number of electrocardiographic changes which were observed during the course of embolization in a number of dogs. These changes were attributed to myocardial ischemia secondary to constriction of the coronary arteries. This constriction was believed due to a vagal reflex set up by lodgement of the pulmonary emboli. As further evidence for this hypothesis he noted that the electrocardiographic effects were not so marked in animals previously treated with atropine or papaverine or previously vagotomized. Other investigators, however, have not confirmed the findings of de Takets.[43] Katz has reported that experimental studies on the dog failed to show any evidence of a pulmono-coronary

reflex leading to coronary artery spasm. His experiments demonstrated, in fact, that vagal impulses lead to coronary dilitation rather than constriction.

Eichelter,[21] in 1932, published evidence which suggests that a pulmono-coronary reflex does not exist in man. He demonstrated at operation that pressure stimuli applied to the wall of the pulmonary artery, including clamping of a fold of the arterial wall, caused no disturbance in cardiac activity.

Hara and Smith[36] found that medium sized emboli in moderate amounts failed to produce vascular responses or cardiac changes and they found it impossible to produce reflex circulatory effects by application of mechanical stimuli to the inner walls of medium size arteries by means of a metal rake.

Megibow, Katz, and Steinitz[55] feel that when the factors which influence coronary blood flow are considered, it is seen that pulmonary embolism may well lead to myocardial ischemia in the absence of any coronary artery spasm and a reflex theory is not needed to explain the electrocardiographic changes. They believe it more likely that if any reflexes affect the heart the mechanism is the establishment of an ectopic rhythm which easily converts to ventricular fibrillation.

III. PULMONARY VASCULAR REACTIONS TO EMBOLI OF MEDIUM SIZE

Embolic particles that obstruct secondary and tertiary branches of the pulmonary vascular tree, if sufficiently numerous, will produce critical mechanical arterial occlusion resulting in acute pulmonary hypertension, right ventricular failure, and peripheral circulatory collapse.[44,52] The question of whether embolism of this size is attended by reflexogenic pulmonary arteriolar constriction causing pulmonary hypertension has engaged the attention of numerous investigators. Jaques and Harrison[41] have interpreted the elevation of pulmonary artery pressure following embolism with small clots of the animal's own blood as the result of reflex vasoconstriction.[38] Other workers, however, employing small foreign body emboli, have noted only the effects expected from mechanical blockage of the pulmonary arteries. Mann,[50] using small paraffin emboli, observed rises in the pulmonary artery pressure that appeared clearly obstructive. Steinberg and Mundy[87] embolized dogs with lead shot of a size which would obstruct lobar arteries. Following introduction of the shot they injected an opaque material for purposes of study. They found that at least 79 per-cent of the pulmonary circulation

had to be blocked before serious consequences ensued and concluded that their experiments did not justify the concept that emboli of this size caused immediate or delayed death by reflex vasoconstriction. Gibbon and Churchill,[27] in a similar experiment, reported similar results and conclusions. Megibow, Katz, and Steinitz[55] noted that with multiple pea seed emboli there was an abrupt rise in pulmonary artery pressure which became progressively more marked until terminally. This progressive rise was explained, however, on a purely mechanical basis when at autopsy the seeds were found to be covered with fibrin and ante-mortem clot, the deposition of which apparently produced increasing mechanical obstruction prior to the death of the animals. Megibow, Katz, and Steinitz did not find any evidence of pulmonary vasoconstriction with emboli of this size.

Further evidence against reflex pulmonary vasoconstriction occurring in obstruction of lobar arteries was introduced by Haynes and his co-workers in 1947. These authors reported that when a balloon was inflated in a lobar artery to a pressure higher than the pulmonary artery pressure, they were able to demonstrate no pressure changes in the pulmonary and femoral arteries

of both anesthetized and unanesthetized dogs. Hara and Smith[36] likewise found that medium sized emboli in moderate amounts failed to produce vascular responses and they also found it impossible to produce reflex circulatory effects by application of mechanical stimuli to the medium sized and smaller pulmonary arteries.

At this time, the bulk of available evidence favors the concept that emboli of medium size do not provoke reflexogenic responses. It is notable, however, that two independent investigators[38,41] have reported evidence favoring reflex concepts using thrombotic emboli, whereas the bulk of the evidence against the reflex theories has been reported by investigators who employed only foreign body emboli. It should also be remembered that it is quite possible for a medium sized thrombo-embolus to lodge in a lobar artery, and thereafter, because of the turbulence of the blood, to break into smaller fragments at its proximal end and thus embolize other vessels. This mechanism may be the basis for miliary embolism in some cases.[63]

IV. PULMONARY VASCULAR REACTIONS TO VERY SMALL OR MILIARY EMBOLI

Much clinical and experimental evidence indicates that sudden death may result from microembolization of the lungs. Because of the probable clinical importance of miliary embolism the condition has been the object of extensive experimental study. It is true that many patients are found to have small emboli at autopsy. However, the discovery of multiple, minute pulmonary emboli at autopsy does not necessarily mean that they were the cause of death.[9]

With unusual exceptions, only blood clots act as embolic particles in man. However, in experimental animals the physiology of pulmonary embolism has been studied in most cases with finely divided foreign material. In a sense these "foreign" emboli are preferable because they are easily prepared and can be readily identified after impaction in the pulmonary arteries. In another sense, foreign body emboli are not preferable because they do not conform to the composition of emboli which occur in the clinical situation.

Much interest and controversy have centered about possible mechanisms of pulmonary hypertension from very small emboli. Some of the evidence is contradictory

and the problem is far from being solved. It is well documented that small quantities of particulate material injected intravenously in experimental animals provoke acute pulmonary hypertension, respiratory distress, acute right heart failure, shock, and death. This train of events closely resembles the succession of signs in fatal acute embolism in man.[44,93,96] Some investigators have interpreted such pulmonary hypertension to be the result of widespread dissemination of the particles to produce a purely mechanical obstruction to blood flow.[18,40,75,97] Others have interpreted this to indicate that miliary embolism causes reflex constriction of the pulmonary arterioles, producing critical circulatory obstruction in this manner.

It has been reasoned that if the "trigger mechanism" for generalized reflex pulmonary arterial constriction from miliary embolism lies in the stimulation of vessels of a critical size, localization of the embolic substance to one area or lobe of the lung with production of severe pulmonary hypertension would constitute adequate experimental evidence for a reflex mechanism. A number of investigators have attempted this by injecting small particles directly into the lobar arteries.[40] Haynes and his co-workers, for example, infused

lycopodium spores through a catheter into a single lobar artery and found that this produced increased respirations, rising pressures in the pulmonary artery and right ventricle, a falling femoral artery pressure, and electrocardiographic changes. Death ensued if the infusion was continued long enough. Their findings were, at the time, attributed to reflex pulmonary arteriolar spasm, but in the light of recent work it is now believed that the particulate matter was not confined to a segment of the pulmonary circulation as the authors believed.[97]

Weidner and Light have observed widespread scattering of embolic particles throughout the pulmonary vascular tree when these were introduced into the lobar arteries.[63] Smith and his associates injected suspensions of barium-sulfate into selected lobar arteries at various rates of speed and found that this produced severe acute pulmonary hypertension, shock, and death. Examination of these lungs microscopically after death revealed much barium distal to the catheter tip, but evidence of barium dissemination to the other lobar arteries was difficult to find microscopically. However, when the individual lobes of these lungs were subjected to ashing and gravimetric

analysis for barium, the analysis invariably indicated that some dissemination of the material to all of the lobes of the lungs had occurred.[63] Nelson and Smith feel that these experiments indicate, first, that careful microscopic examination is inadequate for evaluating embolic scatter outside the selected lobe; and second, in the course of embolization with fine material, eddying and swirling of the pulmonary blood stream proximal to the occluded vessel must account for dissemination of the material.

Some investigators have attempted to limit microemboli to one lobe by injecting the material distal to an occluding balloon or ligature placed around a lobar artery.[16,63] The severe effects of embolization were apparently prevented by this method, however, when the balloon was deflated, pulmonary and systemic reactions typical of miliary embolism occurred. These results were interpreted as demonstrating that retrograde disseminarion of the particles had occurred when the impacting balloon was removed. However, it should be remembered that the distension and trauma to the pulmonary vessels by the balloon or ligature might have prevented a reflex from occurring.[63]

Another study has shown that minute particles[44] may adhere to one another in the vascular lumina, producing variable sized and unpredictably larger emboli. Such findings add uncertainty to the problem. In the face of many uncertainties, such as these, it has been extremely difficult to clarify the fundamental physiologic process concerned with miliary embolism.

Several authors have presented evidence which supports the reflex theory.[85] Smith and Hara obtained negative results when care was taken to prevent retrograde passage of infused lycopodium spores, glass beads, and poppy seeds injected into lobar arteries. However, these authors found that the injection of very fine material, such as starch or barium-sulfate suspensions into the lobar artery produced a marked rise of pulmonary arterial pressure. They reasoned that pulmonary capillary emboli, affecting a restricted portion of the pulmonary vascular bed, may cause death with apparent pulmonary spasm and circulatory failure. In the light of present knowledge concerning the uncontrollable retrograde dissemination of particulate matter, however, it appears that such retrograde dissemination may have taken place with resultant mechanical

blockade rather than reflex vasospasm.

Singer[82] has presented evidence that reflexes may be involved in the reaction to pulmonary microemboli. He injected starch granules into the pulmonary circulation through a catheter in wedge position and noted subsequently the occurrence of generalized pulmonary edema. Most of the starch remained confined to the given lobe. However, when the starch suspension was introduced into the right ventricle, pulmonary edema did not occur until four to five times the previous quantity had been administered. It should be recalled, however, that pulmonary edema is not usually a prominent feature of pulmonary embolism.

Niden and Aviado[65] attributed two findings in dogs to reflex vasoconstriction. The first was that while glass beads 250 to 420 microns in diameter caused only a single sharp rise in pulmonary artery pressure, 60 to 200 micron beads caused an additional gradual rise. Knisely and his co-workers[44] believe that these results could be explained by the formation of additional fibrin precipitate on the beads, such precipitate forming relatively more rapidly on the smaller beads. The second finding was that beads injected into a part of the lung perfused by the animal's own heart caused

a pressure rise in a pump-perfused segment of the lung. The published tracing, however, shows only an approximate 1 mm. Hg rise in pressure in the pump perfused segments.[44] Knisely and his co-workers believe that unless the pump-perfused lobes were specifically examined for beads, a minor scatter to that part could account for a change of this magnitude and such an examination apparently was not carried out.

Some of the earliest evidence for the reflex concept was published in France in 1935 by Villaret, Justin-Besancon, and Bardin.[88] These investigators embolized dogs with three sizes of particles. With the "massive" emboli (glass beads the size of the jugular vein) and with "medium" ones (large mucilage granules) they found it difficult to kill the animals. However, a minimal amount (which was never stated) of powdered pumice stone which had been passed through a seive with 150 micron openings, caused death within a few minutes. The authors apparently assumed that all the embolic particles in this case were of the 150 micron size and that therefore only the pulmonary arterioles had been embolized. They believed that such irritation of the arteriolar walls caused local vasomotor disturbances, and, at a distance, an inhibition of respiration

and the heart; they concluded that sudden embolic deaths resulted from such reflex stimulation. In 1939,[89] however, Violet reviewed the clinical and experimental evidence regarding reflexes from pulmonary emboli. He then showed that when pumice powder was seived, as had been by Villaret and his associates, one-fourth of the total weight of the injected material consisted of particles 1 to 5 microns in diameter, rather than 150 microns as Villaret and his associates had assumed. Violet then repeated the experiments of Villaret but removed the very fine particles and embolized animals with pumice stone granules 100 to 200 microns in diameter. No apparent distress occurred in dogs or guinea pigs until enough was injected to cause considerable mechanical obstruction. It appears from the works of Villaret and Violet that if such reflexes do exist, they must originate in vessels ov very small size, probably either arterioles or capillaries.

Abundant evidence has been published favoring mechanical blockade of the pulmonary circulation as the cause of the reaction to miliary embolism. Knisely and his associates[44] studied embolization in rabbits and cats using intravenous injections of particles 50 to 150 microns in diameter. Direct in vivo visualization

of the pulmonary vessels with a magnification of 16 to 900X was attained by quartz rod transillumination and special microscopic equipment. The lethal dose of 50 to 150 micron beads was found to be the same in awake, anesthetized, thoracotomized, and vagotomized rabbits. Observation of arteries devoid of emboli during the process of embolization revealed no visible decrease in diameter while embolized arteries showed no visible constriction proximal to the embolus and did so distally only when collateral flow to a particular segment was markedly reduced or stopped completely. These authors also noted that these small particles could stick together to form larger emboli and that they could flow backward around the catheter tip to embolize other lobes. Some of the microemboli were noted to collect fibrin precipitates to form larger emboli. They concluded that mechanical blockage rather than reflex vasospasm is the cause of death in miliary pulmonary embolism.[96]

Williams studied the pressure in the pulmonary artery of dogs during intravenous injection of known amounts of 60 micron glass beads. Each injection of beads resulted in a temporary increase of the pressure in the pulmonary artery and right ventricle,

together with a small decrease in systemic blood pressure. Repeated injections caused right heart failure and a fall of pressures in the right ventricle, pulmonary artery, and femoral artery, ending in death. Pressure changes were found to be unaffected by denervation of the lung or by hexamethonium. The author concluded that evidence for reflex vasoconstriction in pulmonary microembolism was lacking and that all his findings could be explained on mechanical grounds alone.

The fact that minute emboli scattered widely through the pulmonary circulation may produce a large total area of mechanical obstruction is suggested by the work of Miller[58] who recorded the number, diameters, and cross-sectional areas of all branchings of the pulmonary arteries in 7 kg. dogs. He found 192,000 atrial and sac arteries averaging 165 microns in diameter. From these, all capillaries arose, averaging 7 microns in diameter. The total cross-sectional area of all capillaries was estimated to be about 23,000 sq. mm. A blockage of capillaries throughout both lungs with fine embolic material would therefore appear capable of causing severe hemodynamic effects on a purely mechanical basis. It has been shown that the previous

administration of ganglionic blocking agents will modify the severe reaction to microembolization in the experimental animal and in animals so pretreated the lethal dose of microemboli is larger. Some workers[75] have taken this to suggest that reflex pulmonary arteriolar spasm does occur. However, Moore[60] has presented evidence suggesting that the modification of the reaction results from relaxation of the arterioles by the ganglionic blocking agent before embolization, thereby allowing the particles to pass through the arterioles to the capillaries where the total cross-sectional area of the vascular bed is proportionately larger and the influence of blockade less. The lethal quantity of embolus then must be increased before critical mechanical obstruction is accomplished.

From the available information it is clear that the physiologic response of the pulmonary vascular bed to miliary embolism is not clearly defined. It may be one of active reflex vasoconstriction or a purely passive acceptance of mechanical blockade. A number of technical difficulties have hindered attempts to solve this problem and more experimental work is obviously needed.

V. POSSIBLE HUMORAL MECHANISMS IN PULMONARY EMBOLISM

Recently good evidence has been presented that the circulatory and respiratory responses to pulmonary embolism are dependent, at least in part, upon the release of humoral agents that have direct effects upon the heart, pulmonary vessels, and air passages. It has been postulated that the offending substance may be liberated from the embolus itself or from the lung tissue involved by the embolic process. Humoral substances presently under suspicion are serotonin, histamine, acetylcholine, and the epinephrines. Of particular interest in connection with postulated humoral mechanisms is the work of Miselli[59] in Italy, who has recently demonstrated that if an aqueous extract of rabbit lung, after embolization, is injected into a second normal animal, signs of pulmonary embolism may be produced in this normal animal.

Serotonin, or 5-hydroxytryptamine, a substance present in blood platelets, gastrointestinal mucosa, liver, kidney, brain, and probably also lung,[94] has been shown to be the most potent of the known humoral substances giving rise to pulmonary hypertension when it is given intravenously.[3,78] Intravenous administration

of a sufficient quantity of serotonin in the experimental animal is followed by elevation of pulmonary arterial pressures, tachycardia, systemic hypotension, and ventillatory changes; symptoms quite similar to those of a pulmonary embolus.[63] Smith and Smith[84] have presented experimental evidence that serotonin may be an important humoral agent liberated either directly or indirectly by an impacted thrombo-embolus to account for many of the associated symptoms of this disorder. Attinger[3] and Rose and Lazaro[78] have independently shown that in man a single intravenous injection of serotonin provokes only a transient elevation of pulmonary arterial pressure, while Rudolph and Paul[79] showed that with a constant infusion of the substance in dogs, serotonine results in persistent and severe pulmonary hypertension as long as the infusion is continued and when the serotonin is stopped pulmonary artery pressures rapidly fall again to normal levels.

The mechanism by which serotonin brings about elevations of pulmonary arterial pressures is accepted by most authorities as a direct stimulation of the smooth muscle of the pulmonary arterioles, although some investigators have questioned this and other mechanisms have been suggested. A number of workers

have also demonstrated the propensity of serotonin to produce bronchoconstriction and ventillatory changes such as hyperpnea which is often preceded by a brief period of apnea, and systemic arterial oxygen desaturation.

The fact that the hypoxia induced by serotonin or pulmonary embolism does not respond to hyperventillation but may be abolished by administration of oxygen, suggests a temporarily diminished diffusion capacity of the lungs.[96] Since pulmonary venous oxygen desaturation invokes pulmonary arteriolar constriction,[96] [61] Motley and Rivera-Estrada[77] have suggested that at least part of the pulmonary hypertensive action of serotonin was mediated through the action of hypoxia. Moreover, severe bronchoconstriction with elevation of transpulmonary and airway pressures are thought by some to be additive to this effect.[63]

Carlson, Brodie, and Shore,[14] in 1957, concluded that most probably serotonin acted directly upon the pulmonary arterioles although they felt that the possiblity of neurogenic reflex effects could not be completely excluded.[17] It has been shown by Davison, however, that the action of serotonin on the pulmonary vascular bed is not affected by anticholinergic drugs or adrenergic blockade.

It has been shown that serotonin will provoke histamine release and histamine liberators will, in turn, induce serotonin liberation from body tissues.[68][6] Some investigators[78] have shown that the use of antihistaminic drugs seems to partially block the action of serotonin and there has been some intimation that histamine, also released from blood platelets, may account for some of the pulmonary and systemic vascular reactions to embolism.[63] Histamine introduced into the pulmonary arteries, however, does not produce pulmonary hypertension though it does pulmonary venous constriction with an increase in the lung blood volume, increase in capillary pressures, and a tendency toward pulmonary edema.[48,83] The action of acetylcholine on pulmonary veins is similar to that of histamine.[4,83] It is thought by some that acetylcholine actually dilates pulmonary arteries.[37] There is no very good evidence that either histamine or acetylcholine is responsible for the vascular reactions to pulmonary embolism.[63] It has been suggested that the systemic hypotension frequently observed following pulmonary embolism or serotonin infusion is caused by secondary release of histamine although this has not been proved.[23,68][69] Nelson and Smith feel that while histamine is not the provocateur of either the pulmonary

hypertension or the systemic hypotension in pulmonary embolism, although it may serve to enhance the systemic hypotension and shock state.

Another explanation for the pulmonary hypertension induced by serotonin was offered by Knisely and his associates. They noted that serotonin produced a fine white precipitate which appeared transiently in the smaller pulmonary arterial segments and which disappeared soon after lodgement. They felt that the precipitate might represent minute emboli and the pulmonary hypertension might, therefore, be on the basis of simple mechanical blockage of a significant portion of the pulmonary circulation. Of great interest in this connection is the work of McKinnon[54] and his co-workers. Using a fluorescent technique with labelled antigen, they showed that anaphylactic shock in the rabbit, previously believed to be due to reflex vasospasm, may actually be due to antigen-antibody precipitates forming in the circulation and lodging in the capillaries of the lung.

It is rather difficult to correlate strictly embolic phenomena and mechanical blockage with an increase in cardiac output produced by serotonin as recorded by Page[69] unless there is a stimulus also to

the myocardium which is of relatively greater magnitude than the mechanical blockage.[10] Bulle, however, has presented evidence that serotonin directly stimulates the heart, thereby inducing tachycardia and increasing output. He has shown also that serotonin may provoke small areas of myocardial necrosis.

Attinger[3] and Rudolph and Paul[79] have independently presented good evidence that the pulmonary hypertension resulting from serotonin infusion is not due to other mechanisms but is due to direct stimulation of the arterioles with resultant constriction. Rudolph and Paul[79] showed that the pressure rise produced by a given dose of serotonin was unchanged when the arterial oxygen saturation was maintained at normal levels by the use of artificial respiration and oxygen, thus dispelling theories that the action was mediated through hypoxia.[78] Rose and Lazaro performed experiments similar to those of Rudolph and Paul and again concluded that serotonin acted directly upon the pulmonary arterioles.

It is of interest in connection with a discussion of serotonin's action that Rapport[76] and his associates have demonstrated that extracts of normal lung tissue are capable of destroying serotonin rather rapidly.

Presumably this action is due to the high concentration of monamine oxidases, enzymes which convert serotonin (5-hydroxytryptamine) to 5-hydroxy indolacetic acid, in the lungs.[26] It is also of interest that amine oxidase inhibitors have been shown to potentiate the action of serotonin by blocking its enzymatic inactivation.[17]

Some other drugs have been shown to affect the action of serotonin.[84] Smith and Smith showed that some of the vascular effects of serotonin could be blocked by previous administration of heparin. The mechanism of this block is not entirely clear although Smith and Smith believed that it might be due to a direct neutralization of the serotonin or possibly the prevention of further platelet rupture. Rose and Lazaro[78] showed that antihistaminic drugs may modify the reaction to serotonin while Salmoiraghi[81] has shown that lysergic acid diethylamide may antagonize some serotonin effects. It has also been demonstrated that administration of serotonin analogues may block the action of the substance. It has also been shown that chlorpromazine and reserpine may protect the heart from the action of serotonin.

There is some experimental evidence indicating that sympathomimetic agents will produce mild constriction

of the pulmonary arterioles.[63] Norepinephrine has been shown to have the dominant constrictor action on the pulmonary arterioles[72] while both epinephrine and norepinephrine seem to constrict large pulmonary arteries and veins.[28,83] The vasoconstrictor action on the pulmonary vessels, however, appears to be quite weak[8] and these agents are probably not of much importance in the pulmonary vascular reactions to embolism.[63]

VI. GENERAL SYSTEMIC PHYSIOLOGY IN FATAL PULMONARY EMBOLISM

Whether or not reflex vasospasm occurs in fatal pulmonary embolism, the major physiologic derangement in this condition is an obstruction to and increase in resistance to blood flow through the pulmonary circuit.[55] With pressure representing a product of flow and resistance, according to Poiseuille's law, then the pressure must rise if flow is to be maintained. In fatal cases pulmonary embolism the magnitude of resistance increase occasions both a rise in pressure and a decrease in flow. Acute pulmonary hypertension and right ventricular failure, then, are two of the prime accompaniements of large pulmonary embolism, and most of the signs, symptoms, and physical findings, as well as the clinical course of the patients may, in one way or another, be attributed to these two secondary derangements.

Severe pulmonary hypertension may be accompanied by a dilitation of the main stem of the pulmonary artery. In some cases the pulmonary artery dilitation is great enough that this structure encroaches upon the pericardium and anterior chest wall, giving rise to a prominent systolic pulsation in the second left intercostal space[30] and a "pleuropericardial" or "pseudo-pericardial" friction rub,[53] usually best heard in the second and third left

intercostal spaces. With an increased pressure in the pulmonary artery and an increased pressure gradient between this structure and the right ventricle at the end of systole, there is naturally an increased impetus of the pulmonic valve cusps as they close, giving rise to a loud, sometimes described as "snapping" or "booming" pulmonic second sound which may become louder than the aortic second sound.[53]

Both systolic[73] and diastolic[30] murmurs in the second left intercostal space have been described as physical signs of pulmonary embolism. It is conceivable that a systolic murmur could result from turbulent blood flow around an embolus or possibly from a relative pulmonic stenosis occasioned by dilitation of the pulmonary artery and right ventricle with relatively less dilitation of the pulmonic valve ring.[73] Diastolic murmurs, again, might be the result of turbulent flow around a partially occluding thrombo-embolus during diastole or possibly due to a stretching of the valve ring with the resultant pulmonic valvular incompetence allowing retrograde flow during diastole. It is also of note that an interscapular systolic bruit has been reported as a physical sign of massive pulmonary embolism.[30] Apparently this is caused by turbulent flow around a

partially occluding thrombo-embolus.

The acute right heart dilitation and failure is, in most cases, quite apparent clinically when there is a large or massive pulmonary embolus. An increase in the area of percussion dullness to the right of the sternum has been reported as one of the most reliable physical signs of massive pulmonary embolism.[30,53] The marked increase in venous pressure accompanying acute right heart failure is usually quite readily apparent.[13,97] Some authors state that prominent systolic pulsations of the neck veins are occasionally apparent, this apparently reflecting some degree of tricuspid valvular insuffeciency occasioned by dilitation and stretching of the valve ring. The liver may enlarge rapidly due to passive congestion;[77] in such cases the liver is found to be very tender to palpation and the hepatojugular reflex is easily elicited.[97] The venous stasis, no doubt, contributes much to the cyanosis so frequently noted in these patients.

An interesting physical sign of pulmonary embolism was discribed in the German literature many years ago,[30] and is apparently related to temporary dislodgement of an occluding embolus permitting a larger volume of blood to pass through the lungs momentarily. This is

"Die rote Blutwelle" (the red blood wave), discribed as a sudden, momentary flushing of the face which is otherwise pale, ashen, and cyanotic.

With an increased resistance to blood flow in the pulmonary circuit and right heart failure, it is obvious that the left ventricle will recieve a reduced volume of pulmonary venous blood. The systemic cardiac output falls, and, as a reflection of this, the systemic blood pressure declines, often drastically. Some investigators[55] have postulated the presence of reflexes arising somewhere in the lungs which produce systemic vasoconstriction in a compensatory attempt to maintain the systemic blood pressure but none of these have been proven. The tachycardia so often noted in patients with pulmonary emboli may be largely caused by reflex effects of hypotension mediated through the aortic and carotid pressure receptors.[55] The fall in systemic cardiac output is apparently the cause of the pallor so often noted in conjunction with cyanosis in these patients.[30]

Ventillatory changes in these patients usually consist of extreme dyspnea and hyperpnea with both an increase in respiratory rate and deapth. This is apparently the result of acute hypoxia of the medullary

respiratory center with resultant stimulation.[31] The fact that the hypoxia induced by pulmonary embolism does not respond to hyperventillation but may be abolished by administration of oxygen suggests a temporarily diminished diffusion capacity of the lungs.[96] The reason for this is not entirely clear although it has been shown that bronchoconstriction may also result from pulmonary embolism.[42]

Ischemia and hypoxia of the various organ systems is the natural result of a markedly reduced cardiac output, hypotension, and arterial oxygen desaturation. Cerebral and myocardial ischemia are probably the most important of these. It has been noted by some authors that 20 to 25 per-cent of patients dying of massive pulmonary embolism complain of severe chest pain while others do not.[33] A marked amnesia for pain has also been noted in patients who survived massive pulmonary emboli.[33] It has been proposed that the reason for this is that the brain, particularly the higher centers suffer from hypoxia more quickly than the lower centers concerned with respiration and the heart.[30] It is well documented that the presenting symptom with massive pulmonary embolism may be a sudden hemiplegia or convulsion or other neurologic

symptom. Apparently these are due to the sudden, rapidly developing cerebral ischemia which is the natural result of a sudden fall in cardiac output and blood pressure.[30] Gorham states that in his series, mistaken diagnoses of cerebrovascular accidents were second in frequency only to mistaken diagnoses of myocardial infarction.

Myocardial ischemia and hypoxia in pulmonary embolism may arise by several different mechanisms. The sudden reduction in systemic blood pressure occasions a decrease in the coronary artery perfusion pressure. Tachycardia may further complicate this by shortening the total time in diastole when coronary inflow is normally greatest. The high pressure in the right ventricular cavity is attended by an increase in the transmural pressure of the right ventricular myocardium and this serves to increase resistance and therefore decrease flow.[55] In addition, a high pressure in the right atrium is accompanied by a high pressure in the coronary sinus and the coronary veins. This may serve to reduce the coronary arteriovenous pressure gradient and still further reduce flow.[55] It has also been suggested that the dilated pulmonary artery may in some cases, actually compress the coronary

vessels extrinsically.[86] Complicating all this is the fact that many of these patients already have arteriosclerotic coronary artery disease. It has been proposed by some authors that the substernal and precordial pain complained of by some of these patients may actually be due to myocardial ischemia.[19] It is true that the pain is frequently indistinguishable from that of myocardial infarction. However, the generally accepted opinion at present is that the pain is due to stretching of the pulmonary arterial wall which has been shown to possess stretch receptors1

VII. SUMMARY

The blood supply of the lungs comprises two separate systems, the pulmonary and the bronchial systems respectively. The pulmonary arterial system is a low pressure, low resistance circuit and the arteries are end arteries. Bronchial arteries are a portion of a separate high pressure, high resistance circuit, and the bronchial vessels are the direct opposite of end arteries. Communications between the two arterial systems occur in the respiratory bronchioles and under normal conditions, the amount of blood passing from the high pressure (bronchial) to the low pressure (pulmonary) systems is very small. Nevertheless, the amount of collateral may be relatively or absolutely increased in some pathological conditions, and, in embolic occlusion of the pulmonary end artery system, the collateral flow may be sufficient to prevent the development of a pulmonary infarction.

All of the factors which determine the amount of resistance, and therefore, pressure in the pulmonary arterial circuit are not well defined. The major resistance to blood flow is probably in the pulmonary arterioles and, therefore, those factors which affect the arterioles also affect pulmonary resistance and

and pressure.

The concept of "critical closing pressure" of the pulmonary arterioles takes into account the often demonstrated tremendous vascular reserve of the pulmonary circuit. Increases in pulmonary flow, which would ordinarily cause increases in pressure, by this mechanism produce increments in the size of the vascular space being utilized, and the additional flow causes no rise in pressure. The action of the arterioles themselves in this mechanism is apparently one of passive opening when flow increases and passive collapse when flow decreases. However, the general tone of the arterioles is apparently influenced by a number of factors, such as sympathetic and parasympathetic nervous influences and humoral influences, as well as airway and transpulmonary pressure. All the factors which influence pulmonary arteriolar tone, and, therefore, critical closing pressure are not known.

Because of the well known vascular reserve capacity of the pulmonary bed, it has been very difficult for some observers to reconcile embolic occlusions of relatively small segments of the pulmonary circulation with death of the patients.

This apparent discrepancy in observations led to the development of a theory that the lodgement of an embolus in the pulmonary bed led, in some way, to a generalized spasm of pulmonary arterioles with resultant acute pulmonary hypertension, right heart failure, shock, and death.

Several theories were brought forth to explain the postulated arteriolar spasm. The oldest of these theories is the "reflex theory" which postulates that lodgement of a pulmonary embolus in one segment of lung triggers reflexes which produce generalized arteriolar spasm. In addition, theories have been developed that a reflex inhibition of the heart or constriction of the coronary arteries.takes place.

Newer theories have suggested the possibility that humoral agents released directly from the impacted thrombo-embolus or from the segment of lung directly influenced by the embolus, might cause generalized pulmonary arteriolar spasm.

Other theories concerning the possible effects of hypoxia, epinephrine, norepinephrine, histamine, and acetylcholine in the embolic process have been presented also.

In contrast to suggestions that the pulmonary

arterioles respond to embolization by undergoing constriction, there are many authorities who believe that all the vascular reactions to embolization may be accounted for by the purely mechanical blockade to flow suddenly imposed upon the pulmonary circuit. These authors believe that the only arteriolar reaction to embolization is purely passive acceptance of the obstruction.

All of these theories have some merit and there is some experimental evidence indicating the truth of all of them. Many pitfalls and technical hazards have hindered efforts at investigation of the physiologic processes concerned with pulmonary embolism, however, and the validity of many experimental observations and subsequent conclusions is in doubt.

Pulmonary emboli may be classified according to the size of the vessel that they obstruct as follows:

1. Very large or massive (those that occlude the main pulmonary artery or either of its major branches)
2. Medium-size (those occluding secondary and tertiary branches of the pulmonary artery and those smaller branches down to, but not including arterioles)

3. Very small or miliary (those microscopic emboli which lodge in pulmonary arterioles and capillaries)

With the very large and the medium-size emboli the bulk of experimental evidence supports the theory of simple mechanical obstruction. Evidence previously stated to be in support of the reflex theory with emboli of this size has largely been explained by other mechanisms in the light of more recently acquired knowledge. However, in order to accept the purely mechanical hypothesis, one must assume that foreign body emboli and thrombotic emboli provoke an identical reaction on lodgement in the pulmonary bed. Several authors have suggested that this might not be the case.

With very small or miliary emboli, available experimental data is somewhat contradictory and confusing. There is a great deal of evidence supporting both reflex and mechanical theories and both theoretical mechanisms have their contradictory and confusing points. A great number of technical hazards have plagued investigation of the physiologic process concerned here. Again the question of the similarity of reactions to thrombotic and foreign body emboli arises since almost all the experimental work with this size embolism has been carried out using foreign body emboli. At

present, it is very difficult, if not impossible, to draw any concrete conclusions from the available evidence concerning miliary emboli. It is very obvious that more experimental work is needed on this aspect of the problem.

The exact role that serotonin plays in the process of pulmonary embolism is not clear. It is true that some authors have presented evidence that it may have some role. Since serotonin is known to be present in blood platelets and its release by clotting of blood has been shown, there is some question as to whether the presence of serotonin in thrombotic emboli causes the vascular reaction to such emboli to differ from that to foreign body emboli.

Regardless of whether or not the mechanism involves pulmonary arteriolar spasm, the systemic reaction to pulmonary embolism in fatal cases consists of pulmonary hypertension, right heart failure, dyspnea, hypotension, and death. The essential feature of such a reaction is a suddenly imposed high resistance to blood flow through the pulmonary arterial system.

VIII. CONCLUSION

A great deal of controversy has centered about the vascular reactions to pulmonary embolism. From available experimental data, it appears that with massive and medium-size emboli the vascular reactions represent purely obstructive phenomena although this can not be stated with certainty since most of the experimental evidence was obtained with non-thrombotic foreign body emboli. In the case of very small or miliary embolism, it is not possible to conclude whether or not pulmonary vasospasm takes place because of the contradictory nature of a large body of the experimental evidence.

The role of serotonin and other humoral agents is not clear. There appears to be more than a casual relationship between the action of serotonin and the action of a pulmonary embolus, although this can not be stated with certainty.

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