THE PHARMACOLOGY OF THE PULMONARY CIRCULATION[1]

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I. INTRODUCTION

In 1921, Wiggers concluded his review article entitled "The Regulation of the Pulmonary Circulation" (831) with the following statement: "While the nervous and chemical control of the pulmonary vessels undoubtedly play an important, if not as yet fully understood part in the distribution and flow of blood in the lungs, it is obvious that the total volumes of blood contained in the pulmonary vessels must be governed by the relative discharges of the two sides of the heart." Thirty-nine years later the same statement can well summarize the state of affairs regarding the nervous and chemical regulation of the lung circulation. Information on the effect of drugs on the lung vessels has been accumulating at a rapid pace in recent years so that it might be appropriate now to summarize the established facts and point out uncertainties.

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It is certain that some drugs can alter pulmonary blood flow, pulmonary blood pressures, and pulmonary vascular resistance. The reactions of pulmonary vessels to epinephrine and acetylcholine were reviewed by Daly in 1933 (185) and the perfusion technics his group had developed have been adapted and modified by other investigators to demonstrate pulmonary vasoconstriction or vasodilatation induced by numerous other drugs. The introduction of cardiac catheterization by Forssmann, Cournand (168) and Richards (672) has made it possible to measure drug effects in human subjects in the presence or absence of cardiovascular disease.

However it is still uncertain why closely related drugs have different effects on pulmonary arterial pressure or, why the same drug has an opposite effect when tested in man as compared to animals or even in the same species when different technics are used. It is also uncertain as to whether a specified effect of a drug is harmful or useful. The development of pulmonary edema by drugs has been reviewed by Visscher *et al.* (803) and there is no question that drugs leading to edema are undesirable. But can other drugs acting directly on the lung vessels improve the oxygen uptake of the lungs, reverse the development of pulmonary edema or protect the heart from failing? An attempt will be made to answer these questions in this article.

II. ANOXIA AND THE PULMONARY CIRCULATION

The effects of drugs on the pulmonary circulation have been expressed in terms of their actions on each of the following: a) pulmonary vascular pressures; b) pulmonary blood flow; c) pulmonary vascular resistance; and d) pulmonary blood volume. The various methods used to obtain each of the desired types of information concerning drugs have been utilized rather extensively for the study of the effects of anoxia. It therefore becomes appropriate to use oxygen lack as a prototype of an agency that can influence the pulmonary circulation in a variety of ways. The general plan is to discuss each individual measurement in terms of the nature of the observed change during anoxia and the significance of the change. The latter will include a discussion of how the observed change is brought about, and how it affects the other measurements of the pulmonary circulation.

A. Pulmonary vascular pressures

1. Pulmonary arterial pressure. Recent interest in the effects of anoxia on the lungs started with the observation of von Euler and Liljestrand in 1946 that the ventilation of 10% oxygen in nitrogen in cats with open chests caused a rise in pulmonary arterial pressure (271, 517). This was subsequently confirmed using mixtures ranging from 8 to 15% oxygen (505, 522).

Shortly after the pulmonary hypertensive action of anoxia in cats became known, a similar action was reported by Motley *et al.* (577) in 5 human subjects inhaling 10% oxygen. Four other groups have confirmed this observation in normal human subjects inhaling mixtures ranging from 9 to 15% oxygen (233, 626, 756, 828).

The experimental animal that has been studied most extensively is the dog. In 1902, Wood (844) described pulmonary arterial hypertension during asphyxia but did not test the lack of oxygen uncomplicated by the accumulation of carbon dioxide. This information became available in 1942 (73) when pulmonary arterial hypertension by asphyxia and by pure anoxia (inhalation of 10% oxygen) were shown to be the same in anesthetized dogs. This has been confirmed by at least 13 groups of investigators using dogs anesthetized with either chloralose (22, 24, 507, 509, 617, 618, 801) or pentobarbital (64, 90, 433, 676, 763, 764) and using unanesthetized dogs (592). All groups reported an immediate increase in pulmonary arterial pressure ranging from 10 to 50% of the value during inhalation of room air, with the exception of one group which reported a slight fall in pressure of 5 to 30% in some dogs (592). Mixtures containing as low as 2.5% oxygen have been administered with the dog inhaling spontaneously or by means of a respiratory pump with the chest opened. Resumption of the administration of room air resulted in immediate recovery from the pulmonary hypertensive response.

Significance of pulmonary arterial hypertension. The rise in pulmonary pressure indicates that the stimulus has affected the pulmonary circulation. The fact that hypertension has been observed whether the chest is opened or closed shows that respiratory stimulation that always accompanies anoxia is not essential in eliciting the rise in arterial pressure. Beyond this, the ultimate causes of the hypertension cannot be identified. The hypertension could result from increased blood flow, increased pulmonary vascular resistance, or failure of the left ventricle with retrograde transmission of the increased left atrial pressure to the arteries of the lung. The role of the last factor will be considered next.

2. Left atrial pressure. The information on left atrial pressure changes during anoxia has been derived exclusively from dogs. During the pulmonary arterial hypertension induced by the inhalation of 5 to 12% oxygen, left atrial pressure remains unchanged (22, 24, 64, 592, 676, 764). A rise occurs if anoxemia becomes so severe (arterial oxygen saturation less than 15%) that there is failure of the heart (341, 832). Otherwise, a rise in left atrial pressure can be dismissed as a cause for any change in pulmonary arterial pressure during anoxia.

Significance of alterations in left atrial pressure. Although changes in left atrial pressure do not accompany the pulmonary arterial hypertension of moderate degrees of anoxia, they may be involved in the effects of some drugs. A rise indicates a relative failure of the left ventricle to empty the pulmonary veins and would result in a retrograde rise in pulmonary arterial pressure. The extent of increment in the latter does not equal the pressure rise in the left atrium and pulmonary vein. If pulmonary blood flow is maintained constant and left atrial pressure is elevated, the pressure gradient from pulmonary artery to left atrium is reduced, indicating a reduction in resistance of the normal lung (372) and perfused lungs (95, 142, 143). This applies only to acute changes in left atrial pressure because prolonged rises are suspected of inducing some compensatory constriction of the pulmonary arteries (see section V-A). The above remarks may be reversed to apply to reduction of a previously high

atrial pressure. The absence of any change in left atrial pressure does not guarantee the lack of any pressure change in the pulmonary veins. This is discussed in the next section.

3. Pulmonary wedged arterial pressure. The insertion of a catheter wedged into the pulmonary artery was introduced by Hellems *et al.* (407) as a means of approximating pulmonary capillary pressure. The year following, Lagerlöf and Werkö (488a) reported that pressures so recorded display phasic variations and mean pressure levels resembling those in the pulmonary vein and left atrium. The induction of anoxia does not alter the pulmonary wedged arterial pressure in human subjects (233, 828). In anesthetized dogs, the earlier measurements of Dow and Gorlin (231) failed to show, during anoxia, a significant gradient between wedged arterial and left atrial pressures (the latter by a catheter inserted retrogradely via a femoral artery, aorta, left ventricle and the left atrium). The recent measurements by Rivera-Estrada *et al.* (676), using dogs with open chest (atrial pressure being measured by the insertion of a catheter into the atrial appendage), showed an entirely different situation. This group administered 5 or 10% oxygen and found left atrial pressure to be unchanged, wedged arterial pressure to be increased, and pulmonary arterial pressure to be increased but to a lesser extent. Thus during anoxia, the gradient from pulmonary artery to wedged artery was reduced (average of 11 mm Hg during control, to 5 during anoxia) whereas the gradient from pulmonary wedged artery to left atrium was increased (from 1 to 10 mm Hg). The total pressure gradient between pulmonary artery and left atrium was increased during anoxia (from 12 to 15), with the level of left atrial pressure remaining essentially unchanged.

Significance of a rise in wedged arterial pressure. The demonstration of a gradient between wedged arterial and left atrial pressures is completely unexpected after a decade of assuming wedged arterial pressure to measure left atrial pressure. Two other experimental procedures have recently been shown to induce a gradient similar to that of anoxia. a) Eliakim *et al.* (257) injected hypertonic sodium chloride solution and observed a gradient from wedged pulmonary vein to left atrium of as much as 50 mm Hg (see section III-A4 for details). b) Singer and his collaborators (738) embolized the lungs with starch and noted a gradient as much as 7 mm Hg. This observation may serve to explain some earlier observations that intravenous injection of lycopodium spores caused a rise in wedged arterial pressure (183, 407) or a rise in wedged venous pressure but no change in left atrial pressure (572).

Although the above observations were made without simultaneous measurements in flow, the investigators concluded that the gradient means constriction between the site of arterial wedging (pulmonary artery or vein) and the left atrium. This conclusion is justified particularly when the gradient increases by as much as 50 mm Hg. The greatest use of wedged arterial pressure is its applicability in human subjects for the estimation of pressure gradient between the pulmonary artery close to its origin, and its branches small enough to be occluded by the catheter. This is in turn used to calculate arterial vascular resistance in the lungs, which is a component of total vascular resistance (see section II-C).

B. Pulmonary blood flow

1. Indirect measurement of cardiac output. There is almost unanimous agreement that one prominent feature of inhalation of low oxygen mixtures is an increase in cardiac output. The earlier report of Motley and his collaborators (577) of a slight reduction in output encountered in 5 subjects has been subsequently retracted (164) because of the lack of a steady state while measuring output by means of the Fick principle. Subsequent use of the Fick principle by Westcott (828), McGuire (541) and their collaborators, and by Storstein (756) revealed a rise in output ranging from +10 to + 70%, and in a few instances a decrease. The latter instances were probably due to technical errors inherent in the Fick method, because when the indicator-dilution technic was utilized in 5 subjects, each of them showed an increase in output during inhalation of 10% oxygen (233).

A similar situation exists in dogs subjected to anoxia. When the Fick principle was used to measure cardiac output, although the usual response was an increase (12, 396, 509, 617, 764), a reduction was encountered just as frequently (509) or exclusively (592). When the indicator dilution technic is used, the effect is almost always an increase ranging from +10 to +100%. Unanesthetized dogs (592) showed a more significant increase than dogs anesthetized with morphine and chloralose (504) and the latter more than dogs anesthetized with pentobarbital (763).

Significance of cardiac output measurements. The use of the Fick principle in estimating cardiac output during anoxia has been criticized by Nahas *et al.* (591) chiefly on the basis of the difficulties in obtaining a steady state of oxygen consumption, and of arteriovenous oxygen difference. The various groups that have consistently relied on the method have taken precautions to assure a steady state, but admit an analytical error of 10 to 15% between duplicate measurements. A similar error would apply to the dye dilution technic but the necessity for assuring a steady state becomes less important. Leusen and Demeester (501, 503, 504) have criticized the use of the Fick principle in anesthetized dogs during prolonged anoxia. They showed that in the course of several hours, the spontaneous changes in output even without anoxia might equal or even exceed the observed changes during anoxia. It is therefore impractical to measure output in anesthetized dogs subjected to anoxia for several hours unless control studies are meticulously performed.

If the results indicating a reduction in output during anoxia are temporarily ignored, and those indicating a rise are accepted as the usual finding during anoxia, the task of understanding the effects of anoxia becomes simpler. One conclusion becomes justified, namely, that the rise in cardiac output may participate in the causation of the pulmonary hypertension of anoxia. However, certain questions remain unanswered: What are the ultimate causes for the increase in cardiac output? Is the increase in output entirely responsible for the pulmonary hypertension? The former will be answered in another section, the latter in the section that follows immediately.

2. Direct measurement of pulmonary blood flow. The insertion of a rotameter

into the artery of one lung has allowed the estimation of blood flow changes more accurately. Hürlimann and Wiggers (433) noted that the administration of 10% oxygen by means of a pump in dogs caused an increase in pulmonary arterial blood flow of 3 to 60% (average increase of 26%) above the control values during ventilation with room air. The authors recognized that insertion of such a rotameter to one lung may have shunted the blood to the other lung, and recognized further that the control flow and its change were probably smaller than in reality. If pulmonary blood flow was measured by means of a rotameter inserted into one pulmonary vein, with adequate provisions (use of collapsible reservoir and pump) to maintain resistance in the rotameter equal to the normal left atrial pressure, ventilation with 10% oxygen induced responses almost equivalent in intensity to those elicited by the arterially inserted rotameter: average increase of 18% for the venous rotameter (24). The threshold for the first rise in flow was a decrease of 10% in oxygen saturation of the systemic arterial (or pulmonary venous) blood, and this is the same threshold value for the observed increase in pulmonary arterial pressure (24). All these direct measurements may be criticized because they were performed in dogs with open chest, using anticoagulants, perfusion pumps and rotameters. Lewis *et al.* (510) have shown that the changes in cardiac output measured by the Fick principle were similar, whether they were derived from dogs breathing spontaneously, or artificially with open chest.

Significance of increased pulmonary blood flow. The major importance of the direct measurement of pulmonary blood flow is that the technic establishes the coexistence of pulmonary hypertension and increased pulmonary blood flow during anoxia. Since the thresholds for the occurrence of each one have been shown to be a reduction in arterial blood oxygen saturation of 10%, one might conclude that increased blood flow can always be regarded as a factor in the hypertension. This threshold value for increase in flow is less than those derived by the Fick principle: 20 to 30% reduction in oxygen saturation in human subjects (164, 756) and 30 to 50% reduction in anesthetized dogs (396, 509). This discrepancy should be expected because of the inaccuracies in the Fick method discussed in the preceding section. Unfortunately the direct measurements of pulmonary blood flow during anoxia have not been extended to other procedures that would help identify the ultimate causes of the increased flow. The increase undoubtedly reflects an increase in output of the right ventricle which may in turn be due to humoral, nervous, or other factors, but there is no assurance that the collected venous outflow is equal to the arterial inflow to the lung. If these are not equal, there might be a gain or loss of blood in the lungs, but such an occurrence might mean a discrepancy within the error of the rotameter (within 5%). Although the use of the rotameter or other similar direct recording flowmeters may fail in indicating changes in blood volume in the lungs, it may indeed be relied upon to obtain the most direct measurement of flow in one lung or lobe, and this in turn represents a good estimation for changes in total pulmonary blood flow or cardiac output.

C. Pulmonary vascular resistance

1. Pulmonary total vascular resistance. The combined measurements of blood pressures and flow in the lung vessels allow the calculation of pulmonary vascular resistance by dividing pressure gradient by blood flow. The resistance value has been calculated by two ways depending on the nature of the available pressure measurements. The most direct way is to divide the pressure gradient between the pulmonary artery and the left atrium by the corresponding value of cardiac output, and then calculate the percentage change in total vascular resistance as a result of the inhalation of a low oxygen mixture. The values are not available in human subjects because of the lack of values for left atrial pressures. In dogs anoxia causes an increase, a decrease, or no effect on calculated total vascular resistance. The resistance changes utilizing the dye dilution technic for cardiac output measurements range from −15 to +20% (592), whereas those utilizing the Fick method range from −50 to +225% (507, 592, 764). When pulmonary venous outflow is measured directly, the changes range between −15 and +20%, regardless of whether 10 or 5% oxygen is used to ventilate the lungs (24).

An alternative way of expressing total vascular resistance is to measure mean arterial pressure only and to assume left atrial pressure to remain unchanged. The results in dogs are essentially similar to those obtained when left atrial pressure is measured directly, *i.e.*, variable effects on resistance (524, 525, 526, 763). In normal human subjects, the inhalation of 10% oxygen causes a variable effect on calculated resistance, ranging from −40 to +100% (577, 756).

Significance of variable effect on total vascular resistance. Anoxia causes a variable effect on total vascular resistance in human subjects and dogs, irrespective of the manner of measuring pulmonary blood flow, and regardless of measuring or assuming left atrial pressure. The ideal way would be to measure directly left atrial pressure and this has been possible in dogs, and will be expected to be available in human subjects as a result of the recent development of the transthoracic and transseptal approaches to the left side of the heart.

It is important at this point to discuss the significance of the variability of total resistance changes during anoxia. Some dogs and human subjects responded to anoxia in such a way that the percentage increase in pressure was equal to the percentage increase in flow; thus the resistance was unchanged. However, there were some responses in which the percentage increase in pressure was larger than the percentage increase in flow, and the pulmonary total vascular resistance during anoxia was increased. A similar rise in resistance was also encountered in some dogs and human subjects in which the rise in pressure was accompanied by no change or even a slight fall in flow. All of these examples suggest that the increase in pressure cannot be accounted for entirely by an increase in flow so that pulmonary vasoconstriction can be accepted as an additional cause.

On the other hand, the responses in which the percentage rise in pressure was

less than the percentage increase in flow indicated that anoxia was capable of decreasing vascular resistance. The final causation of this reduction is not a simple one because in addition to active dilatation, the vessels can dilate passively as a result of a primary increase in blood flow.

2. Resistance effects of increased flow. It has been shown repeatedly in perfused lungs of dogs (43, 251, 330, 492, 820, 836) and cats (143, 330, 413) that an increase in pulmonary blood flow may of itself lead to a reduction in total vascular resistance. Burton (129, 130) has called attention to the fact that the observed reduction in resistance is not determined by the increased flow but by the accompanying increase in pressure. The reviewer subscribes to this concept but also feels that the primary interest in the pharmacology of the pulmonary circulation lies in the contribution of pulmonary blood flow in the causation of the calculated vascular resistance. The passive reduction in vascular resistance brought about by an increased blood flow will be alluded to as such for brevity, but with the understanding that the increase in pressure is the intermediary cause.

Other experiments have been utilized to demonstrate the resistance effects of increased flow. In the intact lungs, supplied by the dog's own heart, calculation of vascular resistance (based on direct measurement of pulmonary venous outflow and of arteriovenous pressure gradient) indicates that the maximum effects in total resistance is a reduction of 30% which could be elicited by blood transfusion or by passive movements of the extremities (to increase flow by 90%) (24).

In human subjects, the most direct calculation of total vascular resistance is not available because measurement of left atrial pressure has not yet been performed during experimentally induced increases in flow. If the calculated resistance values based on an assumed unchanged left atrial pressure are considered, the following conclusions can be drawn. In normal subjects, increased cardiac output by as much as 100%, through muscular exercise, causes a reduction in resistance by as much as 50% (86, 120, 170, 218, 412, 454, 605, 674, 706, 707, 773, 799). The infusion of physiological saline or 6% dextran solution elicits an entirely different result, consisting in increased flow by as much as 50% but usually an increased total vascular resistance (232, 842). Venous congestion of the extremities causes a reduction in output with a proportionate increase in resistance such that pulmonary arterial pressure remains essentially unchanged (455). All the above-mentioned results were obtained in normal human subjects but the results from patients with diseased lungs and heart are different and will be discussed in other sections (IV and V).

One outstanding difference between anoxia and muscular exercise becomes apparent. Whereas both cause increases in cardiac output in man, the total vascular resistance during muscular exercise is usually decreased but is either decreased or increased during anoxia. One explanation for this difference is that muscular exercise may cause not only passive reduction in resistance similar to that encountered in the perfused lung, but also an active one brought about by chemical or nervous factors so far undiscovered. Another explanation is that the resistance is affected entirely by a passive effect of increased cardiac output

during muscular exercise, but anoxia induces both this passive effect plus an active constriction which is unrelated to the increased blood flow. The intensity of each of these changes may be estimated by consideration of dog lungs, in which direct measurements of pulmonary venous outflow during anoxia, passive exercise, and blood transfusion were performed. It is conspicuous in the same dog that for the same amount of increase in flow, pulmonary pressure and resistance are higher during anoxia as compared to those measured during transfusion or exercise (24). The identification of the factors bringing about the active increase in resistance will be considered below (II-E).

3. Pulmonary arterial resistance. The use of wedged arterial pressure has afforded an opportunity to study the arterial component of the total vascular bed of the lungs. During anoxia of human subjects, measurements reveal an increase in the gradient from pulmonary conus to wedged artery, and the corresponding calculated arterial resistance is always increased. This is fortunate because it adds an encouraging feature to resistance measurements in general, and to the understanding of the behavior of pulmonary arteries during anoxia in particular.

Significance of increased arterial resistance. The most important conclusion arising from measurements of pulmonary arterial resistance is the localization of constriction in the arterial side of the vessels during anoxia. The causation of this arterial constriction can be analyzed in a manner similar to that of changes in total resistance. The observation that anoxia causes more frequently an increase in resistance whereas muscular exercise causes more frequently a decrease, means that the former is associated with active constriction not related to increased blood flow (218, 605, 773, 799).

The fact that arterial constriction can contribute to the increase in total vascular resistance does not exclude constriction of the remaining vessels. The increases of pressure gradient between the wedged arterial and left atrial catheters indicate postarterial constriction in dogs but the corresponding information in man is not available.

D. Pulmonary blood volume

The measurement of cardiac output by the indicator dilution technic has afforded an estimation of blood volume from the site of injection to the site of sampling of the substance. In man during anoxia, circulation time was shown to be shortened (76) but calculated pulmonary blood volume did not show any significant change (233). In anesthetized dogs in which the indicator used is potassium^{42} injected directly into the right atrium, there is a consistent increase in pulmonary blood volume averaging 23% during inhalation of 5% oxygen (763). This increase is also reflected when erythrocytes tagged with phosphorus^{32} are injected intravenously in the dog (443). The radioactive measurement from the pleural surface of the lungs by means of a Geiger counter tube (inserted between the ribs with provisions to allow spontaneous respiration) shows a significant increase of pulmonary blood volume (22). This radioactive isotope method has not been calibrated but the extent of increase during inhalation of 5% oxygen can be expressed as one-fourth of the total reduction induced by

complete obstruction of the pulmonary artery by inflating a balloon lodged inside it (22).

Significance of pulmonary blood volume measurement. If the results obtained from dogs are considered exclusively, the end-result of anoxia is increased pulmonary blood volume, estimated by either the indicator dilution technic, or by the continuous measurement of radioactive tagged erythrocytes on the surface of the lungs. The causes of the increase in pulmonary blood volume are not yet known, but it appears to be a consequence of a number of factors which have been shown individually to bring about an increased volume of blood in the lung vessels (237, 709): 1) increased cardiac output; 2) pulmonary venous constriction; 3) pulmonary capillary dilatation; 4) severe constriction of systemic vessels with shifting of blood into the vessels of the lungs; and 5) failure of the left ventricle. These conclusions are based on direct estimation of blood volume on the exposed lungs (237, 518, 709). During the degree of anoxia under discussion the last factor can be excluded because it has been shown that left atrial pressure is unchanged. The relative importance of the remaining factors in contributing to the congestion of the lungs must await further experimentation. The various indicators (heavy water, thiocyanate, chromium[54]) for detailed studies of the blood hematocrit in the lungs (515, 661) should be extended to the identification of mechanisms responsible for congestion during anoxia.

E. Local effects on lung vessels

There has been no attempt so far in this article to explain the observed increases of cardiac output, pulmonary arterial pressure, and pulmonary blood volume, and the variable effect on pulmonary total vascular resistance. The plan is to specify the local effects on the lung vessels in this section, and then to proceed with other types of action. It should be stated at the outset that the hypothesis of von Euler and Liljestrand (271) in 1946, and of Cournand and his collaborators in 1947 (577) that anoxia can locally constrict lung vessels has been both confirmed and denied.

1. Perfusion of excised lungs. The first direct confirmation that anoxia can constrict lung vessels locally was offered by Nisell in 1950 in excised lungs of the cat (597). Ventilation of the lungs with nitrogen or mixtures containing up to 10% oxygen caused a rise in perfusion pressure of the lungs supplied at a constant flow. This observation has been confirmed in cat lungs (240, 244) and dog lungs (203). All the investigators have concluded that the constricting response was independent of changes in tidal air and of the nature of the perfusing fluid (blood, dextran solution or Ringer's solution). The vasoconstriction could be elicited even after the addition of the following autonomic blocking drugs: dihydroergotamine, Dibenamine (N,N′-dibenzyl-β-chlorethylamine), tetraethylammonium chloride, atropine and mepyramine (203, 240, 244, 597). The general conclusion has been that anoxia causes local constriction of the lung vessels, which is indeed justified on the basis of the above information.

Unfortunately, there are as many observations that show the absence of local constriction or the presence of active dilatation when perfused lungs are subjected

to anoxia. On administration of 5 to 10% oxygen in nitrogen to dog lungs perfused at a constant flow with mixed venous blood derived from living donor dogs, there was no rise in perfusion pressure but either no effect or a fall, indicating a local dilatation (22 24). Reduction in oxygen content of the blood caused a reduction in perfusion pressure in such preparations (22) and also in excised lungs of the cat (597). Other investigators failed to confirm this finding in the cat (242). Finally, the excised pulmonary artery and vein of man, swine, dog and cat show no contraction when oxygen content of the suspending fluid is reduced (741).

Significance of excised lung perfusion. The variable effects of anoxia derived by various investigators from perfused lungs are quite distressing and would serve to discourage many from taking such results seriously. It is the opinion of the reviewer that the perfusion of excised lungs has so far failed to answer the fundamental question as to the nature of the local action of lack of oxygen. This failure is reflected in the varied results obtained, which remain unexplained. A similarly confused situation exists for investigation of some drugs, but more uniform results have been derived for other drugs which will be discussed elsewhere in this article.

One explanation can be offered for the variability in results from perfusion experiments, other than the more obvious differences in species, technics, anticoagulants, temperature and type of perfusion pump. It is possible that the perfused vascular bed has two or more reactive areas which behave differently in the presence of anoxia: arterioles, capillaries, venules, arteriovenous anastomoses and bronchopulmonary anastomoses. The reactivity in some areas may be lost but retained in others, depending upon technical differences. The development of technics to study individual areas may help explain the variability in response by the entire vascular bed.

2. Perfusion of lung in situ. In the living animal, when the artery to one lobe or to one lung was perfused at a constant flow with mixed venous blood derived from the same animal, the inhalation of 0 to 11% oxygen caused varied effects. The earlier investigations in dogs (22, 73, 79) showed no effect or a slight fall, but later experiments by others in dogs (24, 90, 243) and cats (243) revealed a rise in perfusion pressure. During constant pressure perfusion of one lobe, anoxia reduced flow (433). Both results indicate increased pulmonary vascular resistance. Although the pulmonary vein of the perfused lobe in all these preparations remained intact, the conclusion regarding total pulmonary vascular resistance remains valid because left atrial pressure was unchanged. When the artery and vein of one lobe *in situ* were both cannulated to allow complete perfusion, the effects of anoxia were variable (24, 374).

Significance of perfused lung in the living animal. Although the effects of lung perfusion in the living animal appear superficially to be variable and confusing, application of additional procedures has helped to clarify the situation. When one lobe of the dog is perfused incompletely (arterial cannulation only) or completely (both artery and vein cannulated), the response to systemic anoxemia is usually a vasoconstriction if precautions are taken to keep the innervation

to the lobe intact (24). The elimination of such nerves, either by removal of the sympathetic thoracic ganglia, or by direct cannulation of the lobar artery such that the accompanying nerve fibers are injured, brings about the loss of constrictor response and the inhalation of a low oxygen mixture causes no effect or even a fall in perfusion pressure. These experiments in the living dog have served one purpose regarding the investigation of local effects of anoxia: demonstrating that the constriction of lung vessels is not entirely a local response of the lung vessels, if at all, but is mediated through the nerve supply of the lungs. The details of this nervous mechanism will be discussed below (section II-F).

3. Bronchospirometry. The first evidence for local pulmonary vasoconstriction demonstrable by the application of a low oxygen mixture to one lung only was offered by Dirken and Heemstra in 1948 (221, 222). They noted in rabbits that this procedure caused an initial reduction in oxygen content and saturation of systemic arterial blood, which gradually disappeared in about 8 hours. These results and the calculation of flow by comparing oxygen uptake of both lungs revealed a reduction in flow of the anoxic lung with shunting of blood towards the nonanoxic lobes. In more recent experiments Heemstra (406) has described the local constriction response as occurring in two phases, an initial transient one which was maximal 15 minutes after the onset of anoxia, and a second progressive one which reduced calculated flow at the end of 8 hours to 60% of the original value. All these findings derived from rabbits have not been challenged.

The corresponding information on dogs and man has been less consistent. Some investigators have shown constriction of the lung subjected to low oxygen (87, 102, 119, 168, 411, 634, 658) but others have failed to arrive at the same conclusion (24, 96, 288, 493, 684).

Significance of bronchospirometry experiments. The major justification for using bronchospirometer tubes is to facilitate the comparison of blood flows for the normal and anoxic lung under conditions closely approaching the physiological state. This has forced most investigators to devise indirect methods of estimating flows which are based on a number of assumptions.

The use of direct measurement of blood flow and vascular resistance has added the use of perfusion pumps, anticoagulants, flowmeters and opening of the chest, but the results are more definitive and have taken one of three patterns: a) complete absence of constriction in the lobe perfused at a constant flow (24); b) variable and small reduction regarded as insignificant in venous outflow of the anoxic lung (493); and c) no constriction of perfused lung within 8 hours after the start of perfusion, but beyond this period, sometimes a constrictor response (96). All three observations were made in the anesthetized dog and suggest that the lung ventilated with low oxygen by means of a bronchospirometer tube does not show constriction that is physiologically important. Direct flow measurements should be used in the rabbit and cat to determine if this conclusion may be extended to include most animal species.

F. Nervous and other mechanisms participating during anoxia

The local action of anoxia on the lung vessels remains a controversial problem. If the available information is taken to mean that local constriction is not

physiologically important, it becomes necessary to consider nervous mechanisms that may account for each of the following effects outlined above: increased pulmonary arterial pressure, increased pulmonary blood flow, variable effect on pulmonary total vascular and arterial resistance, and increased pulmonary blood volume.

1. Role of chemoreceptors. The first indication that the chemoreceptors of the carotid and aortic bodies participate in the response of the pulmonary circulation during anoxia was derived from denervation of the carotid and aortic receptors in dogs. Anoxia then no longer caused the immediate rise in arterial pressure of the lungs supplied by blood from the animal's own heart (22). A similar denervation also eliminated the vasoconstriction of the perfused lung induced by systemic anoxemia (24). The effect of denervation on the anoxic increase in cardiac output has not been investigated by direct methods of measuring flow but the ultimate death of the denervated animal during anoxia would suggest either inability of the heart to increase its output or interference with venous return.

Significance of denervation experiments. The simplest interpretation of the above experiments is that the carotid and aortic body chemoreceptors, which are activated during anoxia, can initiate sympathetic excitation manifested by increased cardiac output and pulmonary vasoconstriction. When these receptors are denervated, these reflex mechanisms are lost and the local effects of anoxia on the lung vessels (probably dilatation) and heart (depression) occur simultaneously with the liberation of epinephrine.

The above explanation is challenged by two additional facts. First, the denervation of the chemoreceptors in the carotid and aortic bodies by surgical excision of the nerves from the sinuses and aorta is not a selective one but also includes the baroreceptors of the carotid sinuses and aortic arch. This is not a serious objection because the baroreceptors are not known to be stimulated directly by anoxia, and because increased activity of such baroreceptors (by increased arterial pressure or by electrical stimulation of sensory nerves) causes pulmonary arterial hypotension (8, 730, 797) and reduced pulmonary blood flow (200, 202) but has a variable effect on lung vessels (25, 188, 730). Since these effects are not similar to those occurring during anoxia, baroreceptor activity can be excluded as participating during anoxia.

M. and I. de Burgh Daly (189) have recently perfused simultaneously the carotid bodies and one lobe in the dog. The alteration of the carotid body perfusate from arterial to mixed venous blood caused a reduction in pulmonary vascular resistance, which was eliminated by section of the nerve supply of the carotid area, by cervical vagotomy or by administration of atropine to the entire animal (including perfused areas). This reflex dilatation of the lung vessels is the exact opposite of the reflex vasoconstriction concluded from the denervation experiments when the entire dog is rendered anoxic. The discrepancies may be explained by the differences in the extent of anoxia. The carotid body perfusion experiments consisted in application of blood containing lower oxygen and higher carbon dioxide than the control arterial blood, limited to the carotid bodies only. The other group of experiments (24) consisted in reduction in oxygen content of blood reaching the entire body except the perfused lobe. This

difference in extent of anoxia may account for the fact that reflex vasodilatation is encountered in one set of experiments whereas reflex vasoconstriction is encountered in the other. The most important conclusion that can be drawn at the present time is that anoxia can stimulate the carotid and aortic body chemoreceptors and that this results in reflex changes in pulmonary vasomotor tone. The latter may result either from sympathetic-induced vasoconstriction or vagus-induced vasodilatation.

2. Role of sympathetic innervation. Some confusion exists as to the effect of thoracic sympathectomy on the anoxic response of the pulmonary circulation. This is true for the rise in pulmonary arterial pressure during anoxia, which has been reported to be absent following various types of denervation: thoracic sympathectomy in dogs (764) and human subjects (453), thoracic epidural anesthesia in man (453), and combined sympathectomy and adrenalectomy in dogs (405). On the contrary, thoracic sympathectomy in one human subject (166) and in six dogs (590) did not completely eliminate the hypertensive response. This discrepancy can be accounted for by the fact that thoracic sympathectomy alone eliminates only the reflex sympathetic constriction of the lung vessels and the reflex stimulation of the heart. Nervous and humoral mechanisms that serve to increase venous return could account for the occasional appearance of pulmonary arterial hypertension (24).

Significance of sympathetic vasoconstriction. The interpretation of the above experiments as indicating that anoxia can increase sympathetic pulmonary vasoconstrictor activity becomes more easily acceptable if other items of information are considered. Daly and his collaborators have shown in lung perfusion experiments that electrical stimulation of the upper thoracic chain usually causes pulmonary vasoconstriction (190, 191, 192). This has been confirmed by other investigators using different technics (127, 322, 419, 420, 739). The following intracranial procedures have been shown to cause activation of the sympathetic innervation to the lungs, manifested as pulmonary hypertension and even edema: electrical stimulation of hypothalamic areas (461), electrolytic lesions (319, 553), intracisternal injection of veratrine (19, 442, 673) and of fibrin (135), increased intracranial pressure (530), and traumatic lesions to the cranium (551). The exclusive participation of the pulmonary sympathetics is not widely accepted, and many investigators believe that the pulmonary hypertensive response is the outcome of excitation of sympathetic innervation to the heart (138, 140) and systemic vessels (708, 713).

Thoracic sympathectomy is said to cause the loss of the following: reflex pulmonary vasoconstriction initiated by pulmonary embolization (500, 596, 651), a similar reflex induced by pulmonary venous occlusion (283, 692), and a predisposition to development of experimental pulmonary edema (279, 482). There are just as many reports denying the physiological importance of the sympathetic innervation to the lungs.

3. Role of adrenal medulla. It has been difficult to determine the consequence of uncomplicated adrenalectomy on the anoxic response of the pulmonary circula-

tion. Nahas *et al.* (590) found no increase in cardiac output or in arterial pressure in 5 adrenalectomized dogs but these dogs were anemic and possessed a high resting cardiac output.

Inasmuch as anoxia is known to cause the liberation of adrenal medullary hormones, it is reasonable to suspect that the liberated epinephrine may account for some of the effects on the lungs. Epinephrine injection is known to cause pulmonary hypertension and this happens even while the dog is inhaling low oxygen (22). The pulmonary hypertensive response is unlike the concurrent systemic hypertensive effect of epinephrine, which is reduced during anoxia (410, 767). Blood derived from the inferior vena cava (which includes adrenal venous drainage) was perfused to a denervated lobe. The induction of anoxia in such dogs did not cause a humoral vasoconstriction (24) but this may not be true in an unanesthetized dog.

4. Role of vagal innervation. Vagotomy in dogs and cats has not been shown to alter essentially the pulmonary arterial hypertensive response to anoxia (223, 271, 433, 586). The only report that ascribes some importance to the vagi during anoxia is the reflex pulmonary vasodilator response from activation of carotid body chemoreceptors (see section II-F1).

Electrical stimulation of the peripheral end of the cut vagus reveals a dilator mechanism for the lung vessels (196, 197, 420). This response coexists with bradycardia (139) and bronchoconstriction (196) which may in turn serve to complicate the detection of the neurogenic dilatation of the lung vessels. It is of course possible that, physiologically, the efferent impulses in some vagal fibers may affect the lung vessels exclusively, by activation of highly specific receptors from the lungs. Such receptors have been postulated for embolization (580) but attempts to obtain positive experimental proof have failed (21, 23). The interrelationships between vagotomy and pulmonary edema are too complex to review here. The interested reader may consult recent reviews for details (533, 803).

5. Reactions of various constituents of the lung vessels. Another manner of analyzing the detailed effects of anoxia on the pulmonary circulation is to describe them in terms of each of the vascular components of the lungs. A review of the existing facts and theories might help in the design of future experiments.

Pulmonary arteries. The behavior of the arterial segment during anoxia is still uncertain. Among the four basic mechanisms by which anoxia may influence this vascular section (local, nervous, humoral and passive effect of increased pressure or flow), only the local effect on excised arterial segments is known. Smith and Coxe (692) observed that a reduction in oxygen content of the suspending fluid had no effect on vessel tone. In the perfused lung, the available results are not helpful in detecting any response of the arterial segment, chiefly because the pressure gradient from pulmonary artery to wedged artery is not usually measured. This has been measured in the intact dog and human subject but the results have been variable (see section II-C3).

Pulmonary capillaries. Numerous technics demonstrate the existence of capillary dilatation during anoxia. Histological examination after death from anoxia shows widening and disruption of capillaries [see refs. cited by Hurtado *et al.* (434)]. Direct visualization through the intact pleura of cats did not show any response of the capillaries to anoxia (548, 816, 817) but this may not reflect the behavior of the deeper capillaries. Indirect measurements of capillary blood volume by tagging erythrocytes with phosphorus^{32} showed an increase in radioactivity measured from the surface of the lungs which was interpreted to mean dilatation of the capillaries (22, 443). The end-result of anoxia is described by Warren *et al.* (815) as increased capillary permeability, accompanied by increased pulmonary lymphatic flow. The ultimate formation of pulmonary edema by such a mechanism has been questioned on the basis of more recent observations based on chemical and gravimetric analysis of excised lungs (171, 408, 623).

Pulmonary veins. The evidence for constriction of pulmonary veins during anoxia is based entirely on demonstrations of increased pressure gradients between the wedged artery to left atrium in intact dogs (see section II-A3). Burch and Romney (125) have recently reviewed the anatomical and physiological studies responsible for the so-called "throttle valve" action of the atrial portion of the veins. Such an action by drugs has received some recent interest and several examples will be enumerated elsewhere in this article.

Arteriovenous anastomoses. The recent demonstration of arteriovenous anastomoses [see refs. cited by Daly (185) and by Niden (596)] poses a question as to any difference in behavior between the vessels attached to the capillaries, and those bypassing them (anastomoses). There is suggestive evidence that anoxia causes constriction of such anastomoses (596, 675) in the same manner as it constricts the anastomoses in the limbs (718).

Bronchial vessels. The anastomoses between the bronchial and pulmonary vessels may account for a number of indirect effects on the latter brought about by primary anoxic effects on the former. A number of facts support this suspicion. a) Anoxia increases aortic blood pressure, and this may in turn increase bronchial arterial pressure and blood flow; perfusion experiments indicate further that such increases would be reflected by a slight rise in pulmonary arterial pressure (71). b) The bronchial vessels in the dog are affected in the same manner as the systemic vessels by injections of acetylcholine, epinephrine, *etc.*, and by stimulation of sympathetic nerves (114). If these similarities include the response to anoxia, this would mean that the bronchial vessels dilate locally, but constrict reflexly during anoxia, and therefore exert some remote action on the pulmonary vessels. c) Inasmuch as the bronchial vessels supply primarily the bronchial smooth muscles, the primary response of this area during anoxia may in turn influence the amount of effluent blood allocated between the pulmonary vessels (via bronchopulmonary anastomoses) and the bronchial veins. Although the exact behavior of bronchomotor musculature is not clearly defined, its role in affecting pulmonary vascular resistance has been repeatedly stressed (683).

G. Summary of present status of anoxic effects

The foregoing sections, as well as a number of recent review articles on the effects of anoxia on the pulmonary circulation (167, 214, 516, 805), emphasize the existence of numerous conflicting claims. This situation may serve to exemplify the status of other problems relating to the pulmonary circulation, such as intrinsic nervous mechanisms (187), gas diffusion (296), reflexes from the lungs (27, 209), pulmonary edema (30, 803), expectorants (116), antitussive drugs (98), and the action of drugs, noted below. It is important to list a number of generalizations as to the present status of anoxia, and these will be grouped into three categories ranging from those statements that are generally agreed upon or accepted, to those that are unsettled or controversial, with a middle group of statements between the two extremes.

1. General agreement. a) Pulmonary arterial pressure rises during anoxemia of sufficient severity, in all animal species and human subjects. b) Increased left atrial pressure does not ordinarily occur, unless the anoxia is severe enough to cause failure of the heart. c) Increased cardiac output occurs during anoxemia and could contribute to the pulmonary hypertension but may cause a reduction in calculated pulmonary vascular resistance. There is no agreement as to the importance of these changes relative to others.

2. Evidence strongly in favor but general agreement not yet present. a) Anoxia causes increased sympathetic nerve impulses that constrict lung vessels, which are initiated probably by excitation of carotid and aortic body chemoreceptors. This may contribute to an increase in calculated pulmonary vascular resistance, occurring concurrently with other changes. b) The outpouring of pressor substances from the suprarenal medulla occurs during anoxemia. This may contribute to the cardiac stimulation, to increased venous return and to pulmonary vasoconstriction, as a component of the response to chemoreceptor excitation, or as a primary response of the adrenals to anoxemic blood.

3. Unsettled or controversial. a) Anoxia causes directly a constriction or dilatation of the pulmonary vessels. The reasons for this discrepancy remain to be discovered. b) The exact site of constriction or dilatation by neurogenic or local mechanisms is unknown. The participation of the arteries, capillaries, veins, arteriovenous anastomoses and bronchial vessels in bringing about the observed anoxic responses of calculated pulmonary vascular resistance (usually variable) and of estimated pulmonary blood volume (usually increased) remains to be elucidated.

Anoxia as a prototype of drug action. The review of the complexities of the anoxic effects on the pulmonary circulation is a lengthy prelude to the actual discussion of drugs. The writer has justified this in a number of ways. The technics utilized for investigating anoxia retain the same merits and limitations when applied to pharmacological studies. The mechanisms that are known, and those that are suspected of participating during anoxia can be activated or inactivated by drugs, and it is important to make a distinction between accepted and postulated ones. Finally, the reader can be guided in the understanding of

drug action by using the response to anoxia as a standard response with which the individual drugs are compared.

III. DRUGS CAUSING PULMONARY HYPERTENSION PREDOMINANTLY BY VASOCONSTRICTION

Several drugs cause pulmonary arterial hypertension predominantly by constriction of lung vessels. Their action is like that of anoxia in that they cause pulmonary arterial hypertension but they differ from anoxia in two respects: a) anoxia causes variable effects on vascular tonus (constriction or dilatation) whereas these drugs consistently cause constriction; and b) anoxia consistently increases pulmonary blood flow whereas the hypertensive drugs have variable effects on flow. As the members of this group are described, it will become apparent that the local constriction may be the sole cause of the arterial hypertension, or may share the causation with increase in pulmonary blood flow, or the constriction may be intense enough to induce secondary effects that will ultimately lead to fatal cardiac failure or pulmonary edema. A summary of these complications will be attempted after the actions of each of the various drugs are described.

A. 5-Hydroxytryptamine and other constrictors liberated from blood

The interest in the circulatory effect of substances released from blood started in 1900 when Brodie (109) observed that cats developed marked systemic hypotension following the intravenous injection of either autogenous or heterogenous serum. A rise in pulmonary arterial pressure was subsequently described as an important accompaniment to the systemic shock of this phenomenon (666). This pulmonary hypertensive response has been elicited by two normal constituents of blood, namely 5-hydroxytryptamine (5-HT; serotonin; enteramine) and adenosine triphosphate (ATP). The intravenous injection of hypertonic salt solution or bacterial toxin is suspected of liberating the same two constituents of the blood or others like it.

1. Local vasoconstriction by 5-HT. The first evidence that 5-HT causes local pulmonary vasoconstriction was offered by Reid in dogs and cats (667) in which he noted that intravenous injection of this substance caused an immediate rise in pulmonary arterial pressure, whereas injection directly into the pulmonary veins (to bypass lung vessels) did not cause a similar immediate response. These experiments were performed with the vagi cut and the observations have been confirmed in cats with intact vagi (742).

The most direct proof of local pulmonary vasoconstriction by 5-HT has been derived from perfusion experiments involving lungs of guinea pigs (74), cats (243, 313, 314, 335) and dogs (93, 417, 688, 702). The constriction was deduced from either an increase in pressure during constant-flow perfusion, or a reduction in flow during constant-pressure perfusion. This response is blocked by antagonists such as lysergic acid diethylamide (74, 243, 688), brom-LSD (688), promethazine (688) and 2-ethyl, 3-methyl, 5-nitro-indole (742).

2. Effects of 5-HT outside of lung vessels. Comroe and his collaborators (158) noted flattening of pressure-volume curves of intact lungs of dogs following the

intravenous injection of 5-HT and attributed this to bronchoconstriction. This response was observed within two seconds after the injection into the right side of the heart, and was regarded as a reflex response mediated through the vagi. Bronchoconstriction can still be elicited after vagotomy if larger doses are used, and this is probably the same bronchoconstriction encountered in the perfused lungs by other investigators (74, 314). The mode of entry of the injected drug in doses sufficient to produce local spasm of the bronchiolar smooth muscle appears to be by way of both the pulmonary and bronchial vessels. Rose and Lazaro (688) injected 5-HT into the pulmonary artery of dogs with a left ventricular bypass which delayed the arrival of the drug in the systemic and bronchial arteries. The arrival of the injected drug in the pulmonary vessels caused an immediate increase in endotracheal pressure (bronchoconstriction) whereas, after a reasonable latent period, the arrival of the drug in the bronchial vessels caused a second period of increase (also bronchoconstriction). These observations pertaining to a reflex and local bronchoconstriction by 5-HT have suggested the possibility that pulmonary vasoconstriction may actually be secondary to the increase in bronchomotor tone. Borst *et al.* (93) observed that the reduction in flow of one lung subjected to serotonin was unaccompanied by changes in airway pressure, so that pulmonary vasoconstriction apparently can occur without bronchoconstriction.

Reid (666) postulated that the fall in pulmonary venous and carotid pressures accompanying pulmonary hypertension meant that the intravenous injection of serotonin caused vasoconstriction intense enough to cause reduction of systemic blood flow in cats. This concept does not hold true for dogs because pulmonary hypertension is usually accompanied by systemic hypertension. Furthermore, measurements of cardiac output with the indicator dilution method (547, 607, 732) or the Fick principle (698) show an increase, which averages 60% following continuous infusion of 5-HT. This undoubtedly contributes to the pulmonary hypertensive effect of 5-HT but the local constriction is more important, since calculated resistance values can increase by up to 500%. In experiments in unanesthetized dogs, the foregoing results are accompanied by an unexplained fall in oxygen saturation of arterial blood by about 10% (698). This might be related to bronchoconstriction, or to the increase in pulmonary blood flow exceeding the capacity of the capillaries to oxygenate completely the mixed venous blood, or to opening of arteriovenous shunts initiated by the rise in pulmonary arterial pressure. The corresponding observations in man reveal no rise in pulmonary arterial pressure following 1 μg/kg (594), but a rise following 1 mg total dose intravenously (36). It would be desirable to obtain measurements of cardiac output during prolonged infusion, particularly because 5-HT has been implicated as a cause of pulmonary hypertension during pulmonary embolization (157), metastasizing carcinoid tumor (811) and anaphylactic reaction (821).

3. Adenosine triphosphate (ATP) and its probable liberation. Emmelin and Feldberg (261) observed pulmonary arterial hypertension in cats when ATP was injected into the jugular vein, but not when equal amounts were injected into the left atrium. Although blood flow was not measured, these observations

can be regarded as evidence for a local constrictor action, particularly since perfusion experiments in cats (315) and rats (350) have provided confirmation. Davies *et al.* (206) reported stimulation of respiratory and cardiac rates following intravenous injections of the same substance in human subjects, but pulmonary circulatory measurements are still lacking. A rise in pulmonary arterial pressure has been observed following the injection of adenosine monophosphate but a reduction has also been encountered (570).

The pulmonary circulatory effects of ATP are important because the lungs have been suspected of inactivating this substance when it is liberated during traumatic shock (81, 437). Furthermore, it is believed to be present in stored plasma (332) and hemolyzed erythrocytes (80, 219) so that the pulmonary hypertension resulting from the injections of a number of hemolytic agents may actually be due to ATP.

4. Hypertonic solutions. Binet and Burstein (82, 83) noted that the intravenous injection of 20% sodium chloride solution caused pulmonary arterial hypertension but systemic shock in dogs. Eliakim and his collaborators (257) have recently confirmed these observations, and have also observed a conspicuous rise in pulmonary venous pressure and no change in left atrial pressure. The pulmonary venous constriction suggested by all these measurements affords a mechanism by which toxic substances, such as hypertonic solutions, may be trapped in the lungs temporarily. The heart is therefore protected from a high concentration of the salts which potentially can depress the myocardium (67).

5. Bacterial toxins. The endotoxin derived from *Escherichia coli* has been shown to elicit pulmonary arterial hypertension and systemic shock in anesthetized dogs and cats (487). Several other observations indicate that the pulmonary hypertension is due primarily to pulmonary vasoconstriction, namely: a) cardiac output measured by the dye dilution technic is reduced, at least in dogs (819), b) pulmonary hypertension still occurs if the volume of blood reaching the right atrium and ventricle is kept constant by a pump (487), and c) excised lungs perfused at a constant flow still respond by an increase in pulmonary arterial pressure following the injection of endotoxin (487). The constriction of the perfused lung vessels is accompanied by an increase in weight of the lungs and by an increase in venous resistance, greater than that of arterial [calculated on the basis of wedged arterial and wedged venous pressures (487)]. This special type of constriction by endotoxin can be elicited only if heparinized whole blood is used for perfusion but is absent if either gelatin or dextran solution is used (417). Unlike serotonin, endotoxin is dependent on some component of whole blood for pulmonary vasoconstriction, but the identity of the constituent remains unknown. Toxins of *Meningococci* (249) and of *Clostridium oedematiens* (481) depress the heart and systemic blood pressure but their corresponding actions on lung vessels are not yet known.

B. Histamine and related substances

Although the investigation of the pulmonary vascular effects of histamine preceded by several years the study of 5-hydroxytryptamine and adenosine

triphosphate, confusion still prevails regarding the nature and significance of the pulmonary vasoconstriction by histamine. The release of histamine from the lungs is more certain than that of the other two substances. The use of antihistaminic drugs has completed the pharmacological details regarding histamine action, but has also confused the interpretation as to the exact role of histamine in the formation of pulmonary edema.

1. Pulmonary vasoconstriction by histamine. The constrictor action of histamine on the lung vessels was first suspected by Abe in 1920 (2) who noted that the systemic shock brought about by its intravenous injection was accompanied by a rise in pulmonary arterial pressure. This observation has been repeatedly encountered in dogs (226, 230, 309, 536, 848), rabbits (226), cats (54, 226, 260), and guinea pigs (284). An attempt to elicit a similar response in 5 human subjects failed to show any effect of histamine in a dose (0.55 mg total) that caused systemic hypotension (594). This should not be interpreted to mean a lack of action on lung vessels because of species difference. It is probable that the primary effect of histamine on the human lung may be balanced by the outcome of its action on the heart and systemic vessels. The extent of the complexity of hemodynamic effect of histamine can be judged from other types of animal experiments.

The most direct evidence offered for a local constriction of the lung vessels by histamine consists of perfusion experiments of the lungs of dogs (14, 194, 315), cats (315, 597), rats (292) and monkeys (186). Three sets of observations are worth noting because they indicate the site of constriction initiated by histamine. Gaddum and Holtz (315) noted by perfusion that both arterial constriction and venous constriction occurred. Daly *et al.* (194) observed an almost proportionate constriction whether the lungs were perfused the normal way (via artery) or the reversed way (via veins). As far as the extrapulmonary portions of the vessels are concerned, Okada (603) and Smith and Coxe (741) demonstrated a greater sensitivity of the pulmonary veins than of the pulmonary artery. It is unfortunate that none of the technics introduced recently, which have successfully demonstrated a greater sensitivity of the venous side of the intact lungs for 5-HT, has been applied to the identification of the site of vasoconstriction of histamine.

2. Other effects of histamine. The fact that histamine constricts bronchiolar smooth muscle has introduced the possibility that bronchospasm may contribute to the increase in pulmonary vascular resistance. In addition to the results on excised vessels, a number of other observations do not support this suspicion. a) The intravenous injection of histamine in guinea pigs causes pulmonary hypertension that may not necessarily be accompanied by bronchoconstriction (284). b) Intrapulmonary arterial injection into dog lungs elicits a rise in arterial perfusion pressure but no detectable bronchoconstriction (14). c) Intrabronchial arterial injections into the same perfused lungs (14) cause bronchoconstriction but no rise in pulmonary arterial pressure. The inhalation of histamine in aerosol form into one lung of rabbits has been shown to reduce oxygen uptake of the same lung (223) but this cannot be entirely due to bronchoconstriction inasmuch as the participation of pulmonary venular constriction has not yet been excluded

(625). Tsuji has even postulated that bronchoconstriction can be reflexly initiated by vascular effects of histamine (786), but direct confirmation is lacking.

The peripheral vascular and cardiac effects of histamine are worth noting, because in the intact dog the intravenous dose of histamine that will cause a rise in pulmonary arterial pressure will always initiate systemic hypotension. The indirect outcome of systemic vasodilatation may take one or more of several alternatives. Friedberg *et al.* (309) postulated an increase in venous return and an increase in pulmonary blood flow which would contribute to the pulmonary hypertension, but direct proof of this effect is surprisingly absent. The left atrial pressure may rise sufficiently to cause a retrograde increase in pulmonary arterial pressure (93, 553) but there are also reports indicating a reduction (260, 536). Failure of the heart and systemic circulation with a reduction in pulmonary blood flow has been demonstrated to be a cause of pulmonary hypotension (757, 848). Comparison of the sensitivities of all the above mechanisms remains to be elucidated.

3. Role of histamine and antihistaminics in the formation of pulmonary edema. The complexity of the pulmonary circulatory effect of histamine, combined with the complexity of the pathogenesis of pulmonary edema, has accounted for the lack of unanimity regarding the role of histamine in the formation of pulmonary edema. On the affirmative side are the observations that the injection of histamine causes pulmonary congestion and edema in guinea pigs (445, 662) and rabbits (472). Furthermore, histamine potentiates the formation of edema induced by intravenous injection of epinephrine in rabbits (46, 47, 49). On the other hand, in the same species, histamine failed to produce edema even after direct pulmonary arterial injections (152).

The differences in results derived from various animal species extend to the use of antihistaminic drugs. Phenothazine (RP-3277; Phenergan) prevented edema in rabbits induced by epinephrine (384), phosgene (385), bilateral vagotomy (4) and intracisternal injection of fibrin (176, 177). Contrariwise, the same antihistaminic drug failed to prevent epinephrine edema in rabbits (755). In rats and guinea pigs, success against oxygen-induced edema (366) and failure against ammonium-induced edema (840) have been encountered. A similar situation exists for other antihistaminic drugs, including chlorprophenpyridamine (Chlor-Trimeton) (496,606), mepyramine (Pyranisamine) (177, 755), and Antergan (N-benzyl-N′, N′-dimethyl-N-phenylethylenediamine) (179, 366).

The primary effects of the various antihistaminic drugs on lung vessels, independent of their participation in the formation of pulmonary edema, are not completely known. The pulmonary vasoconstrictor effects of histamine are claimed to be either blocked completely (68, 223, 558) or not at all (387, 800). At least one of these drugs, diphenhydramine, has been shown to elicit a local pulmonary vasoconstriction (700) but it is not yet known if other members behave similarly.

4. "Histaminergic nerves" to the lungs. One of the most attractive of the theories that have been proposed regarding the ultimate function of histamine in the lungs is that it is liberated by sympathetic nerves. This suggestion is based on the

detection of histamine in the pulmonary sympathetic nerves (270) and on the collection of histamine in the lung perfusate or in the circulating blood as a result of injection of epinephrine (466) and of intracranial electrical excitation (632). The ultimate effect of such a liberation is believed to be an increase in permeability of the lungs resulting in pulmonary edema.

Ungar *et al.* (793) postulated that the "histaminergic nerves" reach the lungs via their sympathetic innervation but actually originate from the posterior roots of the phrenic nerve. Since this was based entirely on pathological changes in the lungs, application of physiological methods is necessary for confirmation.

At the present time attempts to confirm most of the evidence supporting the existence of "histaminergic nerves" have failed. Stimulation of nerves (549), the injection of epinephrine (549) and intracranial excitation (441) failed to show the liberation of histamine. It is possible that the instantaneous inactivation of the released histamine can account for the difficulty in detection. Two compounds that liberate histamine have been shown to cause pulmonary hypertension and edema similar to that of histamine: horse serum (126, 239) and pumice stone (247). Substances which have been shown to liberate histamine and initiate pulmonary edema, but with which pulmonary pressure changes are not known include ammonia (320), ammonium chloride (440), tubocurarine (644, 665), and chloropicrin (778). Finally, there are substances that have been shown to liberate histamine without producing pulmonary edema: diphtheria toxoid (785), ovalbumin (107, 446, 682), cobra venom (277), compound 48/80 (278), trypsin (660, 680, 681), estradiol (784) and protamine (746).

C. Pulmonary vasoconstrictors and edema

The next group of vasoconstrictors act on lung vessels without the liberation of substances from the blood (ATP and 5-HT) or from the lung tissue (histamine). The justification for placing them in this category is not based on negative evidence, *i.e.*, not on the failure of these compounds to liberate 5-HT, ATP and histamine, because this information is not yet available. The assumption of their direct action on the lung vessels is based on either of two types of information: a) When the substances were administered by inhalation, pathological changes occurred in the lungs, chiefly pulmonary edema. b) When the compounds were administered into the blood reaching the lungs exclusively, they caused pulmonary hypertension or edema or both. The common feature is the production of pulmonary edema most probably by a local action on the lung vessels; compounds that have been shown to produce pulmonary edema by primary actions on the heart, systemic vessels or autonomic nervous system have been excluded. On the other hand, the substances belonging to category a), administered by inhalation, may initiate edema not only by local action on the lungs but also by other mechanisms which will be discussed briefly.

1. Excess oxygen. The inhalation of 60% or more of oxygen for a few hours or several days has been shown to be fatal in guinea pigs (3, 77, 346, 409, 513, 639), rats (97, 346, 513, 627, 663), mice (77, 513), pigeons (77), rabbits (513, 627), cats (627), and dogs (65, 513). The conspicuous changes in the lungs consist

of increase in weight, atelectasis, fibrinoid necrosis, congestion and edema. The hemodynamic events preceding the formation of edema are not known, chiefly because of difficulties in measuring pressures and flow in smaller animals in which this stimulus has been largely studied. At least four mechanisms have been invoked in explaining the edema of high oxygen. Direct irritant action on the pulmonary capillaries has been the favored explanation (483) for some time until the recent introduction of three others. Penrod (627) believes that the development of simple atelectasis during oxygen inhalation is the primary mechanism initiating the edema and congestion. Bean and Johnson (61) showed that epinephrine injection prior to oxygen exposure enhanced the adverse effects of the latter on the lungs whereas adrenalectomy reduced the effects. The increased activity of the sympathetic nervous system during hyperoxic edema has been suggested by the observations that procaine (346), phenoxybenzamine (Dibenzyline) (327), phentolamine (628), or chlorpromazine (58) prevented edema formation. Bean and his collaborators (57, 59, 60, 63) have studied the additional role of hypophyseal, adrenocortical and thyroidal factors in potentiating the formation of this type of edema but elucidation as to how the hormones initiate edema is not complete. All of these observations do not necessarily exclude a local constrictor action of high oxygen tension on the lung vessels. This effect is plausible particularly because low tension of oxygen has been shown to cause local pulmonary vasodilatation (see section II-E1).

2. Excess carbon dioxide. The capacity of inhalation of 15 to 25% carbon dioxide in oxygen to induce pulmonary edema in mice has been reported by Poulsen (645). The exact mechanism for the formation of edema is not clear. Poulsen postulates that the accompanying bronchoconstriction is the major cause but the local action of hypercapnia on the lung vessels requires some consideration. Unfortunately, the local vascular effects are not certain (633). Local constriction has been shown in perfused lungs of cats (240, 523, 597, 598, 599) and dogs (62, 78, 96, 240, 244, 556, 820). The inhalation of up to 30% carbon dioxide in intact dogs, with or without anesthesia, produces either no increase in pulmonary vascular resistance (764) or an actual fall (588). In human subjects, the behavior of pulmonary arterial pressure is variable during hypercapnia (304, 828, 527). The situation of hypercapnia is similar to that of anoxia in which its local effects on the lung vessels occur simultaneously with its cardiac and systemic effects. This adds to the difficulty in assessing the relative importance of local vasoconstriction and bronchoconstriction in the causation of pulmonary edema.

3. Inhalation of phosgene and other irritant gases. Numerous observations have been made which suggest that the pulmonary edema of phosgene inhalation is due to effects in the lung parenchyma. Histological examination of lungs from gassed dogs shows intravascular clotting, alveolar thickening and swelling of the bronchial mucosa (155, 246, 782). Since unilateral gassing does not initiate edema in the contralateral side, the formation of a circulating "pneumotoxin" can be dismissed (782). Finally, edema can be produced in perfused lungs so that extrapulmonary factors can be excluded (37, 193, 403).

The exact mechanism of the action of phosgene in the lung parenchyma has

not been identified. Pulmonary vasoconstriction, similar to that of alloxan (see III-C4) has not been ascertained. On the contrary, Gibbon *et al.* (328) found no increase in pulmonary arterial pressure in phosgenized cats. In the perfused lungs of dogs, a rise in perfusion pressure is observed but it is difficult to attribute the rise to local vasoconstriction since bronchoconstriction is a conspicuous accompaniment (37, 193, 403). The bronchospasm must be considered a local response because it can be elicited not only in isolated lungs but also in animals following vagotomy or atropinization (113). It is of course impossible to exclude a primary increase in capillary permeability which will bring about increased lymphatic drainage from the lung and high protein content of edema fluid (134). As long as hemodynamic factors have not been completely excluded, it is not necessary to blame edema formation on changes in capillary permeability.

The following inhalants have been reported to cause pulmonary edema in human subjects or animals: ammonia (37, 428, 571), carbon monoxide (363), nitric oxide (290, 571), carbon tetrachloride (373, 489, 791), trichloroethylene (39, 807), methylene chloride (432), vinyl propionate (91), sulfur dioxide (16, 184, 624) and tetranitromethane (463). The occurrence of local pulmonary vasoconstriction has not been tested. Such substances are entirely toxicological in nature but the following agents are therapeutic agents, not ordinarily inhaled, and have been shown to produce pulmonary edema when administered intratracheally in animals: penicillin (316), erythromycin (725), streptomycin (137, 559) and para-aminosalicylic acid (559). This may contribute to the failure of these antibiotics in some cases of pneumonia and bronchopneumonia.

4. Alloxan and other compounds administered parenterally. The major shortcoming in the elucidation of edema produced by inhalants (like phosgene) is that the route of administration makes it inevitable that bronchoconstriction may reasonably be suspected to be the cause of the pulmonary vascular changes. This has been overcome by parenteral administration and the best prototype is alloxan. In the course of investigating its diabetogenic action, Peralta (629) first described the production of pulmonary edema in cats. The effect has been confirmed by others in cats (172, 430) and in dogs (28).

The immediate pulmonary vascular effect of intravenous injection of alloxan in the anesthetized dog is manifested as a pulmonary arterial hypertension (28). This occurs at a time when cardiac output is not increased, and when capillary blood volume in the lungs is reduced. In about ten minutes, the pulmonary hypertension is less intense but capillary blood volume is increased and this is followed by the onset of pulmonary edema (28, 31). A similar sequence is observed in the perfused lungs (28, 367), and these changes have been interpreted in the following manner. Alloxan causes an immediate generalized vasoconstriction of the lung vessels, but after about ten minutes, a postcapillary or venous constriction persists which can account for the capillary congestion and edema (28). It is not known if the high protein content of the edema fluid, which implies an increase in capillary permeability, is due to a primary action of alloxan or is simply an unavoidable outcome of the congested capillaries.

The pulmonary edema that follows the administration of alpha-naphthyl-

thiourea is more complex than that of alloxan (575, 835). Drinker and Hardenbergh (238) demonstrated an increase in lymphatic flow from the lungs during the development of edema, but its ultimate cause is not clear. Halmagyi and his collaborators (376) failed to show pulmonary hypertension but this is contrary to the results derived from perfused lungs, which show pulmonary vasoconstriction similar to that of alloxan (21). The latter appears to be a more dependable tool than thioureas (367) in producing pulmonary edema in dogs. Alpha-naphthylthiourea, like other thioureas, excites the central and sympathetic nervous systems (467). Thiosemicarbazide possesses similar actions (775).

Several compounds have been shown to produce vasoconstriction in perfused lungs: polypeptides (128), lysolecithin (92), peptone (69), iodoacetamide (367) and oxyphenarsine (367). The similarity of their site of vasoconstriction to that of alloxan requires elucidation.

D. Sympathomimetic pulmonary vasoconstrictors

The earlier literature on the pulmonary effects of epinephrine has been reviewed by Daly (185) and Wiggers (831). Subsequent studies have largely confirmed the ability of many sympathomimetic amines to either constrict or dilate the lung vessels. Only those that constrict and bring about pulmonary arterial hypertension will be discussed in this section.

1. Epinephrine. The demonstration of local vasoconstriction by epinephrine is based largely on lung perfusion experiments in dogs (29, 127, 195, 251, 315, 600, 765), cats (597), monkeys (186), rabbits (101, 268), rats (292) and guinea pigs (181, 186). Dilatation has been encountered in some preparations (186, 292, 315, 599, 635). The bronchodilatation has been used as an explanation for reduction in resistance when it is encountered (599) but excised pulmonary vessels are still able to dilate as well as constrict to epinephrine (306, 602, 741). The blood volume change that accompanies increased resistance is usually a decrease (315, 765), which indicates precapillary or capillary constriction, although an increase indicating postcapillary constriction has also been observed (331).

Lung perfusion has shown that like other excitatory smooth muscle actions of epinephrine, the constriction of the lung vessels is blocked by ergot alkaloids (101, 597, 635, 636) and even reversal has been reported to occur (292, 306). Interference with vasoconstriction has also been reported for piperoxan [compound 933 F; 2-(1-piperidylmethyl-1:4-benzodioxan)] (127) and Dibenamine (597). Sensitization by cocaine (127) completes the list of pharmacological similarities between epinephrine action on pulmonary and that on systemic vessels.

One possible manifestation of local vasoconstriction by epinephrine in the intact lung is the rise in pulmonary arterial pressure when this amine is injected intravenously. This has been noted in dogs (225, 447, 468, 600, 804), cats (54, 225, 329), and rabbits (322). The local effects on the lungs are difficult to segregate from other actions of epinephrine which individually can give rise to pul-

monary arterial hypertension. The other actions are as follows: primary increase in venous return resulting from the peripheral actions of epinephrine (329); increased cardiac output by cardiac stimulation (29, 667); and relative failure of the left ventricle with rise in left atrial pressure (225, 390, 804) partly due to bradycardia (447). The behavior of left atrial pressure is variable, and a decrease has been reported (600). The gradient from pulmonary artery to wedged artery is either unchanged (468) or reduced (804) but calculation of pulmonary vascular resistance for the entire vascular bed shows an increase, at least in the cat (54). The local effect on resistance is probably antagonized by the passive effect of changes in pressure. The end-result as far as oxygenation of the blood is concerned is a reduction in oxygen content of blood leaving the lungs. García Ramos and Rudomin (322) have detected this in dogs and rabbits and have regarded it as independent of the increase in blood flow induced by epinephrine. When administering epinephrine to one lung of rabbits by aerosol, Dirken and Heemstra (221) noted a reduction in oxygen uptake. These facts indicate that the local constriction by epinephrine involves the vessels intimately related to the alveolar capillaries. Angiocardiopneumography (144) in the same species also shows the disappearance of the pulmonary veins, suggesting arteriolar constriction by epinephrine.

The hemodynamic picture derived from human subjects confirms the results with epinephrine in animals described above. Intramuscular or intravenous injection usually causes a rise in pulmonary arterial pressure amounting to 25 to 75% in normal subjects (295, 337, 833, 841), as well as in patients suffering from chronic pulmonary hypertension (841), bronchial asthma (856), and systemic hypertension (295, 337). The inhalation of epinephrine aerosols by normal and emphysematous subjects causes pulmonary hypertension (15). Cardiac output is usually increased by epinephrine (15, 337, 544, 751, 841). The calculations of pulmonary total vascular resistance, or of arterial resistance (based on the gradient from pulmonary arterial pressure to wedged arterial pressure) show either an increase or decrease ranging from -50 to $+60$%. The increase in flow with increase in resistance which sometimes occurs can be accepted as presumptive evidence that local vasoconstriction can be induced by epinephrine. On the other hand, a reduction in resistance may not necessarily mean the occurrence of active dilatation since it may simply be the effect of increased cardiac output.

The literature on the causation of pulmonary edema by epinephrine has been intentionally omitted because this has been covered by Visscher *et al.* in their recent review article (803). The influences of the several drugs on the formation of edema by epinephrine are briefly mentioned throughout this article.

2. Levarterenol. The effects of levarterenol (*l*-norepinephrine) are similar to those of epinephrine in the isolated lung preparation. Vasoconstriction has been observed in the perfused lungs of dogs (93, 194, 331, 478, 687), cats (597), and sheep (789). Konzett and Hebb (478) noted a reduction in volume of blood in the lungs and this has been confirmed by Daly (198). In the intact dog, the pulmonary arterial pressure is increased (29, 52, 159, 305, 536, 589, 729), but

pulmonary blood volume is either increased (729) or decreased (536). Nahas and MacDonald (587, 589) noted that the rise in pulmonary arterial pressure occurs immediately after intravenous injection, and is actually accompanied by a reduction in pulmonary venous pressure, at a time when the heart rate has not started to accelerate. When the heart rate increases, then the cardiac output is augmented (299, 334, 508), an occurrence which is related to the positive inotropic and chronotropic actions of levarterenol (162, 336, 416, 528, 827). Reduction in output has been reported with doses smaller than that causing increase in output, and this is probably due to reflex cardiac slowing overcoming the cardiac stimulant action (20, 153, 201, 211).

Pulmonary arterial hypertension following intravenous infusion of levarterenol has been repeatedly encountered in man (295, 768). Cardiac output is usually decreased by as much as 25%; when this happens, the accompanying hypertension may be accounted for by other factors (38, 337). Since pulmonary wedged arterial pressure may also be increased (301, 593), the gradient from pulmonary artery to wedged artery may actually remain unchanged. There are, however, some subjects (620) in whom the gradient is increased but output is unchanged; in these pulmonary arterial constriction can be deduced. The behavior of the pulmonary venous side is unknown. This side is probably less active, if animal experiments are considered. The development of pulmonary edema when levarterenol is used to treat myocardial shock has been reported (520, 781). Left atrial pressure will potentially rise if the damaged heart cannot adjust to the systemic pressor action of this powerful sympathomimetic amine.

3. Epinine, tyramine, tuaminoheptane and metaraminol. In the anesthetized dog, epinine, tyramine and tuaminoheptane (Tuamine) induce pulmonary arterial hypertension in a manner similar to that of epinephrine: local pulmonary vasoconstriction (29, 195, 335) and increased pulmonary blood flow (29). The latter is primarily due to increase in myocardial contractile force, as shown by Jackson (438) and by Goldberg and his collaborators (336). Metaraminol (Aramine) has been reported to cause an increase in pulmonary arterial pressure in dogs (29, 272) but an increase in pulmonary blood flow is not a dependable cause. Cardiac output is either increased (85, 710), unchanged (521) or variable (29). In spite of this, calculated pulmonary vascular resistance is usually increased in the intact dog (29) and human subject (521). Confirmation has been derived from the perfused lungs which show vasoconstriction (29, 94).

4. Phenylephrine. This amine is different from the above-mentioned sympathomimetic agents because it causes local pulmonary vasoconstriction (29) but consistently reduces cardiac output in dogs (29, 429). The outcome is therefore a variable effect on pulmonary blood pressure (29) and pulmonary edema (670) depending on the combined consequence of both actions. It is surprising that hemodynamic measurements in man are not available for this widely used pressor amine.

5. Hydroxyamphetamine, pholedrine, ephedrine and naphazoline. The pulmonary arterial hypertensive action of hydroxyamphetamine (Paredrine) in unanesthetized dogs was noted by Friedberg *et al.* (309). The major cause for this

hypertension is the increased pulmonary blood flow and its local action on the lung vessels is unimportant (29). Pholedrine has essentially similar actions (29, 122). Ephedrine and naphazoline (Privine) cause hypertension predominantly by increasing pulmonary blood flow but larger doses are likely to depress the heart and would result in unpredictable behavior of pulmonary venous and arterial pressures (29, 32, 173, 601, 619, 700, 813, 814). The remaining sympathomimetic drugs are discussed under the section of vasodilators (IV-C).

E. Significance of pulmonary vasoconstriction by drugs

The various agents described in this section have the following common features. They are capable of constricting perfused lung vessels. In the intact animal, these agents cause pulmonary arterial hypertension, predominantly but not exclusively by inducing pulmonary vasoconstriction. The information regarding their hemodynamic effects in man is limited to epinephrine and levarterenol, both of which cause increases in calculated pulmonary vascular resistance, and an increase (for epinephrine) and decrease or no change (for levarterenol) of cardiac output. The corresponding effects in man of 5-HT, ATP, histamine, alloxan and other compounds producing pulmonary edema are uncertain, chiefly because their administration would be hazardous.

The list of pulmonary vasoconstrictors becomes more interesting if the actions of the individual members on the systemic circulation are considered. Epinephrine and levarterenol constrict systemic and pulmonary vessels, but the large doses necessary to induce constriction of the perfused lung imply that these vessels are less sensitive than the systemic components. In the intact anesthetized dog, the minimal dose of such amines that will cause a rise in systemic blood pressure does not always cause a significant rise in pulmonary pressure. On the other hand, suprathreshold doses of either amine will cause a more conspicuous and more prolonged rise in pulmonary arterial pressure, particularly if the vagi have been cut or atropine has been given. The systemic circulation has sensitive buffer mechanisms (carotid and aortic pressoreceptors) that will hasten the recovery from the pressure rise, but a corresponding mechanism for the pulmonary system has not yet been identified.

Although epinephrine and levarterenol have a constrictor action on the pulmonary vessels, similar to but less powerful than on the systemic, the other vasoconstrictors are diversified. Serotonin and alloxan can constrict both beds but the pulmonary is more sensitive than the systemic. Histamine usually dilates the systemic but constricts the pulmonary vessels. On the other hand, posterior pituitary extract is a systemic vasoconstrictor but is a weak one for the lungs (see section V-B1). The similarities and differences become more complex if the individual components of the various beds of the systemic circulation (the coronary, cerebral, renal, splanchnic and limbs) are compared with the various components of the pulmonary, *i.e.*, the arteries, capillaries, veins, shunts and bronchopulmonary anastomoses. It is hoped that future experiments will identify the site of vasoconstriction more intimately than simply stating that a drug can induce pulmonary vasoconstriction.

The phenomenon of vasoconstriction induced by drugs raises a question as to the possibility of limiting right ventricular output by intense pulmonary vasoconstriction. Reid has postulated that 5-HT can kill cats in such a manner, but the ability of the right ventricle to compensate should also be considered. This will be discussed in detail below (section V-A2). Suffice it to mention now that unless a drug depresses directly the heart muscle, the heart can largely overcome obstruction to blood flow in the lungs.

IV. DRUGS REDUCING PULMONARY HYPERTENSION PREDOMINANTLY BY VASODILATATION

Before proceeding to discuss the pulmonary vasodilators, it is necessary to characterize the pulmonary circulation in patients with chronic lung disease because these drugs have been investigated largely in such patients. The most outstanding feature is that muscular exercise causes a significant rise in pulmonary arterial pressure in such patients. While cardiac output may increase by as much as 75% of resting values, pulmonary arterial pressure may even double in value, and calculated pulmonary total vascular resistance is usually increased. These observations are based on patients with pulmonary hypertension of varied etiology (120, 653, 806, 823) including pulmonary emphysema (412, 579, 605, 674, 675), bronchiectasis (735) and postpneumonectomy (170). Unlike normal subjects in whom muscular exercise usually causes a reduction in resistance (see section II-C2), diseased lungs are less distensible and become more susceptible to an increase in pressure during exercise, although the increase in output is less intense.

The inhalation of mixtures containing low oxygen causes effects among patients with lung disease that are similar to those encountered among normal subjects. The pulmonary arterial mean pressure rises, the pressure gradient from pulmonary artery to wedged artery rises, cardiac output increases by as much as 50% but pulmonary total vascular resistance may decrease by as much as 35 to 100% (215, 233, 289, 585, 735, 850). This is an indication that diseased lungs probably maintain to some extent all the hemodynamic features of normal lungs. If the pulmonary hypertensive drugs were tried in such patients, hypertension and vasoconstriction would be expected to occur.

There is some evidence that anoxemia contributes to the pulmonary hypertension in patients suffering from lung disease. The correction of anoxemia by inhalation of high oxygen causes a conspicuous reduction in pulmonary arterial pressure in most patients (217, 236, 289, 579, 756, 828, 837, 838). Since even when anoxemia is completely corrected the relief of hypertension is not absolute, other factors contribute to the pathological increase in vascular resistance. The local pulmonary vasodilators have been tried in the hope that the constriction resistant to oxygen inhalation can be partially if not completely reversed.

A. Aminophylline and other musculotropic vasodilators

Although aminophylline has been used for several decades as a bronchodilator, its pulmonary hypotensive action has been apparent only during the

past decade. Its shortcomings consist of its poor oral absorption, and the numerous other actions that accompany its pulmonary vasodilator and bronchodilator actions.

1. Aminophylline on perfused and intact lungs. The pulmonary vasodilator action of aminophylline has been documented by several reports derived from lung perfusion experiments (93, 657, 700). Quimby *et al.* (657) tested 40 other xanthines including theobromine and caffeine and found that all the compounds (including aminophylline) that dilated the lung vessels also dilated the vessels of the extremities of the dog. They could not find a compound that dilated exclusively the lung vessels.

In the intact dog, the minimal intravenous dose that will reduce pulmonary arterial pressure will also stimulate the contractile force of the heart as revealed by a strain gauge arch sutured to the ventricular surface. This appears to be a direct cardiac stimulation, similar to that encountered in the isolated heart preparation (398, 744) and accounts for most if not all of the observed increase in cardiac output not only in dogs (657, 717) but also in human subjects (55, 245, 298, 311, 439, 593, 654, 751, 826). Since aminophylline possesses a dual action consisting of cardiac stimulation and pulmonary vasodilatation, it is not surprising that pulmonary arterial pressure responds by an increase (309), no change (468) or a decrease (93, 700).

2. Aminophylline in pulmonary hypertension. In the presence of bronchial asthma, there is a reduction in pulmonary arterial pressure as well as in the pressure gradient between the artery and wedged artery (297, 719, 759, 855, 856). The output may increase by as much as 50%, and resistance is always reduced, but never exceeds −50%. It would be desirable to extend observations to other types of pulmonary hypertension to determine if the reduction in resistance seen among patients with bronchial asthma would hold true for other types of patients, and if the reduction would be even more conspicuous. The effect seen with aminophylline among asthmatics is usually no greater than the effect of oxygen inhalation.

The results derived from other subjects are helpful in understanding the nature of aminophylline action. In several groups of patients with mitral stenosis (245, 759) or with other cardiac disease (compensated) (593, 826), the pressure gradient between artery and wedged artery was usually decreased, cardiac output was variable, but arterial resistance was consistently decreased. Patients in congestive heart failure are affected in a similar manner except that the output is usually increased (298, 311, 439, 826). The reduction in arterial resistance in all such patients can be safely interpreted to mean arterial dilatation by aminophylline for a number of reasons: a) the percentage reduction in resistance is greater than that encountered during muscular exercise; b) the passive effect on resistance induced by increased output may occur in some patients but output is not always increased; and c) aminophylline has been shown to dilate perfused lungs. Correlation of all available and related information forces one to conclude that aminophylline is a pulmonary vasodilator.

3. Papaverine. Papaverine studies are limited almost entirely to animals.

The perfused lungs indicate vasodilatation when papaverine is injected (700). There are no measurements of cardiac output available but this is probably variable and secondary to a potential cardiac depressant action seen in the heart-lung preparation (700), a reduction in venous return due to peripheral dilatation (788) and a reflex tachycardia as a result of transient systemic hypotension (309). Angiographic observations show either a reduction (459) or an increase (444) in the extent of the pulmonary vascular bed. There are scattered reports of relief of spasm of embolized lungs by papaverine (100, 213, 229, 422, 770).

4. Nitrites. Although sodium nitrite and amyl nitrite cause dilatation of perfused lungs, the effects of both and of nitroglycerin on excised pulmonary vessels are variable (54, 526, 550, 685). If there is any local dilatation in the intact lungs, this is often not apparent because in dogs, the inhalation of amyl nitrite (309, 390), and the intravenous injection of either nitroglycerin (525) or sodium nitrite (380) have varied effects on pulmonary arterial pressure. In human subjects, the pulmonary hemodynamic effects of sodium nitrite are known. Halmagyi and his collaborators (380) report a reduction in systolic pulmonary arterial pressure with increase in cardiac output among patients with mitral stenosis and left heart failure. The reduction in pulmonary arterial pressure cannot be interpreted to mean active pulmonary vasodilatation because of the lack of measurements of wedged arterial or left atrial pressure. The sublingual administration of nitroglycerin caused a prompt reduction of pulmonary arterial and wedged arterial pressures but there were no accompanying measurements of flow (449, 582). Other studies have shown that all available nitrite preparations increase the output of the human heart, which is probably due to reflex excitation that accompanies a transient fall in systemic arterial pressure (751, 818, 854). A more complete hemodynamic study is necessary to prove the pulmonary vasodilator action of nitrites in man.

B. Acetylcholine and allied drugs

Although the dilator action of acetylcholine on the systemic vessels is certain, it is surprising that its effects on the lungs are confusing. It may be helpful at the outset to realize that this prototype of a parasympathomimetic drug also possesses nicotinic properties so that the varied actions are the outcome of excitation of the parasympathetic postganglionic neuroeffector junctions as well as of the sympathetic and parasympathetic ganglia.

1. Vasodilator action of acetylcholine. The results derived from human subjects have been consistently interpreted to mean pulmonary vasodilatation when acetylcholine is injected or infused directly into the pulmonary artery via a catheter. Cournand, Fritts, Harris and their collaborators (169, 312, 394) have presented two convincing facts: a) that unilateral injection causes an increase in blood flow in one lung that is rendered anoxic; and b) that pulmonary arterial injection causes a reduction in pulmonary arterial pressure when either one or both lungs are subjected to anoxia (12% oxygen). In the absence of anoxia, the pulmonary arterial injection of acetylcholine resulted in either a reduction or no

change in pulmonary arterial pressure (393). The infusion of acetylcholine reduced pulmonary arterial pressure in patients with mitral stenosis (745, 846) or chronic pulmonary hypertension (733, 845). Since cardiac output remained unchanged, the consistent reduction in calculated total or arterial resistance can be safely ascribed to local pulmonary vasodilatation.

The total amount of acetylcholine injected directly into the human pulmonary artery (1 to 1.5 mg) appeared to affect the lungs exclusively. This conclusion is based on the observations that heart rate and systemic blood pressure remained essentially unaltered. The site of pulmonary vasodilatation appeared to be proximal to the site of wedging of the catheter because the pressure gradient between pulmonary artery and wedged artery was reduced. The occasional rise of wedged arterial pressure indicates that the pulmonary venous side was not dilated and may have been constricted, but this will remain uncertain until the gradient between wedged artery and left atrium is directly measured during the injection of acetylcholine. Until this is settled, the use of acetylcholine in functionally assessing the entire pulmonary circulation will lead to confusing interpretations.

2. Miscellaneous actions of acetylcholine. The simple dilator action of acetylcholine described above becomes complex when other experiments are reviewed. In the anesthetized dog a reduction in pulmonary arterial pressure is encountered only if the dose of acetylcholine is large enough to slow the heart rate (139, 447, 452, 464). This fall is most probably due to a reduction in cardiac output, similar to that initiated by vagal stimulation. The accompanying response of the lung vessels is not known, although Rudolph (697) describes that when 5-HT is infused to increase pulmonary arterial pressure, the additional injection of acetylcholine brings about reversal of the constriction. The recent observations of García Ramos and Rudomin (322) include an increase in oxygen saturation of blood leaving the lungs, independent of reduction in cardiac output. This improvement in oxygenation is paradoxical because of the known bronchoconstrictor action of acetylcholine. If confirmed by subsequent experimentation, the improvement in blood oxygenation may indicate either constriction of arteriovenous shunts in the lungs, or an improvement in diffusion of oxygen in the pulmonary capillaries in a manner so far undiscovered.

The intravenous injection of acetylcholine in dogs, in doses not large enough to slow the heart rate, usually causes pulmonary hypertension (256, 309, 447, 448, 464, 468). A relative failure of the left side of the heart can be excluded because wedged arterial pressure is not regularly increased (448, 468). The peripheral vascular effect of acetylcholine is a more likely explanation, and this may in turn cause an increase in pulmonary blood flow by increasing venous return and/or reflexly accelerating the heart (309, 418, 447). The remaining possibilities are: a) that acetylcholine may cause bronchoconstriction so intense that there is a secondary increase in vascular resistance, and b) that acetylcholine may locally constrict the pulmonary vessels. Both possibilities have been demonstrated in the perfused lungs of dogs (62, 600, 765), monkeys (186), rabbits (268, 269), rats (292, 739), guinea pigs (181, 401, 739) and frogs (105, 456, 458).

Excised pulmonary veins have been shown to constrict more than excised pulmonary arteries (306, 600, 741). On the other hand, pulmonary vasodilatation has been reported by other investigators (93, 223, 293, 315, 636, 686).

The above discrepancies derived from the perfused lungs may be presently explained in the following manner. The vasodilatation can be regarded as the prototype of response to direct vagal excitation, either electrically (of the vagus nerve) or pharmacologically (by acetylcholine). The vasoconstriction may arise as a nicotinic action of acetylcholine on sympathetic ganglia located in the parenchyma of the excised lung, or as a secondary manifestation of bronchoconstriction. Acetylcholine has been detected in the perfusate of guinea pig lungs when the vagi were stimulated electrically (780). This initial observation would suffice to qualify the lung as an organ containing cholinoceptive areas which require further elucidation. The excitation of one may bring about pulmonary vasodilatation whereas the excitation of others may bring about vasoconstriction. It is also possible that although there is gross vasodilatation, the individual components may behave in opposite ways in a manner described under local effects of anoxia (section II-F5).

3. Methacholine, carbaminoylcholine and pilocarpine. It is surprising to note that methacholine has not been utilized as a comparable parasympathomimetic drug with negligible ganglion stimulant action, in contrast to acetylcholine which has nicotinic action. So far its use has been limited to the following instances. Methacholine injected in amounts that slowed heart rate caused a reduction in pressure gradient between the pulmonary artery and left atrium in anesthetized (139) and unanesthetized dogs (390). There was a rise in pulmonary arterial pressure in 10 patients with bronchial asthma during an attack precipitated by methacholine (856). In spite of its bronchoconstrictor action, this drug prevented the formation of pulmonary edema induced by inhalation of high levels of oxygen in mice (326). Pilocarpine caused a reduction in pulmonary arterial pressure in cats, probably because of its bradycardiac action (522). Carbaminoylcholine (carbachol) reduced perfusion pressure of cat lungs, indicating a dilator property (597).

4. Anticholinesterase agents. Physostigmine has been shown to potentiate almost all effects of acetylcholine described above (13, 181, 223, 269, 315, 401). Its reported ability to protect rabbits from developing pulmonary edema induced by epinephrine has been postulated by Bariéty and Kohler to be independent of its primary anticholinesterase action (44). Neostigmine has been reported to cause pulmonary edema in two cases of multiple sclerosis (6). Sarin and tetraethylpyrophosphate caused in dogs a reduction in pulmonary arterial pressure, accompanied by a reduction in pulmonary blood flow (199). Lung perfusion experiments indicated an increase in pulmonary vascular resistance, probably due to the accompanying bronchoconstrictor action (198, 203). In the guinea pig lung, a reduction in vascular resistance was the usual response (75). The situation with anticholinesterase agents is therefore as confusing as that of acetylcholine.

5. Atropine. Almost all of the pulmonary circulatory effects described for acetylcholine and vagal nerve stimulation are prevented by atropine (138, 181,

397). When atropine is administered alone to human subjects, the end-result on the pulmonary circulation varies with the situation. There is usually an increase in cardiac output coincident with cardiac acceleration (342, 544, 822), but this increase may be absent in normal subjects with tourniquets on the extremities to pool blood (822). Regardless of the change in cardiac output, the effect of atropine on pulmonary arterial pressure is either an increase (808) or decrease (1, 342). The reduction in pulmonary arterial pressure has been regarded as a clinically desirable pulmonary vasodilatation in patients with various lung diseases, particularly in pulmonary embolism (131, 581, 771). However, atropine failed to protect dogs from fatal starch embolization of the lungs (539). Perfused lung preparations show a local vasodilator action of atropine (700) but it is not possible to exclude a bronchodilator action. The varied effects on experimental pulmonary edema (48, 496, 648) are probably related to extensive parasympathetic blockade outside of the lungs.

C. Isoproterenol and other sympathomimetic vasodilators

The lung perfusion experiments that have been utilized to establish sympathomimetic vasoconstrictors have been extended to determine the ability of some amines to dilate the lung vessels. Since not all of the proven dilators cause bronchodilatation, a primary vascular action can be more easily accepted.

1. Isoproterenol. This is the most potent pulmonary vasodilator known on the basis of lung perfusion experiments (29, 198, 402, 456). In the intact animal or human subject, this dilatation may be masked by the concurrent increase in pulmonary blood flow associated with direct cardiac stimulation (29, 228, 460, 507, 568). When isoproterenol (Isuprel) is administered by inhalation in emphysematous patients, there is a reduction in pulmonary arterial pressure, partly arising from its bronchodilator action (121).

2. Methamphetamine and mephentermine. These two sympathomimetic amines are essentially similar to isoproterenol in the following respects: they dilate lung vessels (29) but increase cardiac output (29, 85). The pulmonary pressure is usually increased, indicating that blood flow changes are predominant (110, 163, 272, 593). Several other sympathomimetic derivatives that dilate pulmonary vessels and stimulate the heart have been described (29, 495, 562).

3. Methoxamine and its ethoxy derivative. It is conspicuous that the above sympathomimetic vasodilators are also capable of increasing pulmonary blood flow. Pulmonary hypotension can be induced by methoxamine (Vasoxyl) by reducing pulmonary blood flow but the local effects on the lung vessels are variable (29, 272). Its ethoxy derivative [compound 45-50; β-hydroxy-β-(2,5-diethoxyphenyl) isopropylamine] causes a similar reduction in pulmonary blood flow but is also able to dilate the perfused lung vessels in the dog (29) but not in the cat (40). Clinical trial in man reveals a powerful bradycardia response (519) but the pulmonary vascular resistance effects are still under investigation.

D. Tolazoline and other adrenergic blocking drugs

The individual adrenergic blocking drugs exhibit varied effects. Although all of them are generally known to block excitatory actions of epinephrine more

easily than those of sympathetic nerve stimulation, this generalization has not been tested on the lung vessels. It is also generally known that the adrenergic blocking drugs possess other actions on the heart and systemic vessels not related to their blocking action, and the lung vessels are not an exception.

1. Tolazoline. Dresdale *et al.* (235) initially described the ability of intravenously injected tolazoline to cause a significant fall in pulmonary arterial pressure in patients with pulmonary hypertension (see also 302, 552). A reduction in pulmonary arterial pressure was seen also in patients with mitral stenosis (323, 378, 552), congenital vascular anomalies (404), or chronic pulmonary hypertension (302, 699). It usually occurred with a simultaneous increase in cardiac output. This increase in output may account for the observations of either an increase (699) or no change (612) in pressure when tolazoline was injected in patients and in dogs (182, 613).

Reports of the pulmonary vascular resistance changes following tolazoline have varied (235, 302, 552, 699). The reduction in either total or arterial resistance which sometimes occurred cannot be interpreted to represent true dilatation of the pulmonary vessels because the accompanying increase in output may account for the observed reduction. The other patients with unchanged resistance, pressure and output are probably those in whom organic changes in the lung vessels were so extensive that dilatation by tolazoline was not possible. It would be interesting to subject such patients to a comparative study using other drugs, particularly aminophylline, acetylcholine and isoproterenol.

The basic explanation for the reduction in pulmonary arterial resistance by tolazoline is not known. Perfusion of dog lungs failed to show a local dilator action (685). There is a reduction of oxygen saturation of systemic arterial blood in patients with mitral stenosis receiving tolazoline (103). This observation might suggest dilatation of arteriovenous shunts, but other causes will have to be excluded, such as change in direction of flow in bronchopulmonary shunts and increase in flow to segments that are poorly ventilated. In patients with patent ductus arteriosus, tolazoline causes an improvement in blood oxygenation which may simply be a reflection of a favorable reduction in pulmonary hypertension brought about by the drug (524).

2. Dibenamine. Halmagyi and his collaborators observed that the intravenous injection of Dibenamine in anesthetized dogs (380) and in patients with congestive heart failure or mitral stenosis (377) caused a consistent reduction in pulmonary arterial pressure, with insignificant effect on cardiac output. Brod and Fejfar (108) reported that this drug increased output of a failing heart, not by direct cardiac stimulation but probably by release of abnormal vasoconstriction of systemic vessels resulting in an improved emptying of the decompensated left ventricle. The proof that this drug is a pulmonary vasodilator must await additional measurements of vascular resistance in man and in animals.

3. Dihydrogenated ergot alkaloids. Although the hydrogenated alkaloids have a negligible constrictor action on systemic vessels, they appear to have some action on lung vessels as well as the heart (344). The intravenous injection of hydergine in patients with mitral stenosis (552) or chronic pulmonary disease (378, 566)

causes no change in pulmonary arterial pressure or a slight fall. Since the fall occurs without any reduction in output (566), reduction in vascular resistance has been postulated. When dihydroergotamine is used, pulmonary arterial pressure increases (378). This indicates pulmonary vasoconstriction, similar to that encountered in cats (517), dogs (241, 468) and guinea pigs (739, 740).

4. Phentolamine, azapetine and piperoxan. Phentolamine (Regitine) causes a reduction in pulmonary arterial pressure in patients with either mitral stenosis (758) or pheochromocytoma (611) which is not due to any alteration in cardiac output. Piperoxan (Benzodioxane) causes a reduction in pressure but output values are unknown (593). Azapetine (Ilidar) reduces cardiac output in dogs but its pulmonary vascular effects are not known (506).

5. Protection against pulmonary edema. There is almost complete unanimity of opinion that adrenergic blocking drugs prevent certain types of experimental pulmonary edema. The fatal edema induced by epinephrine or levarterenol in rabbits, mice or guinea pigs is prevented by dihydrogenated ergot alkaloids (614, 646, 777, 853), phentolamine (5, 748) or Dibenamine (388). This can be regarded as suggestive of a complete antagonism between both types of drugs acting on the formation of edema. For the pulmonary hypertensive effect, the antagonism of epinephrine by either Dibenamine or dihydroergotamine has been demonstrated (386, 564), but corresponding information for other blocking drugs is not yet available.

Other types of experimental edema have been shown to be prevented or retarded by one or more of the blocking drugs: head trauma in mice (147); intracisternal injection of veratrine or fibrin in rabbits (175, 427); parenteral injection of ammonium salts in rats and guinea pigs (136, 383, 469); intravenous or intracarotid injection of saline in dogs (534); intrapulmonary arterial injection of graphite or starch suspension in dogs (132, 496); inhalation of carbon dioxide by mice (646); and inhalation of excess oxygen by rats (326, 450). All of these results indicate the participation of the sympathetic nervous system in the pathogenesis of the specified forms of edema. The blockade does not necessarily mean the sympathetic nerves to the lungs but can pertain to the innervation to the heart and systemic vessels. The practical implications of the above experiments are apparent from two reports. Harrison and Seward (395) reported the development of pulmonary edema during surgery in a latent case of pheochromocytoma, which could have been prevented by adrenergic blocking agents, if recognized. Wheatley (830) found that tolazoline relieved pulmonary edema secondary to acute left ventricular failure in two cases. Since the ultimate mechanisms for the precipitation of edema are not known, it is difficult to specify how adrenergic blocking drugs would help in therapy of pulmonary edema.

E. Ganglion blocking drugs

The growth of interest in ganglion blocking drugs initiated by Acheson and Moe has extended to the pulmonary circulation in two directions: a) to determine if there is any functional autonomic tone to the lung vessels that can be temporarily eliminated by ganglion blocking drugs; and b) to investigate the

potentialities of such drugs in the treatment of pulmonary hypertension. Since there are no important pharmacological differences among the various drugs, they will be discussed as a group.

1. Pulmonary and systemic normotensives. The behavior of the pulmonary circulation following the intravenous administration of ganglion blocking drugs has been variable. There is usually a reduction in pulmonary arterial pressure following the injection of hexamethonium (555, 659), tetraethylammonium (295, 300, 593), azamethonium (Pendiomid) (435) or pentapyrrolidinium (pentolinium) (555). This reduction in pressure is not dependent on the occurrence of a reduction in pulmonary blood flow. As a matter of fact, cardiac output is either increased or decreased (727, 795).

The observed reduction in pressure may be attributed in part to pulmonary vasodilatation on the basis of the following results (300, 659, 705). a) The reduction in pulmonary arterial mean pressure is also manifested, although not consistently, as a reduction in pressure gradient between artery and wedged artery. Hence reduction in left atrial pressure can be dismissed as the exclusive cause of the fall in arterial pressure. b) In most patients, the fall in pressure amounting to as much as 40% was accompanied by no change or even an increase of as much as 20% in cardiac output. c) The fall in pressure encountered in other patients was as much as 60% and was accompanied by a proportionately lesser reduction in blood flow, so that calculated resistance was reduced by as much as 40%. Unfortunately the pulmonary hypotensive and the supposed vasodilator actions are not always found in ganglion blocking drugs. There were some patients in whom pulmonary pressure was unchanged although output was reduced.

The fundamental question of the mechanism of the suggested pulmonary vasodilatation has not been answered in the above-mentioned results derived from normotensive subjects. Four additional sets of information have been helpful and these will now be discussed.

a. Consistent pulmonary hypotension in the head-down body-tilt position. Sancetta (705) studied 5 subjects and initially tilted them in the head down position. There was no significant alteration in cardiac output, but pulmonary arterial pressure and resistance were noted to increase. While this position was maintained, hexamethonium decreased pressure and resistance without changing cardiac output. Since wedged arterial pressure did not change, all these results can be assumed to mean pulmonary vasodilatation was brought about by ganglion blocking drugs.

b. Disappearance of pulmonary arterial overshoot consequent to Valsalva's maneuver. The release of a sustained high intrapulmonary pressure results in an overshoot of the systemic arterial as well as the pulmonary arterial pressure. The intravenous injection of tetraethylammonium abolishes this response. Greene and Bunnell (351) have interpreted this observation as an indication that the drug abolishes the active neurogenic vasoconstriction of the pulmonary vessels during the overshoot. Lee *et al.* (498) explained the pulmonary arterial overshoot by an observed rise in pulmonary capillary pressure and concluded

that the disappearance of the overshoot following the drug was due to the absence of the primary rise in wedged arterial pressure. The lack of direct measurements of pressure in the left atrium does not permit final interpretation.

c. Pulmonary hypotension in anesthetized dogs. One consistent response encountered in anesthetized dogs is a reduction in cardiac output following intravenous injection of any one of the following: tetraethylammonium (380, 381, 382, 641), hexamethonium (156, 178, 608, 766, 809), pentapyrrolidinium (750), azamethonium (468, 641, 774), chlorisondamine (783), and mecamylamine (561, 693). But the accompanying change in pulmonary arterial pressure has not always been a reduction. The most obvious explanation for the occasional rise in pulmonary arterial pressure is that this group of drugs can actually cause vasoconstriction of dog lungs either by ganglionic blockade of vasodilator nerves or by direct constriction of vascular smooth muscle. Appropriate lung perfusion experiments would be helpful in the identification of the exact cause but they should be performed with one precaution. Autonomic nerves that are resistant to ganglion blocking drugs have been shown to exist in the heart (615), the bronchioles (716) and the adrenals (149), and they may also exist in the pulmonary vessels. The interaction of blocking drugs with ganglion stimulants like nicotine and dimethylphenylpiperazinium (DMPP) has not been studied. This is necessary because nicotine has been shown to constrict the pulmonary vessels of intact cats (225), perfused rabbit lungs (70), and human lungs (321). There is some suggestive evidence that tetraethylammonium blocks the reflex spasm from one lobe to another (294, 678) yet anoxic effects on the lungs are not completely eliminated.

d. Pulmonary hypotension in patients with diseased lungs. Studies on patients have been more rewarding than animal studies in confirming the ability of ganglion blocking drugs to dilate pulmonary vessels. The limitations of such information will be discussed in the remainder of this section.

2. Systemic hypertension. As do normotensive individuals, patients with systemic hypertension usually manifest a fall in pulmonary arterial pressure following ganglionic blocking agents. This is the usual result following the intravenous injection of tetraethylammonium (310, 377, 593), hexamethonium (287, 307, 333, 364, 423, 671, 753, 760, 799, 825), pentapyrrolidinium (174, 743) and trimethaphan (Arfonad) (254). In the absence of cardiac failure, cardiac output is either unchanged or reduced. The reduction in cardiac output is not intense enough to account for the reduction in pulmonary arterial pressure, but may contribute to the increase in calculated vascular resistance. An increase in cardiac output is reported in patients with cardiac failure but calculated resistance is usually reduced (254). The mechanism for the increase in output of the heart in failure is regarded by Freis and his collaborators (307) in the following manner: The peripheral pooling of blood induced by ganglion blocking agents would act as a venesection, reducing the loading pressure of the congested right side of the heart and thereby facilitating its recovery. In addition to this, the blocking of systemic vasoconstrictor tone decreases the systemic peripheral resistance and allows improved emptying of the failing left ventricle. These

events serve to reduce cardiac output in the compensated hypertensive patients but to increase it in decompensated patients.

All the above facts suggest that ganglion blocking drugs may reduce pulmonary vascular resistance independently of changes in pulmonary blood flow. The ultimate reasons for the more usual occurrence of a reduction in pulmonary arterial pressure in systemic hypertensive patients, as compared to normotensives, are not known. The increased sensitivity of pulmonary vessels of the former to any form of vasodilation is the most probable explanation but has not yet been proven.

3. Mitral stenosis. Patients with mitral stenosis uniformly show a reduction in pulmonary arterial pressure following tetraethylammonium (377, 721), hexamethonium (35, 207, 453, 808, 852) and trimethaphan (499). Like the systemic hypertensive patients, the patients in this group show a variable effect on cardiac output, *i.e.*, an increase, no change or decrease. All calculations of pulmonary total and arterial vascular resistance show a definite reduction ranging from 10 to 75%. Since most of these patients show also a reduction in output, one can conclude that the reduction in resistance means pulmonary vasodilatation not secondary to a passive effect of flow.

The causes for the reduced pulmonary resistance are varied. Yu and his collaborators (852) consider two important factors, namely: a) that hexamethonium causes a reduction in left atrial pressure and left ventricular diastolic pressure and that this accounts for a reduction in all pressures in the pulmonary vessels; and b) that the extensive anastomotic connections from pulmonary vein to azygos vein via the bronchial veins are further dilated by the drug, so that left atrial pressure is reduced. The other groups of investigators regard the reduction in resistance as an indication of true pulmonary vasodilatation brought about by paralysis of the sympathetic nerve supply. This is supported by a reduction in calculated pulmonary arterial resistance (35, 721) which is interpreted to mean dilatation of the pulmonary arterioles. The reported relief of paroxysmal dyspnea (207) and the suggested application as a prognostic test for functional vasoconstriction prior to valvulotomy (721) illustrate the practical importance of obtaining more direct proof for the dilating action of ganglion blocking drugs in such patients.

4. Pulmonary hypertension. Patients who suffer from pulmonary arterial hypertension, either as a primary disease of the lung vessels, or secondary to involvement of the lung parenchyma, show a reduction in pulmonary arterial pressure following the administration of either hexamethonium (35, 302, 704, 705, 839) or tetraethylammonium (300). The calculation of pulmonary resistance shows either a decrease or an increase, so that one can conclude that the dilatation from ganglion blockade in pulmonary hypertension is not dependable. The diversified nature of the organic lesions in the lung may account for this diversity in response. Two other features of this group of drugs have added to the unsatisfactory outcome in the treatment of chronic pulmonary hypertension. The accompanying fall in systemic blood pressure is an undesirable accompaniment of the desired action in the lungs, particularly in acute embolism complicated by

systemic shock (843). Prolonged use has resulted in the development of fatal fibrinous pneumonitis (616, 631, 679, 802) and even acute pulmonary edema (542).

The basis for the use of ganglion blocking drugs in the treatment of clinical pulmonary embolism (421, 583, 610) is based largely on several animal experiments. The hypertension of acute embolization in animals is reduced by ganglion blocking drugs (132, 374, 574, 640, 714, 769). Bein (66) reported that the tachypnea of experimental embolism is abolished by azamethonium. This observation might be related to several others in patients which suggest that ganglion blocking drugs can also block sensory receptors in the lungs (7, 250, 352, 415).

5. Pulmonary edema. The experimental basis for the clinical use of ganglion blocking drugs in pulmonary edema consists of experiments in rabbits reporting relief of epinephrine-induced edema by hexamethonium (216, 368) or pentamethonium (51). Similar edema in dogs is not influenced by hexamethonium (465). Another type of pulmonary edema in dogs, induced by intracisternal injection of fibrin, is reported by Sarnoff and Sarnoff (713) to be relieved by trimethaphan. In rats, Halmagyi *et al.* (379) reported protection in various forms of edema by lobeline in doses large enough to exert its ganglion blocking action. Other investigators have reported protection in oxygen-induced edema (366, 450). These facts represent a small fraction of the confusion in the pathogenesis of pulmonary edema. The relief of pulmonary edema in man has been reported for tetraethylammonium (259, 414), hexamethonium (258, 259), trimethaphan (205, 259, 711) and azamethonium (796). The explanation offered for the effect is the reduction in pulmonary blood volume by shifting of blood from the lungs to the dilated peripheral vessels, and by the improved emptying of left ventricle. Direct proof of this widely accepted theory will depend on the development of quantitative assessment of edema in man.

F. Miscellaneous drugs for therapy of chronic pulmonary hypertension

The prototypes of pulmonary hypotensive drugs described in the above paragraphs are as follows: aminophylline, acetylcholine, isoproterenol, tolazoline and hexamethonium. The evidence for their hypotensive action is derived mostly from patients suffering from pulmonary hypertension. The studies that include measurements of cardiac output indicate that calculated pulmonary vascular resistance is usually reduced. The extent of the reduction in pressure and resistance is neither dependable nor remarkable. A reduction of 50% is rarely exceeded and there are some patients who actually show a slight increase in pressure. The increase may occur on account of direct stimulation of the heart rate and contractility by aminophylline, isoproterenol and tolazoline, or by acceleration of heart rate induced either reflexly by their systemic hypotensive action, or by blockade of cardioinhibitory innervation of the heart. An increase in venous return may also contribute to the augmentation of blood flow.

The mechanism for the reduction in vascular resistance in the lung is not certain for all drugs. Lung perfusion reveals vasodilatation for aminophylline

and isoproterenol but the actions of the others are still uncertain. It would be desirable to ascertain the extent of dilatation in the pulmonary vascular bed and the sensitivity of the pulmonary compared to that of the systemic bed. None of the prototypes spares the systemic circulation since all of them produce systemic hypotension. The ethoxy derivative of methoxamine (compound 45-50) is a sympathomimetic vasodilator for the lungs but a vasoconstrictor of the systemic bed. Preliminary trials in chronic pulmonary hypertensive patients by Fox (303) and Ross (691) have shown that the pulmonary hypotension is accompanied by severe bradycardia probably initiated by its systemic pressor action. A drug that can dilate exclusively the lung vessels and spare the heart and systemic vessels has not yet been discovered. Such a compound would not only be helpful clinically but would serve as a tool for investigating the hemodynamic effects of pure dilatation of a previously hypertensive lung. Would the capillaries be exposed to higher hydrostatic pressure in such a way that edema might develop? Would the reduction in pulmonary pressure protect the right side of the heart from developing cor pulmonale? Or would the right side of the heart fail in a manner similar to that encountered in pulmonary arteriovenous fistulas?

The other drugs that have been used in the therapy of pulmonary hypertension have been investigated less thoroughly and will be described briefly in the remainder of this section. Angelino and Levi (17) reported that the intravenous injection of *reserpine* in patients with mitral stenosis caused a reduction in pressure gradient between pulmonary artery and wedged artery. Since this was accompanied by either a slight increase or no change in cardiac output, it is safe to conclude that there is a significant reduction in arterial resistance that is initiated by arterial dilatation. The same conclusion has been confirmed by other investigators in patients with mitral stenosis (375, 720), sclerosis of the pulmonary artery (324) or pulmonary edema (604). The theory is that the reduction in pulmonary arterial pressure is due to blockade of nervous vasoconstriction by an action in the hypothalamus. Animal work has been limited to demonstration in dogs of a pulmonary hypotensive action (318) but central nervous excitation and pulmonary denervation experiments have not been performed.

Chlorpromazine in patients under cyclopropane anesthesia has been shown to reduce pulmonary arterial pressure (251). Bradshaw *et al.* (99) observed that the reduction of the pulmonary arterial pressure was more conspicuous than that of the systemic but there were no accompanying blood flow measurements. Since other investigators reported no reduction in cardiac output in man (265) and in dogs (563), the pulmonary hypotension can be interpreted to mean vasodilatation. Almost all of the remaining information pertains to the prevention by chlorpromazine of pulmonary edema induced by ammonium chloride (347), epinephrine (204), pure oxygen inhalation (365) and trauma to the chest (554). The protective action may be due to either its primary central blocking action or its adrenergic blockade.

The most consistent effect of *hydralazine* (Apresoline) in human subjects is a rise in cardiac output. The accompanying rise in pulmonary arterial pressure

seen in normal subjects (834), in systemic hypertensive patients (454, 753) and in patients with mitral stenosis (10), is probably the outcome of cardiac stimulation. Rowe and his collaborators (695, 696) described some systemic hypertensive patients who showed a reduction in pulmonary arterial pressure, in spite of an increased or unchanged output. Before this observation can be explained entirely on the basis of pulmonary vasodilatation by central blockade, it is important to determine if there is any reduction in left atrial pressure which may in turn cause a reduction in pulmonary arterial pressure.

The *veratrum alkaloids* cause a reduction in pulmonary arterial pressure (308, 426, 584) but this may simply be due to a reduction in cardiac output known to occur when these drugs are administered (33, 248, 426, 584). The effects of *sodium thiocyanate* in man are not known but measurements in dogs indicate a reduction in output but no change in pulmonary arterial pressure (33).

Several bronchodilators have been tried in patients with pulmonary hypertension. *Khellin*, orally or intramuscularly, caused no effect on pulmonary arterial pressure and output (145, 736) but slightly improved respiratory mechanics (690). Condorelli and his collaborators have reported that *nicotinic acid* can bring about subjective improvement in chronic lung diseases but its exact mechanism of action is still uncertain (146, 154, 160, 370, 630, 701). *Cortisone* and *corticotropin* have been used to relieve dyspnea of chronic lung disease (104, 141, 234, 722, 747). These hormones have been shown to protect animals from chronic lung damage (112), acute bronchospasm (275) and acute pulmonary edema (72, 642, 723). *Trypsin* solution has been administered by inhalation (273, 371) but its intramuscular (737) and intravenous administration (677, 734) are more dangerous. *Sparteine* has been administered by inhalation in bronchial asthmatics with some success (794).

Since almost all of the drugs tried for pulmonary hypertension were introduced for the drug therapy of systemic hypertension, it is pertinent to discuss the vascular effects of angiotonin and renin. In human subjects (295, 593), dogs (309), and cats (668), these two substances caused a small but significant rise in pulmonary arterial pressure, but simultaneous measurement of output was not performed. Their local vascular action is still obscure.

V. DRUGS WITH PREDOMINANTLY CARDIAC ACTION

The characteristics of the congested pulmonary circulation can be derived from a review of the effects of the usual types of stress in patients with heart disease. In those suffering from congestive heart failure and mitral stenosis, the response to the inhalation of low oxygen mixtures is like that of normal and pulmonary hypertensive subjects: increases in pulmonary arterial pressure, flow and resistance (233, 849, 850). There is some suggestive evidence derived from patients (494) as well as dogs (389) with mitral stenotic lesions that anoxia causes an increase in shunting of blood through arteriovenous shunts in the lungs, so that the extent of systemic arterial anoxemia is greater than that expected from the reduction of oxygen content of inspired air. When pure oxygen is administered to patients with cardiac disease, there is a consistent

reduction in pulmonary arterial pressure due largely to a reduction in vascular resistance (540).

Muscular exercise in patients with mitral stenosis, but compensated, causes a rise in pressure, flow and resistance (18, 161, 342, 412, 653, 706, 823). Patients in congestive heart failure show a reduction in cardiac output with an increase in pulmonary resistance (412, 511). These facts indicate that the pulmonary circulation of patients with diseased hearts can respond to either muscular exercise or anoxia by a further increase or decrease in flow, but only a further increase of pressure and resistance. In the section on pulmonary hypotensive drugs (IV), it was mentioned that patients with mitral stenosis do react to aminophylline, acetylcholine, reserpine and hexamethonium in such a way that a reduction in pressure and resistance is possible.

The drugs in this section exemplify the effects of either stimulation or depression of the heart, normal or otherwise. It should be stated at the outset that these actions are the predominant ones and the local pulmonary vascular effects are still uncertain.

A. Digitalis glycosides

It would be ideal to precede the discussion of digitalis glycosides with a complete description of the interrelationships between the heart and lungs. This is not possible because important aspects are not settled, particularly the existence of reflexes arising from cardiac receptors and affecting pulmonary vasomotor tone. The rise in left atrial pressure in patients with mitral stenosis has been suspected by Dexter and his associates to initiate a reflex pulmonary vasoconstriction [see monograph by Caini for references (133)]. Stretch receptors in the cardiac wall that can be activated by improved myocardial contractions induced by drugs have been shown to induce reflex effects on the systemic circulation but the efferent effects to the pulmonary circulation have not been considered (23, 27).

The consequences of cardiac stimulation that are nonreflex in nature are more certain. If venous return to the right side of the heart is unlimited, an increase in cardiac output and a passive reduction in pulmonary vascular resistance occur (section II-C2). When the reduction in resistance is limited by cardiopulmonary disease, an increase in resistance may accompany the increase in pulmonary blood flow. Finally, if both sides of the heart are unequally depressed and a cardiac stimulant like digitalis improves the function of the depressed side, the consequences are surprising. The effects of digitalis will be presented as they are modified by the preexisting condition of the heart.

1. Congestive heart failure. The primary action of the digitalis glycosides on the failing heart is manifested as an increase in cardiac output. This is the general finding in patients suffering from primary left ventricular failure secondary to systemic hypertension and/or arteriosclerotic heart disease, following the administration of each of the following digitalis preparations: digitalis leaf (252, 253, 754); digoxin (9, 56, 123, 252, 280, 399, 400, 431, 847); lanatoside C (311, 488, 752, 799); strophanthin (84); ouabain (9, 89); thevetin (479);

and acetylstrophanthidin (851). Although most patients receiving digitalis show an increase in cardiac output ranging from +10 to +80% of control level, a few isolated instances of reduction in output of as much as 25% have been reported (56, 89).

The blood pressure in the pulmonary artery does not passively follow the change in cardiac output. With a few exceptions, the increase in pulmonary blood flow is accompanied by a fall in pulmonary arterial mean pressure or in right ventricular systolic pressure by as much as 50% of control level. The lack of any rise in pressure and certainly its fall during a period of increased pulmonary blood flow indicates a reduction in pulmonary total vascular resistance ranging from 15 to 75%.

The explanation for the reduction in pulmonary arterial pressure is believed to be an improvement of the emptying of the left ventricle, reduction in left atrial pressure and reduction of congestion in the pulmonary vessels (56, 165, 400). This is a valid assumption because the subjective improvement of dyspnea and the reduction in right atrial and peripheral venous pressures all point to an improvement in functional activity of the left ventricle (400). Before this explanation can be accepted as a fact, it will be necessary to measure left atrial pressure by direct catheterization. If pulmonary arterial wedged pressure is regarded to mean left atrial pressure, the results derived from 6 patients show a reduction in pulmonary arterial resistance. Hence a number of other probable explanations remain, namely: a) that the digitalis glycosides are capable of dilating the pulmonary vessels; b) that the reduction in left atrial pressure has inactivated the pulmonary vasoconstrictor reflex from the left atrium; and c) that the increase in vagal tone brought about by digitalis extends to dilate pulmonary vessels. Experiments using the heart-lung preparation (118, 812) and intact animals in heart failure (728) have contributed to the understanding of the effects of digitalis on the heart and systemic vessels. Extension of such experiments to include pulmonary vascular measurements would be helpful. It is surprising to note that local effects of digitalis glycosides on lungs are unknown. Independent perfusion of the systemic and pulmonary systems has been utilized to investigate the systemic effects of digitalis (787). Excised pulmonary arteries show slight constriction (550). In the dog, the pulmonary arterial pressure changes have been variable (600, 609, 790).

2. Pulmonary hypertension and cor pulmonale. The effects of digitalization in patients with cor pulmonale are more varied than those derived from patients with primary failure of the left ventricle. The available information can be grouped into three categories depending on the pattern and onset of change in cardiac output.

a. Immediate increase in cardiac output. An increase in cardiac output has been noted following the intravenous administration of digoxin (89, 123, 281, 400, 579), lanatoside C (349) and ouabain (89, 543, 856). Ouabain has been reported by McMichael (543) to cause a more significant increase in cardiac output than digoxin. The accompanying changes in pulmonary arterial and right ventricular systolic pressures are either unchanged or increased by as

much as 50%. The calculated resistance values ranging from −50 to +40%, are difficult to explain. Until left atrial or even wedged arterial pressure measurements become available, only the difference in calculated resistance resulting from digitalization of cor pulmonale patients from that of congestive heart failure can be noted.

Ferrer and his collaborators (281) call attention to the fact that the increase in cardiac output during digitalization in cor pulmonale is not as great as the increase in left ventricular failure (average increases of 18 and 39% respectively). They enumerate the probable reasons for the differences as follows: a) inequality of the two ventricles in muscle mass; b) differences in pressure-volume relationships of ventricles and of atria; and c) differences in limitation on output enforced by the systemic and pulmonary circulations. The interrelationship between the pulmonary circulation and the right ventricle during digitalization will be discussed under the next topic. If this factor limited the rise in output of the failing right ventricle, its exaggeration would be manifested as a fall in cardiac output.

b. Immediate decrease in cardiac output. This has been reported following digoxin (281, 399, 543, 545, 579) and ouabain (579). The exact cause for this reduction is not known. One important explanation is that the accompanying rise in pulmonary arterial pressure would impose a load on the distended right ventricle. A rise in peripheral venous pressure has been reported by Baum and his associates (53) in 4 out of 18 patients with cor pulmonale receiving acetylstrophanthidin, and by Gray and Gray (348) in 1 out of 9 patients receiving lanatoside C. Although this is presumptive evidence for lack of improvement in the emptying of the right ventricle, a rise in pulmonary arterial pressure is not the necessary cause.

The possibility that during digitalization, increasing pulmonary arterial pressure may decrease the output of the right ventricle can be dismissed by recent experiments of Davis *et al.* (208). Chronic progressive constriction of the main pulmonary artery in dogs induced the syndrome of right ventricular failure (ascites, edema of extremities). In 5 such dogs, the administration of digoxin caused a rise in cardiac output ranging from 11 to 70%. This can be used as evidence for the unlimited ability of digitalis to increase cardiac output even though the resistance beyond its outflow tract is fixed by ligation. Furthermore Selzer *et al.* (724) have shown that ouabain caused an acute increase in tolerance of the dog heart to pulmonary arterial constriction.

One alternative to explain the decrease in cardiac output, suggested by Baum and his co-workers, is that shunting of pulmonary venous blood to the bronchial veins and draining into the right atrium would mean an increase in right ventricular output but reduction of left ventricular output. The anatomical channels responsible for this shunting has been demonstrated by Liebow (514) but their functional participation during digitalization is not proven.

c. Delayed reduction in cardiac output. The remaining explanation for the immediate reduction in cardiac output is that it is caused by the same factors responsible for the delayed reduction in output. After 2 to 5 weeks of digoxin,

orally, there is a reduction in cardiac output ranging from 10 to 40% (281). Unlike the earlier response, this phase is accompanied by a reduction in pulmonary arterial pressure. The calculated resistance is variable, either unchanged or decreased. Ferrer *et al.* (281) have viewed the reduction in pulmonary arterial pressure as reflecting a diminution in distensibility of the diseased lung vessels, so that pressure becomes very sensitive to changes in flow. The roles of diminished anoxia and blood viscosity have not been evaluated.

The ultimate cause of the delayed reduced cardiac output (and possibly the early one, too) appears to be another unusual manifestation of digitalis action on the right ventricle. Ferrer *et al.* (281) have explained the changes in cardiac output in the following manner. The muscle fiber of the dilated right ventricle has been stretched beyond its optimal length so that when it is initially shortened, the immediate effects are increased systolic ejection and decreased residual volume (up the descending limb of Starling's curve). As the heart and circulation continue to improve, the ventricle is emptied more completely, the diastolic size is reduced and cardiac output is decreased (down the descending limb of Starling's curve). The effect of digitalis on the failing right ventricle is a combination of a decrease, similar to the behavior of a normal heart, and an increase, similar to behavior of a failing left ventricle. This explanation does not extend to include why digitalization causes an increase in patients suffering from congestive heart failure. If both ventricles fail there is a prolonged increase in cardiac output encountered even after three weeks of administration of digitalis leaf orally (253).

3. Mitral stenosis. Patients suffering from mitral stenosis have been investigated more thoroughly than others, with the additional measurement of wedged arterial pressure (115). Broustet *et al.* (111) encountered a significant reduction of this pressure following acetyldigitoxin in most (13 out of 15) patients. Yu and his collaborators encountered a reduction in all 4 patients following acetylstrophanthidin (851) whereas Gray and Gray (348) encountered a reduction following lanatoside C in 1 out of 5 patients. The discrepancy in incidence of the reduction in wedged arterial pressure by various groups may be due to differences in drugs, differences in severity of stenosis, and even inconsistencies in the validity of wedged arterial pressure as a measure of atrial pressure. If the reduction in wedged arterial pressure signifies a fall in left atrial pressure, its cause is not entirely an increase in left ventricular emptying, because cardiac output is not always increased after digitalization (111, 117). Broustet and his collaborators (111) regard the reduction in wedged arterial pressure as an indication of local dilatation of the lung vessels, at least distal to the wedged arteries, *i. e.*, the capillaries and pulmonary veins.

Calculation of pulmonary vascular resistance, based on the pressure gradient between the pulmonary artery and wedged artery suggests that digitalization causes dilatation of the precapillary area. Patients who show an increase in cardiac output show a reduction in pressure gradient (111, 348). A reduction in pulmonary arterial pressure with an increase in cardiac output has been reported by other investigators (280, 391, 824) but this cannot be interpreted to

mean pulmonary vasodilatation because the reduction in pulmonary arterial pressure may be entirely due to reduction in resistance on the outflow side of the lungs (pulmonary veins and/or left atrium). It is unfortunate that measurement of left atrial pressure has not been extended to the study of digitalis.

One important outcome of the pulmonary hemodynamic action of digitalis that may extend to the systemic bed is a decrease in oxygen saturation of the blood (111, 348). Gray and Gray (348) have discussed the possible explanation for the reduction in oxygen saturation of systemic arterial blood. They have considered that digitalis has increased the flow of blood through channels in the lungs inaccessible to ventilation, namely: poorly ventilated alveolar capillaries, pulmonary arteriovenous shunts, and reversed flow of blood from right atrium to left atrium through the pulmonary venous-bronchial venous anastomoses. Ventilatory changes were not sufficient to account for the reduction in blood oxygen saturation.

B. Cardiac depressants

The drugs listed in this section are characterized by one important feature: they affect the pulmonary circulation chiefly by depression of the heart muscle. Although this is the primary action, some of the drugs may have other secondary actions elsewhere which will in turn influence the pulmonary circulation (liberation of epinephrine, constriction or dilatation of the systemic vessels), and may even constrict or dilate the lung vessels directly. It is conspicuous that there is no example of a drug that exclusively depresses the heart muscle, except when the drug is administered directly into the coronary artery, or into the substance of the ventricular wall by needle puncture. Direct injections of ethyl alcohol (148), zinc hydroxide solution (569) and silver nitrate solution (151, 643) terminate in ventricular fibrillation, pulmonary edema or systemic shock. The unpredictable nature of the outcome renders the method difficult to use to answer one important question: What will exclusive failure of either the left or right ventricle do to the pulmonary circulation?

1. Pitressin. It is logical to start the list of cardiac depressants with pitressin, the most dependable known coronary vasoconstrictor. When this hormone is given intravenously, the local effect on the lungs does not appear to be important. Studies on lung perfusion indicate that it is a weak constrictor (212, 798) or a weak dilator (700) or ineffective (424, 685). The observed reduction in pulmonary arterial pressure appears to be entirely due to cardiac depression. The reduced output would cause a fall in mean pulmonary arterial pressure and this has been encountered in rabbits (144), anesthetized dogs (212), unanesthetized dogs (309) and human subjects (593). The pulmonary arterial pressure may rise also as a result of considerable increase in left atrial and wedged arterial pressures (804, 810). These measurements should be repeated when the drug is infused directly into a coronary vessel because the results would offer some interesting answers to the question raised above regarding the effect of pure failure of either ventricle.

2. Quinidine and procaine amide. The information on quinidine is limited to

patients with atrial fibrillation. The response consists of a reduction in pulmonary arterial pressure, increased output and reduction in calculated vascular resistance (282, 392, 399, 761, 694). It is difficult, however, to explain the reduction in resistance entirely on the basis of pulmonary vasodilatation for the following reason: there is marked improvement in cardiac emptying to account for the increase in cardiac output; hence unless left atrial pressure is known, it is possible that the reduction in pulmonary arterial pressure is passive. The improvement in ventricular function may be the outcome of reduction in aortic blood pressure by systemic dilatation by quinidine (282, 400) or of conversion of atrial fibrillation to normal sinus rhythm (393, 480, 761). The report of two cases of reduced output following oral quinidine (0.8 g) may be a manifestation of its potential depressant action on the heart muscle. The local effects of quinidine on the lungs are not known even in animals. Dixon and De (224) reported the effects of other derivatives of quinine, some of which cause pulmonary arterial hypertension in the cat, and cause spasm of isolated rings of pulmonary vein (more than the pulmonary artery) of the sheep.

The intravenous injection of procaine amide in human subjects consistently caused a reduction in pulmonary arterial pressure (538). This reduction cannot be interpreted to be the result of reduction in output because this may remain unchanged. It would be helpful to know if perfused lungs would confirm the dilator action that is suggested by measurements in man.

3. Cyclopropane. This inhalant anesthetic agent causes a reduction in cardiac output in human subjects (266, 497, 512, 621, 726, 779). The reduction cannot be explained by cyclopropane alone because cyclopropane was administered in combination with one or more of the following supplementary drugs: morphine, scopolamine, thiopental, nitrous oxide and curare. In dogs, it is possible to use cyclopropane in oxygen alone and the effect is a slight increase in cardiac output (361). The potential depressant action on the dog heart was revealed by a reduction in output when cyclopropane was added to thiopental (359).

The observed reduction in pulmonary blood flow in anesthetized patients is overshadowed by a considerable increase in pulmonary vascular resistance ranging from 75 to 280%, resulting in a significant rise in pulmonary arterial pressure (266). This increase in resistance is not dependent on accumulation of carbon dioxide because it remains even after the addition of controlled respiration (267). There is no available information on its effect on the perfused lung, chiefly because of its explosion hazard when administered by respiratory pump.

4. Ether. The inhalation of ether to the stage of surgical anesthesia (stage III, plane 2 or 3) caused an increase in calculated pulmonary vascular resistance in almost all (11 out of 12) patients studied (451). This increase in resistance appeared to be an indication of pulmonary vasoconstriction because the cardiac output changes were variable. Among 4 patients with decreased output, 3 showed an increase in pulmonary arterial pressure. Pressure was increased proportionally more than flow in 3 other patients, whereas flow was unchanged but pressure was increased in 4.

The variable effect on pulmonary blood flow was encountered in human subjects by Johnson (451) utilizing the Fick principle and the dye dilution method, and by Fletcher *et al.* (291) by the latter technic. The reduction in output was more frequently encountered during deep anesthesia, and this was accompanied by a reduction in intrathoracic blood volume. Most of the measurements in dogs indicated an increase in output using the Fick method (11, 88), the pulse contour method (669) or indicator dilution by the cuvette oximeter (362). The rise in output measured by the last method was conspicuously greater if ether was combined with cyclopropane, as compared to cyclopropane alone (360). Brewster *et al.* (106) explained the variable effect on output by ether as due to the combination of the following: a) release of adrenal medullary hormones which would increase output, and b) direct depression of the heart muscle by ether. [The latter has been documented by various technics which have been recently reviewed by Faulconer and Patrick (274).]

It is surprising that the local action of ether on isolated lungs has not been thoroughly investigated. The local effects on the smooth muscle of the bronchioles and blood vessels are not known. The reduction in movement of the ciliated epithelium reported by Ernst (262) may be an indication of surface narcosis but behavior of the smooth muscle can be expected to be either spasm or paralysis. Injury to the lung may be manifested by the liberation of histamine (462) and if ether is mixed with peroxides, by the development of pulmonary edema (762). In the absence of peroxides, ether appears to relieve experimental pulmonary edema provoked by trauma to the brain in rats (551) and guinea pigs (490) and by inhalation of 20% carbon dioxide in mice (647). These effects have been attributed to different mechanisms: paralysis of the sympathetic nervous system by ether in the former case, and a release of bronchoconstriction in the latter. These proposed mechanisms are not based on facts, indicating that ether can affect either; the lung vessels may respond directly to ether but the results in human subjects indicate a hypertensive response which would preclude improvement of pulmonary edema.

5. Barbiturates. The usual effect of anesthetic doses of various barbiturates in human subjects is a reduction in cardiac output, whether the Fick principle (451) or the indicator dilution technic (227, 255, 264, 285, 451) is utilized. With the latter, there is the additional observation of a reduction in pulmonary blood volume which is related to the reduction in output, and also to the peripheral vasodilator action of the drug, resulting in pooling of blood. This reduction in pulmonary blood flow and volume is unaffected by the supplementary use of curare (451), oxygen inhalation (451), or nitrous oxide inhalation (255, 285). In dogs, although pentobarbital results in a reduction in output (608, 669), thiopental, hexobarbital, Kemithal [5-allyl-5-(2-cyclohexenyl)-2-thiobarbituric acid] and Thiamylal [5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid] all cause increased cardiac output (353, 357, 358). There appears to be a difference in effect of thiopental between man and dogs.

The effect on pulmonary arterial pressure is limited to the use of hypnotic doses of sodium amytal (593) and anesthetic doses of Narkatol [5-(2-bromoallyl)-

methyl 5-isopropyl barbituric acid] (451). There was a significant fall in pressure in 2 but no change in 3, and an overall increase in resistance in all of 5 patients studied. The fact that output may be reduced and yet pressure may remain unchanged indicates that the cause of increased resistance may be partly a local constricting action by this particular barbiturate compound on the lung vessels.

The perfusion experiments of Sai show that some barbiturates dilate lung vessels (70). Kohler and Barbe (471) have shown that intravenous injections of Somnifene (diethylammonium salt of barbital and of 5-allyl-5-isopropyl-barbituric acid) cause pulmonary edema in rabbits. This type of experimental edema is not prevented by compounds that inhibit the central nervous depressant action of barbiturates such as strychnine (473, 474) and succinic acid (475). It is augmented by curarizing agents (50), sympatholytic drugs (45) or atropine (470). These additional facts render the barbiturate-induced edema unique among other experimental types, and its ultimate mechanism remains obscure. The effects of other barbiturates are not known: phenobarbital has been shown to protect against saline edema in rabbits (537). Inkley *et al.* (436) reported 2 cases of primary pulmonary hypertension in which death followed the administration of secobarbital (75 mg) and sodium thiopental (amount unspecified). They attribute these deaths not to respiratory depression but to systemic shock caused by an unknown mechanism.

6. Morphine and miscellaneous depressants. There is no available information on the pulmonary hemodynamic effect of morphine alone in human subjects. The use of morphine combined with scopolamine did not alter cardiac output and pulmonary arterial pressure in 6 subjects, and it reduced output only in 1 subject (451). In dogs, morphine, when used alone, does not affect Fick output (772) but appears to reduce mean output values if it is administered before cyclopropane (355), sodium thiopental (354) and ether (356).

The use of morphine in patients suffering from cor pulmonale has been considered dangerous. Samuelsson (703) reports 14 deaths following the use of ordinary therapeutic doses. The exact causes for such deaths are not known and might be a manifestation of either the potential cardiac depressant action of morphine and other opiates, or of its pulmonary hypertensive action as reported in patients with mitral stenosis (276).

The depressant action of morphine on portions of the central nervous system has been utilized by Luisada (529) to explain its beneficial action in clinical and experimental pulmonary edema. Morphine prevents the development of epinephrine-induced edema in rabbits (41, 476) and carbon dioxide provoked edema in mice (646). Although the protective action is believed to be due to depression of the respiratory center, the motor cortex and even the hypothalamus, it is difficult to exclude effects of morphine elsewhere.

There are other compounds that influence the pulmonary circulation by depression of cardiac function. The intravenous injection of *chloroform* in dogs causes a rise in right atrial pressures but a fall of pulmonary and systemic pressures (565). *Emetine* reduces pulmonary arterial pressure in the dog largely

by cardiac depression (263). The injection of *ammonium salts* in cats causes marked elevation of left atrial pressure and finally pulmonary edema (712). This is not necessarily a sign of cardiac depression, particularly because the intravenous injection of another cardiac depressant, *procaine*, can prevent pulmonary edema in rats (345) as well as in dogs (496). The basis for the use of intravenous injection of procaine to stop hemoptysis remains uncertain (286).

C. Miscellaneous drugs for therapy of acute pulmonary edema

The pharmacological aspects of pulmonary edema have been mentioned briefly in scattered portions of this article. No attempt will be made to discuss fully its pathogenesis except to call attention to a unique mechanism inherent in the lung vessels that can lead to pulmonary edema. It has been shown by indirect measurements of capillary blood volume and vascular resistance of dog lungs that alloxan initially can cause constriction of the entire pulmonary vascular bed, which subsequently persists as constriction of the venous side and terminates in pulmonary edema (section III-C4). Other procedures have been shown to constrict pulmonary veins and the list now includes inhalation of low oxygen (section II-F5), injection of hypertonic salt solution (section III-A4), injection of endotoxin (section III-A5), blast injury to the lungs (150), and the inhalation of steam (26). The last procedure causes venous constriction in a manner probably unrelated to the rise in blood temperature. Although reduction in blood temperature causes a reduction in pulmonary arterial pressure, the most important effect is a reduction in cardiac output (484, 485, 486, 546, 638, 650, 731). Galletti *et al.* (317) described an immediate constriction when blood temperature of the perfused lungs was reduced, and a dilatation when it was increased. This is another example illustrating the difficulties in interpreting results when the same stimulus is applied using various technics. The different results (venous constriction if heat is inhaled but dilatation if blood temperature is increased) may be due simply to the manner of changing temperature (inhaled or via blood). The clinical trial of hypothermia is suggested by the observation that low body temperature protects rabbits from pulmonary edema induced by epinephrine (557).

From the practical standpoint, it would be desirable to determine whether pulmonary edema encountered clinically arises partly from venous constriction. If so, the vasodilators might be helpful, assuming that the pulmonary veins can be dilated. Even if all these conditions were met, it would still be essential to develop an objective quantitative method of assessing pulmonary edema in man before one could safely conclude that a pulmonary vasodilator drug reverses edema.

When pulmonary edema arises from acute left ventricular failure, a number of procedures have been reported to improve cardiac function [see refs. cited by review article (30)]. The use of digitalis has been recommended by several groups. In rabbits and rats, prophylactic digitalization did not prevent edema induced by epinephrine, chloroform or chlorine (776). Gorlin and Robin (343) described 4 edematous patients who improved following the administration of ouabain. Calcium gluconate has been recommended in patients who have not

received digitalis (369). The mercurial diuretics have been reported to increase output but to reduce pulmonary arterial pressure (457, 715). The administration of thiamine in a case of beriberi heart disease caused a reduction in output but the accompanying rise in pulmonary arterial pressure is difficult to explain (491). It is possible that this may be related to the ability of thiamine to sensitize rabbits to edema formation (43).

An improvement in cardiac function has been reported following venesection and pooling of blood in the extremities. The induction of spinal anesthesia causes a reduction in pulmonary blood pressure predominantly by reduction in circulating blood volume (451). In human subjects, sedation by phenothiazine also causes a reduction in pulmonary arterial pressure (749) but all sedatives should not be regarded as safe since Avertin (tribromethanol) has been shown to exaggerate edema in animals (477).

Gas exchange in the edematous lung can be improved by the application of intermittent positive pressure breathing (578). A number of antifoaming agents have been used: ethyl alcohol (124, 210, 338, 339, 340, 535, 829), silicone (34) and 2-ethyl hexanol (664). Their clinical use has been based on a considerable number of experiments which show the relief of edema induced by epinephrine (42, 531 532, 595, 622, 652, 689), phosgene (622, 655) and chloropicrin (655). These antifoaming agents must be used cautiously because intratracheal injection of ethyl alcohol causes acute pulmonary edema, pneumonia and bronchiolitis obliterans in the rabbit (576). Compounds with vitamin P activity have been claimed to protect rabbits from pulmonary edema induced by epinephrine (180) and chloropicrin (573). A similar effect has been described for ascorbic acid (560, 792), riboflavin (220), prednisone (649) and hyaluronidase (325, 656). The results of their clinical use have been difficult to interpret.

VI. CONCLUDING REMARKS

The investigation of any single drug has not yet reached the extent of the available information on the pulmonary circulatory effects of anoxia. Since the latter is pertinent to an understanding of drug-sensitive mechanisms, the review of the drugs has been preceded by a lengthy analysis of anoxia (section II). It is conspicuous that the use of drugs in general has not contributed much to the understanding of the basic mechanisms involved during anoxia. In man, the pulmonary hypertensive response to anoxia is either unchanged or slightly reduced by the previous administration of the following drugs: barbiturates (as anesthetics) (451), aminophylline (765), tolazoline (235), trimethaphan (182) and hexamethonium (453). Likewise in animals, the pulmonary hypertensive response to anoxia is resistant to general anesthesia (96, 502), adrenergic blocking drugs (425, 522) and ganglion blocking drugs (405, 567, 637, 801). All these results are an indication that anoxia indeed causes pulmonary hypertension by numerous mechanisms, and that no single drug can block all such mechanisms.

The questions raised in the introduction have not been categorically answered in this article. The reader can probably formulate a different set of questions; but the particular questions that will now be discussed were formu-

lated because their answers exemplify the state of available information on the pharmacology of the lung vessels.

The explanation for the different effects on pulmonary arterial pressure induced by closely related drugs can be safely answered in the following manner. The pulmonary arterial pressure is a reflection of primary changes in blood flow and vascular resistance. There are sufficient available data for drugs to be characterized not only in terms of what they do to the pulmonary arterial pressure, but also in terms of their effects on pulmonary blood flow and vascular resistance. The information on vasoconstrictor drugs is summarized in section III, and on vasodilator drugs in section IV. The drugs with predominantly cardiac actions (section V) have uncertain effects on the lung vessels. The sympathomimetic group of drugs illustrates how this question can be answered in a specific way. Although epinephrine and methoxamine are both systemic pressor amines, epinephrine usually causes a rise in pulmonary arterial pressure because of its local pulmonary vasoconstrictor and cardiac stimulant actions, whereas methoxamine is more likely to cause a fall because it does not cause pulmonary vasoconstriction and usually reduces pulmonary blood flow. Epinephrine and isoproterenol are both able to stimulate the heart but the latter can cause pulmonary arterial hypotension because of its pulmonary vasodilator action. The ultimate cause for the difference in local action on lung vessels by drugs with minor differences in chemical structure can be answered only after basic mechanisms of constriction and dilatation of any vascular smooth muscle are defined.

It is difficult to explain why the same drug elicits opposite results when tested in man and animal species, and when tested in the same species using different technics. Again, there is abundant information but there is no general agreement. The methods applied to human subjects suffer from the difficulty in identification of basic mechanisms. Mechanisms have been studied in animals usually by using preparations that are remote from the intact state. The results from both extremes should be correlated. Although it would be simple to ignore one set of results, the writer does not approve of this course and firmly believes that the controversial situations should be clearly and completely stated. Their resolution must await further investigation, particularly of the type that will introduce new methods of assessing the function of the lung circulation. Such methods cannot be predicted. If one were to review once more some recent events, one would desire another technical discovery similar in influence to that of cardiac catheterization.

The final question of the desirability or undesirability of drug action on the lung cannot be answered at all because necessary information is still lacking. The exact sites of constriction and dilatation require identification. There is suggestive evidence that the pulmonary veins and the arteriovenous anastomoses can respond to chemical agents but more direct proof is necessary before the possible consequences of such actions on gas exchange can be realized. It would be desirable to reduce pulmonary hypertension, but the extent of improvement possible by available drugs has not been dramatic to the extent that this clinical

problem has been resolved. It has been possible to reduce hypertension in some cases but others have been resistant. The available drugs are not selective enough because they also alter cardiac and systemic vascular functions. Inasmuch as there are some close similarities between the pharmacology of the systemic and that of the pulmonary circulation, a breakthrough in the drug therapy of essential hypertension would be expected to extend to the drug therapy of pulmonary hypertension. The sequence may, of course, be reversed if interest in the pulmonary circulation continues to increase as it has in recent years.

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