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THE AUTONOMIC NERVOUS SYSTEM IN ITS RELATION TO SOME FORMS OF HEART AND LUNG DISEASE*

II. LUNG DISEASE

BY

RAYMOND DALEY, M.D., F.R.C.P.

Physician to the Cardiac Department, St. Thomas's Hospital; Consulting Physician to the Chelsea Group of Hospitals

In this lecture the significance of the autonomic nerve supply to the lung vasculature is discussed. As in my first lecture, I believe that it is appropriate to begin with a description of the anatomy. For this I am indebted to the excellent monograph by Mitchell (1956).

The lung vessels are supplied by sympathetic and parasympathetic fibres which are woven into plexuses and carry efferent and afferent fibres. The sympathetic fibres arise in the second to the fifth or sixth thoracic ganglia. They run mainly to the posterior pulmonary plexus, which lies in the posterior part of the hilar regions and also contains vagal fibres which are distributed to the vessels, bronchi, and glands of the lungs. This sympathetic supply contains afferent and efferent fibres. The preganglionic fibres are the axons of the cells in the lateral columns of grey matter. They form synapses in the corresponding sympathetic ganglia or in the stellate ganglion. The post-ganglionic fibres are the axons of the ganglionic cells. The afferent fibres have their cell stations in the dorsal root ganglia of the upper five or six thoracic spinal nerves.

Preganglionic vagal fibres arise in the dorsal vagal nuclei. Afferent vagal fibres have their cell stations in the inferior vagal ganglia. Above the lung roots each vagus nerve divides and surrounds the root, forming a large posterior and a smaller anterior plexus. Below the roots there is union with sympathetic fibres from the oesophageal plexus and with vagal fibres from the opposite side. The lung vasculature is mainly supplied via the posterior pulmonary plexus which receives direct or indirect contributions from the upper thoracic sympathetic ganglia.

The autonomic nervous supply to the various lung vessels varies greatly in its richness. It is probable that the small bronchial arteries have the best supply, the pulmonary arteries are less well supplied, and the pulmonary veins are very poorly innervated. It has been remarked by many authors how generally poor the whole pulmonary vessel innervation is, especially when compared with the autonomic supply to the systemic vasculature.

There is no marked plexus formation round the pulmonary vessels, the nerves only winding round them and giving off branches at irregular intervals. Cookson

(1953) has demonstrated frequent intercommunication by small bundles of fibres between the perivascular and peribronchial nerves, and he also showed, by special silver and methylene-blue stains, that there are comparatively few fibres around pulmonary capillaries.

Pulmonary Vasomotor Responses

Study of pulmonary vasomotor responses has been intense, producing at times definite results of great interest and at others results which are conflicting and confusing. Much of the work has been carried out on animals which are often in a most unphysiological state when anaesthetized, with bilateral thoracotomies or even as isolated heart-lung preparations. The translation of the results of such experiments to human behaviour may be most misleading. Another difficulty is the lack of appreciation of the important difference between nerve stimulation and ablation procedures. However, much fundamental knowledge has arisen from these experiments, and great credit must be given to the perfection of cardiac and pulmonary vascular catheterization by Cournand and Ranges in 1941 and the following years. It is hardly out of place to stress again the difference between the high-pressure systemic vascular system and the low-pressure pulmonary circulation with its relatively poor nervous supply. The interdependence of one circulation upon the other is becoming increasingly obvious, and stresses the importance of knowing the blood flow, pressure, heart rate, and the blood oxygen and carbon dioxide tensions before drawing firm conclusions.

The evidence which has been collected concerning these problems involves a discussion of the control of pulmonary arteriolar resistance, the control of pulmonary capillary permeability, and the effects of drugs on the pulmonary circulation. The action of various agents and procedures may be directly on the pulmonary circulation (the so-called active effect); it may be secondary to changes in the systemic circulation (the passive effect); or changes in the composition of inspired air or bronchomotor tone may influence pressure and flow in the pulmonary circulation.

Pulmonary Embolism

From time to time there have been a few reports of improvement in the condition of patients suffering from pulmonary embolism by various autonomic-nerve-blocking procedures. In the investigative field reports have covered investigations in several species of animals, in various normal and abnormal conditions. The results have been conflicting. On the one hand, Daly *et al.* (1948) in a series of scrupulous experiments in perfused lungs, has shown that stimulation of the middle cervical ganglion and the stellate and upper thoracic

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sympathetic ganglia increased pulmonary arterial blood pressure by vasoconstriction. He took particular care to preserve the bronchial arterial supply, and stressed the importance and difference of his preparations from those of others. On the other hand, in intact animals and man it is generally believed that mechanical rather than autonomic factors play a far more significant part in the control of pulmonary blood flow and pulmonary arterial pressure.

Is there a Generalized Pulmonary Vasoconstriction Following Localized Pulmonary Embolism?

Six dogs were anaesthetized. In each dog two cardiac catheters were passed, one into the main pulmonary artery, and the other into a pulmonary end-artery. Pressures were transduced by strain gauges and optically recorded on oscillograph Hathaway galvanometers. Then 20 ml. of a 1% suspension of lycopodium spores was injected into the distal catheter. Pressures were again recorded in both catheters. There was an immediate rise in main pulmonary artery pressure. When the catheter used for injection was wedged into a distal artery the rise in pulmonary artery pressure was at first believed to be due to a generalized pulmonary vasoconstriction, but on histological section lycopodium spores were seen in the lobes into which the catheter had not been placed. It was obvious that there had been a reflux past the catheter and the spores had been generally distributed through the lung.

In two dogs the above experiments were repeated, but, using positive-pressure anaesthesia, the chest was opened on the side where the catheter was wedged into an end-artery and a ligature was placed around this artery. The chest was closed and the intratracheal tube was withdrawn. Lycopodium spores were then injected into this catheter and normal pressures were recorded from the pulmonary artery. There is therefore no generalized vascular constriction consequent upon local embolism.

The absence of lycopodium spores in the blood leaving the lungs precluded any possibility of further arteriolar blocking by recirculation of blood. This is interesting, as the dimensions of these spores are only 27 μ by 25.5 μ . The discrepancy between these results and those of Prinzmetal *et al.* (1948), who found that lungs *in situ* were capable of transmitting glass beads of up to 300 μ in diameter, may be related to the different surfaces of these two materials. Certainly when in a separate experiment lycopodium spores were injected into the superior mesenteric artery of a living dog and their fate in the mesentery was observed through a microscope the spores appeared to cling to the vessel walls before finally occluding arterioles.

Haemodynamics of Pulmonary Hypertension Resulting from Pulmonary Embolism and Effect of Autonomic Nerve Section

To assess the effect of nerve section three dogs were anaesthetized and a catheter was placed in the pulmonary artery. Pulmonary hypertension was produced by injection of lycopodium spores through the catheter as before. Main pulmonary artery pressures and pulmonary capillary pressures were recorded. The saphenous-artery pressure in the leg was also recorded and the cardiac output measured. At the height of the hypertension the vagus nerves which had been previously exposed in the neck were severed and all the above measurements repeated. It was therefore possible to calculate the pulmonary arteriolar resistance before and after vagotomy. Similar experiments were carried out in two other dogs, but this time the anterior nerve roots from T1 to T8, which had previously been exposed, were severed, the vagi being left intact.

A single dog was sympathectomized from T1 to T7 by a transthoracic approach in two stages a week apart. Four days after the last operation the dog was anaesthetized and catheterized, and lycopodium spores were injected into the main pulmonary artery. The main pulmonary and end-artery pressures were recorded before and after the injection.

When lycopodium spores were injected into the main pulmonary artery of dogs there was an invariable rise of pressure in the artery. After one injection the rise was not sustained, and fell to near control levels in from two to ten minutes. When the pressure in the pulmonary artery rose to above one-third of the control value, breathing usually became deeper and more rapid. The saphenous-artery pressure and the cardiac output showed no consistent response to the injection of lycopodium spores. With two exceptions the pulmonary arteriolar resistance rose.

Both vagotomy and anterior rhizotomy had no influence on pulmonary arteriolar resistance. After anterior rhizotomy the pulmonary artery pressure was a little lower than before operation. This was probably due to the time interval between injection and observation. In one dog which was injected with lycopodium spores after anterior rhizotomy the pressure again rose in the pulmonary artery.

In the sympathectomized dog injection of lycopodium spores was followed by a rise in pulmonary artery pressure from 24/12 to 50/20 mm. Hg. There was no difference in the response of this dog from the response of dogs that had not been sympathectomized.

Despite common clinical belief that a small pulmonary embolus is capable of causing a generalized pulmonary arterial constriction, it does not seem that, in the anaesthetized dog, localized lycopodium spore emboli cause such a sequence of events.

The results of these experiments are interpreted as suggesting that rises in pulmonary artery pressure following lycopodium-spore embolism are due to mechanical vascular obstruction. The degree of obstruction necessary to raise the pulmonary pressure is not clear, but multiple histological sections showed spores in the majority of large arterioles.

In this form of pulmonary hypertension produced in the animals of this series, no alteration in haemodynamics resulted from vagotomy or severance of the sympathetic efferent fibres; previous sympathectomy offered no protection against a rise in pulmonary artery pressure. Holden *et al.* (1949) produced pulmonary embolism in dogs by means of thrombi released from the iliac veins. They found that the right atrial pressure rose transiently and the systemic pressure dropped temporarily. Section of the cervical vagi, together with the sympathetic chain T1 to T4 inclusive, did not alter the pattern at all.

Mechanical blockage of pulmonary arterioles therefore causes pulmonary hypertension which is probably dependent upon the degree of blockage and is uninfluenced by the activity of known nervous pathways.

These findings are quite consistent with pulmonary embolism in man. In the absence of other heart or lung disease I have never seen a fatal pulmonary embolus which did not render ineffective more than one lung and usually about one and a half lungs; that is, an embolus which becomes impacted at the bifurcation of the main pulmonary artery. This, of course, may not be the case when pulmonary hypertension and increased pulmonary blood volume already exist. Then a comparatively small embolus can raise the pulmonary artery pressure just enough to cause acute right heart failure. The therapeutic implication is that stellate or other ganglia blockade is useless. Ganglionic blocking agents are not only useless but are also dangerous, as they lead to systemic vasodilation, and a limited cardiac output fed into a dilated systemic circuit may lead to a fatal drop in blood pressure.

Apart from defaecation associated with pulmonary embolism, which is discussed later, the only reflex mechanism involved is dyspnoea. This is mediated by the vagus. Atropine diminishes the dyspnoea and bilateral vagotomy abolishes it.

Occasionally pulmonary oedema complicates pulmonary embolism in man and animal. In the latter this occurs when the cardiac output is maintained. This normal right ventricular output then has to reach the left heart by passing

through a very limited pulmonary vascular bed. Presumably when the limit of pulmonary capillary distensibility has been reached the pressure will rise until it exceeds that of the osmotic pressure of plasma proteins and pulmonary oedema results. A comparable mechanism in man can be supposed.

Pulmonary Oedema

The mechanism of pulmonary oedema has interested clinicians for a long time. Why do pulmonary capillaries leak, either acutely or chronically? And has the autonomic nervous system any control over capillary permeability?

It is now established that in the majority of forms of pulmonary oedema transudation occurs when the blood pressure within the capillary exceeds the osmotic pressure of plasma proteins—that is, when it is above 25 to 30 mm. Hg—taking into account, of course, the usual minor pressure changes reflected from the intrapleural respiratory pressure swings. Excessive pulmonary capillary pressure accounts for the pulmonary oedema of mitral or aortic valvular lesions and left ventricular failure due to coronary artery disease or hypertension. Whether such oedema is sudden and catastrophic or chronic depends upon the thickness of tissue between the capillary and internal surface of the alveolar wall. In chronic pulmonary oedema this thickness is considerable and oedema fluid is carried away by the lymphatics, which are seen as horizontal streaks on x-ray plates. When for any reason, especially exercise, the capillary pressure rises further, cardiac asthma is more common than pulmonary oedema. When the so-called capillary alveolar gradient is as thin as normal a sudden rise in capillary pressure is likely to cause acute pulmonary oedema, and this is typically seen some hours after a myocardial infarction. Once pulmonary oedema has occurred there is alveolar anoxia and a fall in blood-oxygen saturation which leads to a further rise in capillary pressure, as is described below, and probably increases capillary permeability.

This sequence of events is comparatively easy to understand, but it has often been thought that the mechanism of pulmonary oedema complicating head injury or bulbar poliomyelitis had a different aetiology, and that nervous influences lead to increased pulmonary capillary permeability. Sarnoff and Sarnoff (1952), in a series of ingenious animal experiments, have shown that cerebral disturbances can produce pulmonary oedema by raising the pulmonary capillary pressure above that of the plasma protein osmotic pressure. They injected fibrin into the cisterna magna of dogs and found that there was a rise in systemic pressure, an increased pulmonary blood volume presumably due to systemic venous constriction, and a consequent substantial rise in pulmonary capillary pressure. Previous adequate sympathetic denervation of the lung did not prevent the oedema occurring. Ganglionic blocking agents, however, if given before the fibrin injection, prevented the onset of oedema, or, if given when oedema had already happened, promptly relieved it. They believed that blocking agents reduced systemic arterial and venous tone and hence secondarily reduced pulmonary blood volume and pulmonary capillary pressure—the inference being that blocking agents relieve pulmonary oedema indirectly by their action on the systemic circulation and that the sympathetic supply of the pulmonary capillaries does not control their permeability.

These experimental findings are compatible with clinical experience in, for example, pulmonary oedema complicating hypertension. I, like others, have found in occasional nervous hypertensive patients, when one records the blood pressure for the second and third time, that instead of a fall there is a rise in pressure. When such vasoconstriction occurs it is wise to auscultate the lung bases, when increasing crepitations will be heard and frothy sputum may be expectorated. Also, treatment of pulmonary oedema by ganglionic blocking agents can be as effective as morphine, and that is high praise for their efficacy.

Is there any form of pulmonary oedema which is not due to a rise in pulmonary capillary pressure? In human experi-

ence war gases, especially phosgene, are probably the only examples. Experimentally there is one substance which has rather remarkable properties, and I shall describe some experiments which McMillan and I carried out with it.

Richter (1952) has shown that the intraperitoneal injection of alphanaphthylthiourea (antu) is consistently followed by the production of massive pulmonary oedema and pleural effusions. He has also demonstrated in the dog that this form of pulmonary oedema is accompanied by negligible changes in pulmonary artery pressures. The present investigation was undertaken in order to find out if the production of such pulmonary oedema in the dog could be influenced by sympathetic denervation.

Twenty-four dogs were anaesthetized with pentobarbitone sodium; 14 of them acted as controls, and eight had bilateral sympathectomies from the stellate ganglion to the eighth or tenth thoracic ganglion, two to six weeks before the injection of antu. Antu in olive oil was injected intraperitoneally into all dogs, and haematocrit readings were taken every 30 minutes.

In one dog a sympathectomy from T 8 to L 2 was carried out in order to assess the effect of low sympathectomy on peritoneal absorption. In two dogs which had intraperitoneal injections of antu, four and five hours later respectively, the ganglionic blocking agent trimetaphan camphorsulphonate ("arfonad") (Sarnoff and Sarnoff 1952) was injected through a catheter into the pulmonary artery. In three the pulmonary artery pressure was repeatedly recorded during the experiment with a mercury manometer.

Of four dogs which received 50 mg. of antu per kg. after sympathectomy, three died, whereas of seven control dogs (not sympathectomized) all died after receiving the same dose of antu. Four dogs received 25 mg. of antu per kg. after sympathectomy, and all died. Similarly, four control dogs died after receiving the same dose. One control dog died after 15 mg. of antu per kg. and one survived, while one dog which received only 10 mg. per kg. survived. It seems, therefore, that the minimum lethal dose of antu is about 20 mg. per kg.

The injection of 0.5 mg. of trimetaphan into one dog with a systolic pressure of 130 mm. Hg produced a catastrophic fall in pressure in three minutes and death within fifteen minutes. In a second dog trimetaphan was used to lower the systemic pressure from 110 to 55 mm. Hg by repeated doses, and maintained there. The initial dose required to produce the fall was 0.05 mg. and the final dose to maintain it was 2.5 mg. Owing to this large increase in the amount of trimetaphan required, its use was abandoned after two hours, during which time the haematocrit had risen 8%. Two hours later the animal died. Both these dogs had gross pulmonary oedema.

In five dogs in which the pulmonary artery pressure was recorded during the development of pulmonary oedema there was no change in mean pressure while the haematocrit was rising, even in one followed through to death.

The period of survival after antu injection appeared to be independent of the dosage, provided it was above the minimum dose, and both this and the rise in haematocrit were not significantly influenced by sympathectomy.

Post-mortem examination in all dogs dying after antu injections revealed gross pulmonary oedema confirmed by microscopy, and bilateral pleural effusions.

As the pulmonary artery pressure does not rise in this form of acute pulmonary oedema it is assumed that the pulmonary capillary pressure does not exceed the osmotic pressure of plasma proteins. Hence pulmonary oedema produced by antu is due to increased capillary permeability, and Richter (1952) has found such oedema fluid to have the composition of plasma.

In these experiments it has been confirmed that ablation of the pulmonary autonomic supply does not affect pulmonary oedema due to increased capillary permeability, nor certainly in two dogs did the ganglionic blocking agent trimetaphan influence the oedema. Therefore it must be

concluded that in no form of pulmonary oedema yet investigated does the pulmonary autonomic supply play a direct part.

Action of Drugs on the Pulmonary Circulation

A number of drugs have been stated to have a direct action on the pulmonary vascular resistance, and some have been used in attempts to lower pulmonary vascular resistance in the hope that they might prove beneficial in such conditions as primary pulmonary hypertension. With the object of assessing whether any drug had a direct effect on the pulmonary arterioles McMillan and I have again conducted a series of animal experiments. The technical procedure was the same in them all. Two cardiac catheters were passed via the jugular veins into the pulmonary artery. The first was used for injection of the drug and the second for measuring continuous pressures. A needle was inserted into each saphenous artery—one for drug injection and the other for measuring systemic pressure. The electrocardiogram was recorded continuously.

Injection of 5 minims (0.3 ml.) of 1 in 1,000 adrenaline solution into the pulmonary artery caused a rise of pulmonary artery pressure of about 10 mm. Hg between seven and eight beats after its introduction. There was also speeding of the heart rate at this time.

Injection of 5 mg. of noradrenaline into the pulmonary artery caused a rise in pulmonary artery pressure and slowing of the heart rate also after seven to eight beats.

Injection of 2 mg. of acetylcholine into the pulmonary artery caused asystole and consequent considerable lowering of pulmonary artery pressure, again after seven or eight beats. Why the pressure did not fall to zero is an interesting matter, for the electrocardiogram showed no myocardial electrical activity. It is thought that this continued evidence of pulsatile flow in the pulmonary artery is due to the pumping action of the lungs; for all this time the apex beat was palpable and it is inconceivable that myocardial contraction could be present with absent electrical activity.

The same dose of acetylcholine, when injected into a femoral artery, caused asystole in 21 to 23 beats.

These facts are interpreted as meaning that none of these drugs have any effect on the normal pulmonary circulation and that the effect is purely secondary and dependent upon their entry at least into the aortic root. The considerable delay in noticeable action of acetylcholine when injected into the saphenous artery suggests that its arrival in the coronary artery is necessary for asystole to occur.

Another drug used in the same way was "dibenyline" (N-phenoxisopropyl-N-benzy- β -chloroethylamine). It is described as an "adrenomotor antagonist," and is regarded as acting against the motor effects of circulating adrenaline, noradrenaline, 5-hydroxytryptamine, and most sympathomimetic amines. It does not interfere with ganglionic transmission or prevent the liberation of peripheral transmitter substances. As it is widely used in the treatment of peripheral vascular disease and the control of hypertension in phaeochromocytoma, the study of its action on the pulmonary circulation appeared to be of interest. When injected into the pulmonary or femoral artery even in doses up to 20 mg., it had no effect on pressure pulses. However, a dose as small as 2 mg., when injected into the pulmonary artery in the same syringe as adrenaline or noradrenaline, completely abolished their hypertensive responses. As might have been expected, it was quite ineffectual against acetylcholine. Dibenyline therefore lived up to its reputation as an effective blockade against adrenaline and noradrenaline.

In order to see if acetylcholine or dibenyline might be of any therapeutic use in pulmonary embolism, talc powder was injected into the pulmonary artery, and when the expected rise in pulmonary artery pressure occurred each drug, in separate experiments, was introduced into the pulmonary catheter. Acetylcholine produced the usual fall in pulmonary artery pressure after seven beats when asystole had occurred, but otherwise was without effect. Small and large

doses of dibenyline also were ineffectual in altering the induced pulmonary hypertension.

These observations are naturally very unfortunate when one is trying to discover some useful therapy for pulmonary embolism, but they do agree with the lack of evidence for mass pulmonary arteriolar vasoconstriction consequent upon pulmonary embolism, and suggest that the advent of a pulmonary embolus does not cause excessive liberation of adrenaline or noradrenaline. They do not, of course, contradict Wood's (1956) work on the effect of small doses of acetylcholine injected through a cardiac catheter on the pulmonary arteriolar resistance of patients suffering from mitral stenosis. He is considering increased arteriolar resistance in left heart valvular lesions. I am considering experimental pulmonary embolism.

Harris *et al.* (1956), working in Cournand's laboratory, infused acetylcholine into the main pulmonary artery of man and observed that it caused a slight fall in pulmonary arterial pressure when the subject breathed ambient air but a greater fall in pressure after pulmonary hypertension had been produced by hypoxia. The fall in pressure was associated with either a constant or an increased cardiac output. There was no alteration in the heart rate, the brachial artery pressure, the arterial saturation, or the ventilation. This is taken as evidence that acetylcholine causes vasodilatation in the lungs and that this action is largely dependent upon the pre-existing tone of the pulmonary vessels. It is a most difficult experiment to understand, and after studying his diagram there is considerable delay between the giving of the acetylcholine and the measurement of its response. To give sufficient acetylcholine to alter pulmonary arteriolar resistance without altering the heart rate is a possibility I find very hard to comprehend.

An interesting side-effect of producing experimental pulmonary embolism is that the dogs usually defaecate as the pulmonary artery pressure is rising. I have often wondered about the "call for the bedpan" story which is so often said to precede by a few seconds the arrival of the embolus, and have conjectured upon some message from above that the embolus was on its way. It must be that it has occurred by the time the bedpan is demanded and is a vagal reaction unconnected with the non-release of sympathetico-mimetic drugs and uninhibited by dibenyline.

The results of investigating the effect of ganglionic blocking agents on the pulmonary circulation have been somewhat equivocal. Storstein (personal communication, 1956) reported his results, using hexamethonium bromide, in 14 patients suffering from various forms of heart disease. He found a statistically significant decrease in cardiac output, systemic blood pressure, and pulmonary artery and pulmonary capillary pressures, while there was no significant change in heart rate or resistances in the systemic and pulmonary circulation. The pressure fall was roughly parallel in the systemic artery, the pulmonary artery, and the pulmonary capillary. He interpreted the pressure fall in the pulmonary circulation to be due to a dilatation of the systemic blood vessels with consequent pooling of blood and reduction of the venous return. In our own experiments in dogs injection of the ganglionic blocking agent trimetaphan into the pulmonary artery did not lower pulmonary artery pressure until it had reduced the systemic pressure. When trimetaphan was injected simultaneously with a pulmonary embolizing material the drop in systemic pressure was greater than if it had not been given, and the induced pulmonary hypertension was unaltered.

The action of ganglionic blocking agents has been investigated by several workers in mitral stenosis, and one of the most complete of these investigations is by Davies *et al.* (1954). As already mentioned, the increased pulmonary arteriolar resistance in mitral stenosis is not comparable to the increased resistance in many other conditions in which there is obstruction in either the lumen or the wall of the vessel. Certainly in many patients suffering from mitral stenosis there are structural proliferative lesions of the pulmonary arterioles, but the dramatic fall in resistance after successful valvotomy indicates an altering functional state.

Davies *et al.* administered hexamethonium via cardiac catheter placed in the pulmonary artery to 12 patients with mitral stenosis and found it produced a sharp fall in pulmonary arterial pressure without a fall in cardiac output. They believed that such a reduction of total pulmonary vascular resistance was probably, although not certainly, due to arteriolar dilatation consequent upon autonomic blockade. They write that they were careful to gauge the dose of hexamethonium so that the drop in systemic pressure was not too profound. Their argument of a primary action of this drug on pulmonary vascular resistance is good but not convincing, because the main fall in pulmonary artery pressure was systolic and in some patients the cardiac output and rate were changing. It is not quite enough to believe that because the change in pulmonary artery pressure is more profound than in the systemic the action of the drug must be on the pulmonary circuit. There are, of course, several drugs which will lower the pulmonary and systemic arterial pressures in patients with mitral stenosis as well as in normal people. An example of this is chlorpromazine. In these types of reaction a shift of blood from the lungs to the periphery may occur. However, the uncertainty of the site of action of these drugs does not detract from their value in lessening the dyspnoea of some patients suffering from mitral stenosis with high pulmonary artery pressure.

Other experiments relevant to this discussion have been carried out with ganglionic blocking agents in patients not suffering from mitral stenosis. Gilmore *et al.* (1952) showed (although hardly conclusively) that in patients with systemic hypertension hexamethonium prevented the normal pulmonary vasoconstriction which occurs on assuming the upright position. Greene and Bunnell (1950) produced a fall in net pulmonary arterial pressure in man following continuous intravenous infusion of tetraethylammonium chloride and thought that the accompanying fall in cardiac output did not fully account for the fall in pulmonary arterial pressure. They also showed that tetraethylammonium chloride abolished the "overshoot" in the pulmonary artery at the end of a Valsalva manoeuvre. They concluded that these results indicated the presence of reflex pulmonary activity. Lee *et al.* (1954) not only were unable to confirm the abolition of the pulmonary artery "overshoot" but also employed the Valsalva manoeuvre to demonstrate the absence of any striking reflex vasomotor changes in the pulmonary arterial system.

At the end of the "blow" in the Valsalva manoeuvre the systemic pressure rises and there is a simultaneous rise in net pulmonary arterial pressure due to an increase in venous return. There are almost identical changes in the net pulmonary capillary pressure. It is thought that the rapid increase in right ventricular filling pressure following the Valsalva manoeuvre causes a rapid increase in stroke output and hence a rise in pulmonary artery pressure. In the experiments of Lee *et al.* there was no rise in pulmonary artery pressure independent of pulmonary capillary pressure. As they say: "This strongly suggests that no pulmonary capillary constriction has taken place, and there is further evidence to the same effect when the pulmonary and brachial arterial tracings obtained during the prolonged Valsalva manoeuvre are compared. During this period venous return is restricted and stroke output reduced; reflex vasoconstriction occurs in the systemic arterial system, indicated by a rise in mean pressure, and later Traube waves appear. These indications of alteration in vasomotor tone do not occur in the pulmonary arterial pressure."

Use of Drugs in Primary Pulmonary Hypertension

Wade and Ball (1956) believe that there are at least three mechanisms operating in different patients classified as suffering from primary pulmonary hypertension: (1) functional narrowing of muscular vessels with or without thrombotic occlusions; (2) primary pulmonary arteritis; and (3) bronchial and pulmonary communications through abnormal vessels, resulting in a dynamic state analogous to that of persistent ductus arteriosus. I have also seen a young woman

patient who died of right heart failure due to pulmonary hypertension but with histologically normal pulmonary arterioles, somewhat analogous to the early stages of essential systemic hypertension. This case is important because it suggests severe functional arteriolar constriction. Unfortunately, ganglionic blocking agents were not available when the patient was alive. However, hexamethonium bromide has been used in a number of cases of primary pulmonary hypertension. Wade and Ball report no relief. When I have used it the systemic vasoconstriction was released and the low fixed cardiac output was frequently inadequate to perfuse the brain, causing most troublesome effort syncope. One of my patients explained, "I do feel a great deal better just before the next injection is due." She actually had attacks of blindness on effort with extreme retinal blanching. This, of course, is what one would expect in view of the failure of the drug to lower pulmonary artery pressure in experimental pulmonary embolism.

The results of operative autonomic denervation are unfortunately conflicting. One author saw no effect of thoracic sympathectomy and plexotomy in a child with this disease, whereas another denervated the left lung in a man with primary pulmonary hypertension and reported that the pulmonary artery pressure became normal in a following three-year observation period.

Wade and Ball also state that in one patient pulmonary hindrance was apparently reduced by tolazoline hydrochloride (priscol). This has not been my experience in one patient whom I recatheterized while on tolazoline hydrochloride. In dogs tolazoline hydrochloride is not active in the pulmonary circulation either when normal or with pulmonary hypertension due to embolism.

Of the numerous other drugs which have been used for primary pulmonary hypertension none has been effective so far as I am aware.

The evidence, therefore, for a primary action of any drug on the pulmonary circulation is extremely slender, and I personally remain unconvinced that there is any such action. The therapeutic implications are negligible.

Hypoxic Reaction

Von Euler and Liljestrand demonstrated in 1946 that anoxia induces a pressure rise in the pulmonary artery of a cat. Since then similar observations have been made on normal man (Westcott *et al.*, 1951; Doyle *et al.*, 1952). In most normal subjects, when hypoxia is produced by breathing low concentrations of oxygen the pulmonary artery pressure rises significantly, the cardiac output increases or does not change, the heart rate increases, and the pulmonary "capillary" pressure remains the same. Thus total pulmonary and pulmonary vascular resistance increases. The systemic artery pressure and peripheral vascular resistance vary in response. They may rise or fall. Storstein (personal communication, 1956) stated that in most investigations with experimental anoxia there is at the same time an increase in blood flow and pulmonary artery pressure, but that there are some patients showing at the same time a fall in cardiac output and a rise in pulmonary artery pressure. He thinks that this finding is in favour of a direct vasomotor action on the pulmonary blood vessels consequent upon changes in oxygen concentration of inspired air. Yu *et al.* (1956) have found the same type of response in patients suffering from mitral stenosis with an already high pulmonary vascular resistance when breathing low oxygen began. In most instances the resistance rose.

In patients with chronic pulmonary disease the hypoxic reaction is much less marked (Fishman *et al.*, 1952). The difference in response may be due to acclimatization of such patients to chronic hypoxia, insensitivity of chronically hypoxic oxygen receptors, or the fact that maximal vasoconstriction has already occurred with chronic hypoxia and a further acute response is impossible. It is of interest in this connexion that I am told that in the hills of Mexico pulmonary hypertension in association with persistent ductus arteriosus is commonplace. Ligation of such so-called high-pressure

ductuses is not the disastrous procedure that it usually is in this country. It may be that the rarefied atmosphere of Mexico produces a functional pulmonary vasoconstriction and that by the time operation is considered in Great Britain structural narrowing has already occurred in the pulmonary arterioles.

Why does hypoxia lead to an increase in pulmonary vascular resistance? Doyle *et al.* (1952) favour the idea that hypoxia has a direct effect on precapillary pulmonary vessels as a result of low oxygen tension in mixed venous blood. On the contrary, Yu *et al.* (1956) found in their mitral stenotic patients that the reduction in oxygen saturation of arterial and mixed venous blood was not statistically related to the magnitude per cent. changes in pulmonary flow, pressures, or resistances. Fishman *et al.* (1952) suggest that acute bilateral hypoxia may cause a shift of blood into the lungs because of peripheral vasoconstriction. This suggestion is based on their experiments in which they administered 10% or 12% oxygen to one lung of patients suffering from minimal pulmonary disease. To the other lung they administered 25% to 30% oxygen in nitrogen, which prevented marked anoxia of arterial or mixed venous blood. There was no rise in pulmonary artery pressure or shift of blood from the anoxic to the hyperoxic lung, indicating that local alveolar anoxia does not cause pulmonary vasoconstriction when arterial and venous oxygen saturation is maintained.

Helen Duke (1954) showed that inhalation of gas mixtures containing 5% to 10% oxygen in nitrogen instead of atmospheric air caused a rise in left pulmonary arterial pressure in the living animal during perfusion of the left lung at constant volume inflow with blood from the right auricle. The response was not dependent upon changes in left auricular pressure, tidal air, or systemic blood pressure. It was found that it was similar in duration and latency to that occurring in isolated lungs perfused at constant volume inflow. She states:

"The tests on cross-perfused and back-perfused isolated lungs were carried out to help identify the vessels which respond to anoxia. It has already been found (Duke, 1951) that ventilation of isolated lungs with nitrogen to produce an approximately 60% oxygen saturation of the pulmonary arterial and venous blood causes a rise of pulmonary arterial pressure. The present experiments show that, in lungs ventilated with air, perfusion through the artery with blood which is approximately 60% saturated with oxygen does not cause a pulmonary arterial pressor response, but that ventilation of the lungs with nitrogen during perfusion with partially deoxygenated blood does produce an increase of pulmonary arterial pressure. Provided gas exchange only takes place in the alveolar capillaries, these findings would indicate that the site in the pulmonary vascular bed sensitive to oxygen lack is in the capillaries or veins. When perfusion was made through the vein and the lungs were ventilated with nitrogen a pulmonary arterial pressor response occurred which was very similar to that obtained during perfusion of the lungs through the artery. It would therefore appear that the alveolar capillaries are the site sensitive to anoxia."

I have repeatedly produced a rise in pulmonary pressure in anaesthetized dogs when they are breathing 10% oxygen in nitrogen. The pressure begins to rise in about one minute and continues until normal ventilation is introduced. There is usually no change in systemic pressure. This reaction is not due to carbon dioxide retention, because it occurs in exactly the same way whether or not there is a carbon dioxide absorber in the circuit. Also, breathing 5% carbon dioxide for one and a half minutes does not have any appreciable effect on the pulmonary artery, pulmonary capillary, or femoral artery pressure. There appears to be a direct correlation between the rise in pulmonary artery pressure and the fall in the oxygen saturation of mixed venous blood. In order to decide whether or not this was a reflex pressure rise, trimetaphan was infused into the pulmonary artery by a cardiac catheter during the inhalation of 10% oxygen. Pulmonary hypertension developed just as before. There was, of course, a precipitous fall in systemic arterial pressure. Thus pulmonary hypertension due to breathing 10% oxygen is a direct response of the pulmonary

vasculature probably due to a falling venous oxygen saturation and not to a nervous reflex mechanism.

Clinically it is my impression that right ventricular failure due to pulmonary hypertension in emphysema is related more to arterial and venous oxygen unsaturation than to other measurable change such as arterial carbon dioxide tension. There are occasional contrasting emphysematous patients in one of whom carbon dioxide retention with venous dilatation and papilloedema is marked, whereas in the other hypoxia and right ventricular failure predominate.

In mitral stenosis there is good correlation between the height of the pulmonary arteriolar resistance and the fall in the oxygen saturation of mixed venous blood (Holling and Venner, 1956).

In atrial septal defect, once reversal of the shunt has occurred, there is arterial oxygen unsaturation, and with normal oxygen extraction by the tissues there is a decrease in venous oxygen saturation. It is therefore hardly surprising that pulmonary hypertension is a progressive disability. The production of an atrial septal defect in dogs is usually accompanied by an initial small right-to-left shunt. This is followed by pulmonary hypertension, which may become marked. Closure of the defect relieves the hypertension.

These facts have considerable therapeutic implication. In cor pulmonale due to emphysema, treatment with thiouracil will reduce tissue oxygen consumption and hence cause a rise in oxygen content of mixed venous blood. This should progressively reduce pulmonary hypertension.

In atrial septal defect once pulmonary hypertension is initiated it is likely to be progressive, and early operation should probably be advised. Experiments are now proceeding in order to try to see if the introduction of better-oxygenated blood into the right heart may lower pulmonary arteriolar resistance and reduce right ventricular work.

Bronchomotor Tone

Rodbard (1953) suggests that changes in bronchomotor tone may influence blood pressure and flow relationships in the pulmonary circulation. Vagal stimulation, by decreasing the calibre of bronchi, reduces the alveolar capillary surface and causes increased resistance to the passage of blood. Sympathetic stimulation has the opposite effect. This idea is attractive and might explain the mechanism whereby blood is shunted away from collapsed and consolidated areas of lung. It would, of course, also explain in part the pulmonary hypertension of asthma.

Summary

I hope that I have shown that pulmonary embolism is unaccompanied by generalized pulmonary vasoconstriction; that clinical pulmonary oedema is a secondary phenomenon to changes in the systemic circulation, albeit facilitated by pre-existing disturbed pulmonary haemodynamics; that the hypoxic reaction is a direct response of the smaller vessels of the pulmonary circulation to blood unsaturated with oxygen; and that drugs known to influence the autonomic nervous system play little part in the vascular economic adjustments of the lungs.

I began by saying that the lung vasculature was poorly endowed with sympathetic and parasympathetic nervous supply and have ended by concluding that the function of even this small supply is far from clear. The lesser circulation appears to have been well named, and I can only hope that my successors will raise the status of a much-investigated and highly controversial field of endeavour.

My thanks are due to Mr. I. K. R. McMillan, who has done so much of this work, and especially for his surgical skill, which was essential; to Dr. W. Boake, who produced many ideas; to Miss Stewart and Mr. Schofield, our technicians, who have made such experiments possible; and to Miss Fairbrace, my secretary, for her kind organization.

BIBLIOGRAPHY

- Aviado, D. M., and Schmidt, C. F. (1955). *Physiol. Rev.*, 35, 247.
 Cookson, F. B. A. (1953). Hons. Anat. Thesis, Manchester Univ.
 Cournaud, A., Ranges, H. A., and Riley, R. L. (1942). *J. clin. Invest.*, 21, 287.
 Daley, R., Wade, J. D., Maraist, F., and Bing, R. J. (1951). *Amer. J. Physiol.*, 164, 380.
 Daly, I. de B., Duke, H., Hebb, C. O., and Weatherall, J. (1948). *Quart. J. exp. Physiol.*, 34, 285.
 Daly, M. de B., and Schweitzer, A. (1956). *J. Physiol. (Lond.)*, 131, 220.
 Davies, L. G., Goodwin, J. F., and van Leuven, B. D. (1954). *Brit. Heart J.*, 16, 440.
 Dirken, M. N. J., and Heemstra, H. (1948). *Quart. J. exp. Physiol.*, 34, 227.
 Doyle, J. T., Wilson, J. S., and Warren, J. V. (1952). *Circulation*, 5, 263.
 Duke, Helen N. (1951). *Quart. J. exp. Physiol.*, 36, 75.
 — (1954). *J. Physiol. (Lond.)*, 125, 373.
 von Euler, U. S., and Liljesrand, G. (1946). *Acta physiol. scand.*, 12, 301.
 Fishman, A. P., McClement, J., Himmelstein, A., and Cournaud, A. (1952). *J. clin. Invest.*, 31, 770.
 Gilmore, H. R., Kopelman, H., McMichael, J., and Milne, I. G. (1952). *Lancet*, 2, 898.
 Greene, D. G., and Bunnell, I. L. (1950). *J. clin. Invest.*, 29, 818.
 Harris, P., Fritts, H. W., Clauss, R. H., Odell, J. E., and Cournaud, A. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, 93, 77.
 Hellem, H. K., Haynes, F. W., Dexter, L., and Kinney, T. D. (1948). *Amer. J. Physiol.*, 155, 98.
 Holden, W. D., Shaw, B. W., Cameron, D. B., Shea, P. J., and Davis, J. H. (1949). *Surg. Gynec. Obstet.*, 88, 23.
 Holling, H. E., and Venner, A. (1956). *Brit. Heart J.*, 18, 103.
 Larsell, O., and Dow, R. S. (1933). *Amer. J. Anat.*, 52, 125.
 Lee, G. de J., Matthews, M. B., and Sharpey-Schafer, E. P. (1954). *Brit. Heart J.*, 16, 311.
 Lewis, B. M., and Gorlin, R. (1952). *Amer. J. Physiol.*, 170, 574.
 Mitchell, G. A. G. (1956). *Cardiovascular Innervation*. Livingstone, Edinburgh.
 Prinzmetal, M. E. N., Ornitz, B., Simkin, B., and Bergman, H. C. (1948). *Amer. J. Physiol.*, 152, 48.
 Richter, C. P. (1952). *J. thorac. Surg.*, 23, 66.
 Rodbard, S. (1953). *Amer. J. Med.*, 15, 356.
 Sarnoff, S. J., and Sarnoff, L. C. (1952). *Circulation*, 6, 51.
 Wade, G., and Ball, J. (1956). 2nd European Congr. Cardiol., abstracts of papers, p. 266.
 Westcott, R. N., Fowler, N. O., Scott, R. C., Hauenstein, V. D., and McGuire, J. (1951). *J. clin. Invest.*, 30, 957.
 Wood, P. (1956). 2nd European Congr. Cardiol., abstracts of papers, p. 271.
 Yu, P. N., Beatty, D. C., Lovejoy, F. W., Nye, R. E., and Joos, H. A. (1956). *Amer. Heart J.*, 52, 683.

PROLONGED ANTIBIOTIC TREATMENT OF SEVERE BRONCHIECTASIS

A REPORT BY A SUBCOMMITTEE* OF THE
ANTIBIOTICS CLINICAL TRIALS (NON-
TUBERCULOUS) COMMITTEE OF THE MEDICAL
RESEARCH COUNCIL

Experience with penicillin and later with other antibiotics has shown that these drugs are effective in the treatment of many acute respiratory infections. The management of chronic bronchial infections, particularly in patients with bronchiectasis, has proved more difficult. Although an initial response may be obtained in individual patients, especially during acute episodes, cessation of treatment is usually followed by an early relapse and the re-establishment of infection.

The therapeutic trial reported in detail below was designed to study the effect of prolonged antibiotic therapy in severe cases of bronchiectasis characterized by abundant purulent or mucopurulent sputum. Since the study was concerned with long-term therapy, patients were treated entirely at home unless some intercurrent infection necessitated admission to hospital. Patients were accepted only if they were able to attend regularly at a special out-patient clinic. As will be seen, the criteria of severity were stringent, and it was surprising how few patients satisfied them.

Since the patient assesses his illness in terms of general health, the amount and character of sputum, and his ability to work and enjoy a full life, the observations

*The members of the subcommittee were: Dr. J. G. Scadding (chairman), Professor J. W. Crofton, Drs. T. Anderson, A. C. C. Hughes, J. Knowelden, A. G. Ogilvie, W. S. Sutton, M. Telling, K. Zinneman, and C. S. Darke (secretary).

The present report was prepared for the subcommittee by Dr. C. S. Darke and Dr. J. Knowelden.

recorded at each attendance were designed to evaluate these criteria. Because of the normal fluctuation in the symptoms of this disease with the change of season, patients were observed over a consecutive period of 52 weeks whilst they received the appropriate drug under a uniform scheme.

The difficulties inherent in a trial of this character will be appreciated, not least of them being the subjective improvement which might be expected when more intense interest is shown. This difficulty was met by introducing a control medicament, lactose, and making the trial a "blind" one in which neither the clinician nor the patient knew which drug was being given. The nature of the trial was explained to the patients beforehand, and all were volunteers. The results of the study, which have been analysed in the various tables, are an attempt to obtain an objective assessment of a number of symptoms and signs common to most patients with infected bronchiectasis.

Plan of Trial

The trial was conducted on out-patients at seven centres—Chester, Edinburgh, Glasgow, Leeds, Liverpool, Newcastle, and Sheffield. Patients had to be between 15 and 55 years of age and to have had symptoms for at least three months. It was required that the bronchogram should show frank bronchiectasis affecting at least two lung segments. Before admission to the trial the patient had to be observed on four visits at weekly intervals, on each occasion bringing a 24-hour specimen of sputum; the total quantity of the four specimens, which had to be either purulent or mucopurulent, had to be at least 150 ml., and the last had to measure at least 25 ml. Patients with tuberculosis were excluded. Patients who had been receiving antibiotics or sulphonamides could be admitted only after a period of at least a month without such treatment.

During the pre-treatment period of four weeks observations were made on cough, haemoptysis, dyspnoea, and disability, as well as on sputum measurement. A postero-anterior film of the chest was taken. On the fourth visit the weight, haemoglobin, red-cell count, and degree of clubbing were recorded and the patient's general condition was assessed. If he satisfied the criteria for admission he was allocated at random, according to a centrally held list, to one of the three treatment groups—penicillin, oxytetracycline, or lactose. The drugs were provided in 0.25-g. capsules which were indistinguishable, and the supply for each patient was issued in bottles which were identified only by the patient's allocation number. As the allocation and supply of drugs was controlled centrally neither the patient nor his physician was aware of the treatment given. The patients were instructed to take two capsules four times a day on two days a week—for example, on Wednesday and Saturday—making a total dose of 2 g. each day or 4 g. a week.

Treatment was continued for a year, and during this time regular visits were made to the out-patient department, at first weekly for a month and thereafter at four-weekly intervals. On each attendance the patient brought a 24-hour specimen of sputum, and observations on the severity of cough, dyspnoea, haemoptysis, and disability were made as on the pre-treatment visits. At the completion of one year's treatment additional observations were made on clubbing, weight, general assessment of progress, and the patient's own assessment of his response to treatment. During the year's treatment it was provided that any acute episode might be treated according to the discretion of the clinician, including, if necessary, penicillin by injection or other antibiotics. All such additional treatment was to be recorded. Provision was made for the routine reporting of any presumed toxic reactions to treatment. In all groups treatment by postural drainage was conducted in accordance with the practice of the physicians in clinical charge of individual patients.