Summary

Cervical spondylosis is present more often than not after the age of 55. Special points which may be brought out by x-ray examination of the cervical spine are discussed.

The clinical features of headache due to cervical spondylosis are described. The headache is associated with a predominant involvement of the upper cervical spine and of the apophysial joints, but precisely how it is produced is still unknown.

The contribution which cervical spondylosis may make to vertebro-basilar ischaemia is discussed. Acute vascular lesions of the cerebellum or brain-stem may occur, and a case is reported in which this happened after therapeutic manipulation of the cervical spine in a patient suffering from spondylosis.

The effects of head movement on the cerebral circulation are considered, including the production of vertigo and drop attacks.

The cases of four patients who suffered from attacks of unconsciousness are described. All had cervical spondylosis. Two in addition had bundle-branch block, and their attacks were attributed to paroxysmal complete heart-block. Some factors which appeared to precipitate such paroxysms are considered. In one patient in whom cardiac asystole could be produced by carotid-artery compression, narrowing of one vertebral artery appeared to be a contributory factor, and its surgical decompression, together with decompression of the spinal cord, was followed by cessation of the attacks.

I am grateful to Mr. Douglas Northfield for allowing me to report Case 10, and to Dr. Marcia Wilkinson for Case 3, to Professor R. J. Harrison for the dissection, and to Mr. Ruddick for the photographs.

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The Ministry of Agriculture, Fisheries, and Food says that the agreement to restrict the use of cereal seed dressings containing aldrin, dieldrin, and heptachlor led to a very marked reduction in the number of birds dying as a result of toxic seed dressings last year, and it reminds farmers and agricultural merchants that these dressings should not be used on any cereal seed to be sown this spring.

OBLITERATIVE PULMONARY
HYPERTENSION AND THROMBO-
EMBOLISM*

BY

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DISCUSSION

Pulmonary Thrombosis and Thrombo-embolism

The occurrence of thrombosis in the larger branches of the pulmonary arteries has been well documented (Ball *et al.*, 1956). Thrombosis in these sites usually, but not always, follows embolism. Pre-existing pulmonary hypertension and pulmonary vascular disease, such as in mitral stenosis, particularly favour thrombosis *in situ*, but thrombosis may also occur in severely debilitated and cachectic patients who are dying of a generalized disease, and also in children with polycythaemia due to congenital heart disease. Pulmonary-artery thrombosis is not infrequently found as an unexpected lesion in patients dying from cardiac infarction or severe valvular heart disease. It may also occur in atrial septal defect (Canada *et al.*, 1953; Bedford *et al.*, 1957). A low cardiac output favours not only thrombosis in peripheral veins with subsequent embolism, but also secondary embolism from the thrombosed pulmonary vessels. Repeated haemoptysis, attacks of pleuritic pain, recurrent syncopal attacks, and acute dyspnoea without obvious cause followed by progressive right ventricular failure have also been reported (Ball *et al.*, 1956).

If thrombosis occurs gradually in a major pulmonary vessel, collateral channels may develop via the bronchial circulation so that pulmonary infarction does not necessarily occur. Nevertheless, correct diagnosis is often delayed and haemoptysis attributed to other lesions such as carcinoma of the lung. By the time that obvious radiological changes suggesting occlusion of major pulmonary vessels have occurred the disease is well advanced. The condition should be suspected in any patient who develops right ventricular failure or signs of pulmonary hypertension without known cause, or who has unexplained dyspnoea or fainting.

While the occurrence of massive thrombosis of the pulmonary arteries following embolism has been well documented in patients with other diseases, the occurrence of a similar syndrome in previously healthy young persons has not been frequently recognized. Ehrner *et al.* (1959) described three cases with the syndrome very similar to those in our first group.

The occurrence of periods of freedom from symptoms may give rise to a false feeling of security that the condition has resolved completely. This point may be important with regard to the incidence of pulmonary embolism, occurring after medical or surgical disease, or spontaneously in fit young people. It is usually assumed that such incidents are self-limiting and that

*Concluded from p. 711 of last week's issue.

if the patient survives the pulmonary embolism or infarct he will make a good recovery. This may not always be true, and we suggest that patients who have had thrombo-embolism after medical or surgical diseases should be kept under observation to exclude the possibility of further silent emboli and the development of pulmonary hypertension.

Often acute pulmonary embolism is discovered only at necropsy, the correct diagnosis having been missed in up to 70% of patients in life (Parker and Smith, 1958), so that the mortality from pulmonary thrombo-embolism is therefore difficult to assess. Iversen (1956) reported 20 cases of thrombosis of the pulmonary artery found at necropsy, and on the basis of necropsy records found that the disease occurred in only 0.5% of patients. Iversen suggests that pulmonary thrombosis should be considered in patients exhibiting pulmonary heart disease of rapid onset without any underlying disease. Short (1952) studied pulmonary embolism in a general hospital during a period of 30 months. The incidence was higher than that of lobar pneumonia. Embolism was directly responsible for death in 30 patients and pulmonary infarction was an important contributory cause in 13 others.

Obliterative Hypertension Involving the Pulmonary Arteriolar Bed

There is now an extensive literature on "primary," "idiopathic," or "solitary" pulmonary hypertension. Brenner (1935) described primary pulmonary arteriosclerosis as "a rare condition in which there is sclerosis of the pulmonary artery for no obvious reason, as well as hypertrophy of the right but not the left side of the heart." It was suggested that primary arteriosclerosis was not a single pathological entity, but several different conditions with certain clinical and pathological characteristics. The condition was characterized by severe cyanosis and oedema with comparatively little dyspnoea; clinical and cardiographic evidence of hypertrophy of the right ventricle; and accentuation of pulmonary-valve closure possibly with a pulmonary diastolic murmur, but without murmurs of valvular heart disease. Brill and Krygier (1941) described intimal proliferation of the pulmonary arterioles resulting in marked narrowing or occlusion of the lumina of many of the vessels. The larger and medium-sized arteries revealed little or no change from normal. Dresdale *et al.* (1954) described the characteristic lesion as occurring mainly proximal to the capillaries.

Evans *et al.* (1957) stated that the condition was far commoner in women than in men, the ages of the 11 patients varying from 7 to 64 years. In contrast to Brenner's (1935) view, the dominant symptom was rapidly increasing dyspnoea on exertion, and their patients often suffered from paroxysmal dyspnoea and orthopnoea. They found the most significant histological changes to be present in the muscular arteries and arterioles, which were partly or wholly occluded by intimal proliferation; thrombosis with subsequent organization may have played a part. In the muscular arteries the intimal changes were related to areas of hypoplasia or aplasia in the media. In nine of their patients the vascular obstruction accounted for the persistence of pulmonary hypertension, but in the remaining two no such obstruction was found on histological examination, although an arteriogram carried out on one of them showed generalized constriction of

the smaller pulmonary arteries, implying that a reduced pulmonary vascular bed predisposed to pulmonary hypertension. Heath *et al.* (1957) described the commonest abnormality in the small pulmonary arteries as thickening of the medial coat. In two of their three cases there was intimal fibrosis leading to occlusion of the lumina of the arterioles, and also medial necrosis in the muscular arteries and arterioles.

The cause of primary or idiopathic pulmonary hypertension is unknown and usually there are no signs of any generalized disease. Wade and Ball (1957) described positive sheep-cell agglutination tests in some patients, but the significance of this is unknown. It has been suggested that all patients who have the disease have had antecedent pulmonary thrombo-embolism; but this seems unlikely in young children, a number of whom have been reported with the disease. Our youngest patient was 2 years old when he developed symptoms, and one other patient had had symptoms from early life. The case of a 6-months-old boy was described by Goodale and Thomas (1954). However, it is well known that small pulmonary emboli to the arteriolar bed can produce progressive cor pulmonale (Owen *et al.*, 1953), while the findings of Evans *et al.* (1957) suggest that thrombosis may well occur as a secondary phenomenon. Dexter (1957) considered that all patients with pulmonary hypertension of undetermined cause should be regarded as having recurrent pulmonary emboli, and we believe this to be true for the great majority.

The resolution of pulmonary hypertension with anti-coagulant therapy, which occurred in Case 16, strongly suggests that thrombo-embolism alone can be the initiating cause and can produce a syndrome indistinguishable from idiopathic pulmonary hypertension. In Cases 12 and 14 there was no evidence of thrombo-embolism in life, yet at necropsy this was found to be the cause. A very similar if not identical picture may be produced by tumour embolism from the pelvis. Brill and Robertson (1937) described three types of pulmonary metastases from chorionepithelioma. A pelvic tumour may not be detectable and there may be no obvious signs of tumour emboli in the lung. Biological tests for pregnancy usually make the condition readily diagnosable, however.

Specific pulmonary arteritis is rare except for biharzial disease, which is well documented (Shaw and Ghareeb, 1938). Polyarteritis nodosa may affect the pulmonary circulation, and diffuse systemic sclerosis may produce pulmonary vascular sclerosis (Harrison, 1960). Carcinomatosis may invade the lymphatics and cause compression of alveolar capillaries without invasion of blood-vessels, or cancer cells may actually invade the small arteries and arterioles, producing a form of pulmonary endarteritis followed by intravascular thrombosis (Brill and Robertson, 1937).

The diagnosis of silent pulmonary micro-embolism is favoured if the patient is a woman who develops symptoms of pulmonary hypertension shortly after a long and difficult labour with forceps delivery, as in our Case 16 (Wilcken *et al.*, 1960). In this situation it is assumed that minute emboli arise from pelvic veins and lodge in the pulmonary arterioles.

The sudden onset of dyspnoea, fainting, chest pain, or cyanosis, particularly in a woman of child-bearing age, should at once arouse suspicion and careful clinical examination should be made. If any signs of pulmonary hypertension are present, then further investigation is

clearly indicated. The same attitude should apply to the onset of such symptoms in patients who have recently undergone a surgical operation or suffered a medical illness, especially if there has been any question of pulmonary embolism during or immediately after the acute phase of the illness. Great care should be taken to exclude or confirm the presence of a metastasizing tumour in the pelvis such as a chorionepithelioma; for, as Bagshawe and Brooks (1959) point out, chemotherapy may have something to offer these patients.

Diagnosis, Symptoms, and Clinical Signs

The symptoms are listed in Table III. Dyspnoea was present in all cases, while syncope occurred in approximately half the patients in each group. Chest pain, usually pleuritic, or haemoptysis, was implicit in the first group, since these were the basis of clinical division of the two groups. Chest pain did occur in the second group, but in only two patients, when it was anginal rather than pleuritic.

Symptoms such as infected sputum and wheezing suggesting lung or airways disease occurred in the minority, but cough was a common symptom in both groups.

The signs of early pulmonary hypertension, although well known, are worth emphasizing, for they may cause difficulty in interpretation (Pappworth, 1960), and it is at this stage that diagnosis is vital if treatment is to be successful.

The appearance of the patient is usually normal and the arterial pulse of good volume. The pinched appearance, malar flush, and cold extremities of advanced obstructive pulmonary hypertension are absent in the early stages of the disease. The jugular venous pressure may be normal apart from a slightly exaggerated pre-systolic "a" wave. The cardiac impulse may show slight right ventricular hypertrophy as indicated by a tapping and diffuse cardiac impulse. The auscultatory findings consist of a short ejection murmur in the region of the pulmonary artery immediately preceded by a systolic click. Murmurs are usually unimpressive, but occasionally a loud pansystolic murmur (as in Case 19) may be due to tricuspid insufficiency. The continuous murmur heard in Case 2 must be exceedingly rare. The pulmonary component of the second heart sound is accentuated and may be as loud as or louder than the aortic. The split is narrow and may be difficult to appreciate, although at this stage the second sound will usually widen on inspiration. The early diastolic murmur of pulmonary incompetence is often absent, but an atrial sound is occasionally heard (Table IV).

In some patients, however, the clinical signs of pulmonary hypertension may be unimpressive, or absent, as in our Cases 10 and 19. Diagnosis then becomes harder, but the condition should be borne in mind in any patient who has dyspnoea of uncertain cause or syncopal attacks (Table III).

The radiological and especially the cardiographic signs may be of considerable value, and are discussed in more detail below.

Signs of intrinsic lung disease, such as rhonchi, wheezing, and infected sputum, are unusual, but occurred in two patients (Cases 11 and 17). We do not know whether the lung symptoms follow the thrombosis or vice versa, but the former is less likely. It is evident, however, from Case 11, that airway obstruction, hypo-

ventilation, and hypercapnoea do not exclude thrombosis of the pulmonary arteries.

Cyanosis is usually absent, but was striking in two patients (Cases 3 and 11) who had considerable polycythaemia, and in one patient (Case 15) who had a patent foramen ovale (Table IV). Cyanosis may be peripheral or central in origin, the former being due to a low cardiac output or polycythaemia, and the latter to right-to-left shunting through a foramen ovale or the lungs to ventilation-perfusion imbalance, or to poor diffusion. Although cyanosis is more likely to occur in patients with massive occlusion of large pulmonary arteries, its presence does not exclude obstruction of microscopic vessels only, as shown in Case 15. Clubbing of the fingers is not usually a feature.

Confirmation of the diagnosis of obliterative pulmonary hypertension depends upon the demonstration at cardiac catheterization of pulmonary arterial hypertension with increased pulmonary vascular resistance in the absence of any pulmonary venous hypertension, obstruction to the left side of the heart, left-to-right shunt, or primary lung disease.

Pulmonary arteriography is usually extremely valuable in showing the level and sites of obstruction, but sometimes may reveal little more than enlargement of the main pulmonary arteries if the obstruction involves merely the microscopic arteries.

Respiratory function tests, showing hyperventilation and ventilation-perfusion imbalance, are of value, while the rapid fall of arterial saturation on effort and rise on 100% oxygen is characteristic.

Clinicopathological Types of Pulmonary Thrombo-embolism

Pulmonary thrombo-embolism can give rise to two distinct clinical pictures—that of occlusion of large pulmonary arteries or of arterioles and muscular arteries. The former type is often associated with an obvious source for embolization with underlying pulmonary vascular disease or heart disease, and is accompanied by pleuritic pain and haemoptysis. The latter type presents with signs and symptoms of progressive pulmonary hypertension without obvious cause. Fainting and dyspnoea may occur in both groups. We are concerned here, however, with patients who do not have underlying heart disease. The physical signs of pulmonary hypertension due to major arterial occlusion are very similar to those in the microscopic group, for the pulmonary vascular bed is usually extensively obliterated as a result of emboli from the occlusion in the larger arteries. It may be that in some cases the obstruction begins in the arteriolar bed and thrombosis tends to spread proximally. In both types parenchymal lung disease is usually absent. It is possible that thrombosis of the leg veins, giving rise to obvious episodes of phlebitis, is more likely to cause dislodgment of large thrombi with resultant larger pulmonary emboli and subsequent occlusion, whereas thrombosis in small pelvic venous radicles may merely give rise to emboli of the microscopic type. This view is supported by the similarity of patients with tumour embolism to those with microscopic thrombo-embolism, rather than to those with occlusion of the major branches.

Although the differentiation into two groups based on the presence or absence of clinical symptoms and signs suggesting pulmonary infarction usually serves to

distinguish those patients with massive occlusions from those with microscopic occlusions, there is some overlap, and exceptions occur. For example, Cases 4 and 8 had haemoptyses, pleuritic pain, and circulatory collapse suggesting embolism and infarction, but necropsy demonstrated only occlusion of microscopic branches and no infarction. By contrast, Case 17 had no clinical evidence of thrombosis or infarction, but her angiogram showed that a number of vessels did not fill in the left mid-zone and lower zones presumably as a result of an old infarct (Fig. 13). Case 10 had a history strongly suggestive of multiple pulmonary infarcts, but when she was seen several years later the clinical evidence of pulmonary hypertension was meagre, and the amount of obstruction to large pulmonary arteries revealed by angiography was unexpected (Fig. 6).

FIG. 13.—Case 17. Postero-anterior projection of pulmonary arteriogram showing area of lack of filling of part of left lower lobe due to obstruction, and tortuosity of segmental vessels typical of pulmonary hypertension.

Nevertheless, we believe that the division into two groups is important to the understanding of the disease, and in helping to arouse clinical suspicion of its presence. The association of frequent haemoptyses and phlebitis of the calf veins strongly suggests that major pulmonary vascular occlusion will be found, whereas dyspnoea, fainting, or merely progressive congestive heart failure without obvious source for embolic or repeated haemoptysis is more likely to be associated with occlusion to very small vessels.

In any individual patient with massive pulmonary artery occlusion it is often hard to say whether this has occurred *in situ* or as a result of embolism. We do not understand why some patients appear to be more prone to pulmonary vascular occlusion than others, but believe that the answer may lie partly in differing patterns of pulmonary vascular reactivity to embolism or to chemical factors which favour intravascular thrombosis. The manner in which the pulmonary vascular system will respond to severe pulmonary emboli, for example, clearly differs in different individuals. In the majority, apparently the disorder is self-limiting, but in some both embolism and pulmonary thrombosis continue remorselessly.

In the microscopic group there clearly exist both thrombo-embolic causes for occlusion and "primary" causes for pulmonary hypertension. Whether the occlusions in the thrombotic group have been initiated by vasoconstriction and medial hypertrophy of the

small arteries by an obscure arteritis or by embolism is unknown, but the final common path of these patients is likely to be thrombosis, for which long-term anticoagulant therapy appears to be the only real hope of relief. We are ignorant of the factors which may maintain pulmonary vasoconstriction in these circumstances and of the differing degrees of sensitivity of the pulmonary vasculature. Biochemical or neurogenic factors of which we know nothing may be concerned, and the situation is made more unsatisfactory by the paucity of our knowledge regarding abnormalities of blood coagulation and thrombosis. Better understanding of fibrinolytic mechanisms may improve knowledge of the disease.

Special Features of Thrombo-embolic Pulmonary Hypertension

Radiological Features

The radiological signs vary considerably, and there is a reasonably good differentiation between the two groups of pulmonary thrombo-embolism. In the group with major arterial obstructions irregular areas of hypertranslucency with absence of vascular markings are highly suggestive. Ehrner *et al.* (1959) have described abscess formation in the lungs, presumably at the site of infarcts, and this may have occurred in Case 10. Calcification in a thrombus in a large branch of the pulmonary artery may occur, as in our Case 1, and careful examination of a plain film, supplemented by tomography, may confirm the diagnosis. The effect of the pulmonary hypertension upon the heart is reflected by enlargement of the main pulmonary arteries, right ventricle, and often of the right atrium.

In the micro-embolic type without clinical evidence of thrombo-embolism the changes in the heart and main pulmonary arteries are very similar, but the lung fields show differences from the first group. Localized areas of hypertranslucency and loss of vascular markings do not occur. In milder cases the pulmonary vascular markings may be normal, but in severe cases there is a general loss of vascularity, so that the small branches appear thin and spidery and are often not seen out in the periphery of the lungs. The appearance may therefore resemble that of pulmonary stenosis of obstructive pulmonary hypertension of the Eisenmenger type. Enlargement of the right main pulmonary artery is commonly seen, however, and this is unusual in pulmonary stenosis.

Angiocardiography

Angiocardiography is of great value, and was carried out in six patients in group 1 (Cases 1, 2, 3, 5, 8, and 10) and in two in group 2 (Cases 17 and 19). In Cases 1, 2, 3, and 10 characteristic appearances were found, consisting of obliteration of medium-sized branches in various zones, and in Case 1 calcification was seen in the right main pulmonary artery. In Cases 5 and 8 the pulmonary vascular bed appeared entirely normal, despite the fact that the right ventricular pressure was greatly elevated to 75/10 mm. Hg. The failure of the angiocardiogram to demonstrate vascular occlusion is related to the presence of obstruction in arterioles and arteries too small to appear on the angiogram, as was confirmed at necropsy in Case 8.

In the second group, Case 17 unexpectedly showed an area of vascular loss in the left lower zone suggesting an old infarct (Fig. 13), and Case 19 showed pruning

of the small pulmonary vessels with great enlargement of the main arteries (Fig. 12). It is thus evident that the angiographic appearances do not always agree with the clinical assessment and mode of presentation (Table V).

Electrocardiography (see Figs. 1 and 9)

The tendency for inversion of the T wave in right precordial leads sometimes extending to left precordial leads has already been mentioned, and is well documented in acute pulmonary embolism (Wood, 1941; Cutforth and Oram, 1958). The absence of dominant R waves in right precordial leads is sometimes striking even in the presence of severe pulmonary hypertension, as shown in Cases 1, 4, 5, and 16. More commonly, however, there are the classical signs of severe right ventricular hypertrophy with a dominant R wave in right precordial leads. The tendency for T-wave inversion appears to be more marked than in right ventricular hypertrophy due to cor pulmonale resulting from obstructive airways disease (Caird and Stanfield, 1962). In the latter condition a deep S wave in V5 is common, but the T wave is frequently upright, whereas usually in thrombo-embolic pulmonary hypertension the T wave in this lead or V4 is flat or inverted, as in 14 of our 19 cases. Even more striking is the T-wave inversion in lead V3 which was present in all but one of our 19 cases, but is unusual in obstructive airways disease. We think this may be partly due to hyper-ventilation, but have not yet been able to substantiate this. Right atrial P waves are seen in thrombo-embolic pulmonary hypertension, but less often than in obstructive airways disease. They do not usually arise in the absence of T-wave changes, in contrast to obstructive airways disease in which right atrial P waves may be the first indirect sign of right ventricular hypertrophy. The axis of the P wave is usually normal in thrombo-embolic pulmonary hypertension (Caird and Stanfield, 1962).

The cardiographic changes in thrombo-embolic pulmonary hypertension may be of sufficient specificity to suggest the diagnosis in some patients, particularly so when T-wave inversion is widespread in chest leads without dominant R waves in right precordial leads.

Haemodynamics of Obliterative Pulmonary Hypertension (Table VI)

Cardiac catheterization was carried out in 15 of our 19 patients. In every case the pulmonary-artery pressure was substantially elevated and there was no evidence of any left-to-right intracardiac shunt or left heart lesion. The arterial oxygen saturation was variable and usually slightly reduced. The general tendency for a higher pulmonary vascular resistance in obliterative hypertension than in mitral-valve disease or obstructive-airways disease reflects the obliteration of the pulmonary vascular bed by organic disease. The levels of pulmonary vascular resistance more nearly approach those found in the Eisenmenger syndrome due to atrial or ventricular septal defect or patent ductus arteriosus. Indirect left-atrial-pressure measurements were not obtained in all patients, for narrowing of the small pulmonary arteries often made the wedging of the catheter in a position suitable for recording retrograde left atrial pressure very difficult. Where the wedge pressure was measured, however, it was within the normal range, indicating that the obstruction lay proximal to the capillary bed and pulmonary veins.

Table VI gives the haemodynamic data in the patients studied.

Effect of 100% Oxygen and Drugs upon Haemodynamics in Obliterative Pulmonary Hypertension (Table IX)

Studies with drugs and 100% oxygen may give some idea of the capacity of the pulmonary vascular bed to dilate, and therefore of the degree of obliteration. Such studies were carried out in six patients (Cases 4, 10, 11, 12, 13, and 16). In Case 4 intravenous injection of hexamethonium bromide resulted in a fall in pulmonary vascular resistance from 12 to 9 units, but the systemic resistance fell also, suggesting that the effect upon the pulmonary vasculature may have been secondary to that on the systemic circulation (Goodwin *et al.*, 1958; *Brit. med. J.*, 1960a). In Case 12 the administration of imidazoline failed to lower the pulmonary vascular resistance, and in Case 13 the administration of hexamethonium bromide resulted in a response similar to that in Case 4, there being a slight fall in systemic and pulmonary-artery pressures. In Case 16 a response was obtained to 100% oxygen but not to aminophylline or imidazoline (Wilcken *et al.*, 1960). In Cases 10 and 11 there was no effect of acetylcholine (Fig. 7) although 100% oxygen reduced the pulmonary-artery pressure in Case 11 but not Case 10.

The response to 100% oxygen in Cases 11 and 16 suggested that the pulmonary vascular bed was capable of dilatation. This finding harmonized with the signs of moderate pulmonary hypertension clinically, and with the scanty symptoms in Case 16, where the reversible nature of the obliteration was subsequently demonstrated by the fall in pulmonary vascular resistance after treatment with anticoagulant drugs. In Case 11 the pulmonary pressure was much higher and no such beneficial result occurred.

The ability of the pulmonary vascular bed to respond to vasodilating measures may depend not only on the extent of the obliteration but also on the level of obliteration. If the obstruction exists proximal to the arterioles it is possible that some response might be obtained, which would not be the case if the obstruction lay dominantly in the arterioles themselves. Our experience suggests that in obliterative pulmonary hypertension the obstruction usually lies in the arterioles and therefore one would not expect a response if the pulmonary vasculature was extensively obliterated by thrombo-embolism or other disease. However, both Dresdale *et al.* (1951) and Wood (1958a) have obtained a fall in vascular resistance with imidazoline and acetylcholine respectively in idiopathic pulmonary hypertension. The response to vasodilator measures might give a clue to the aetiology in some of the true idiopathic patients. It is possible that those in whom the disease begins with an intense vasoconstriction of the arteriolar bed might respond to vasodilating drugs more dramatically than those who start with primary thrombosis.

Polycythaemia

In all patients the haemoglobin was above 14 g./100 ml., and in six it was above 16 g. Three patients had frank polycythaemia (Cases 3, 11, and 12). Investigation did not substantiate a diagnosis of primary polycythaemia, and it is probable that the increased haemoglobin was due to the reduced arterial oxygen saturation.

Serum Proteins

These were studied in 10 patients, the albumin/globulin ratio being reversed in four, but one of these (Case 19) had a protein-losing enteropathy and two others had heart failure.

Respiratory Function Tests (Table VIII)

Respiratory function tests were performed in eight patients (Cases 1, 2, 3, 10, 11, 16, 17, and 18). The most dramatic changes were found in group 1. All but one (Case 11) had a normal forced expiratory volume, expressed as a percentage of vital capacity (F.E.V.% V.C.), but all had some reduction in one-second forced expiratory volume (F.E.V.₁), suggesting a restrictive lesion of the lungs. Hyperventilation was detected in four patients, and imbalance between ventilation and perfusion also in four. The mixed venous PCO_2 was measured in four patients and was elevated in two and low or normal in the others. In one patient (Case 11), who had gross airways obstruction, wheezing, and bronchitis, the PCO_2 was initially raised to between 55 and 70 mm. Hg, but fell terminally to 48 mm. Hg when hyperventilation occurred. Studies of regional pulmonary blood flow with radioactive carbon dioxide labelled with oxygen by the method of Dyson *et al.* (1960) and West and Dollery (1960) showed a reduced flow in all areas consistent with pulmonary hypertension, but with the exception of Case 2 there were no regional differences.

The behaviour of the arterial oxygen saturation measured by ear oximetry on inhalation of 100% oxygen and on effort was studied in nine patients (Table VII). In each patient the low initial level of saturation rose to normal or above on 100% oxygen, and fell substantially on effort. This was considered to indicate impaired perfusion/ventilation relationships, possibly with shunts in the lungs, rather than a right-to-left shunt in the heart.

From these limited studies a pattern of respiratory function could be detected which consisted of restricted lung movement, hyperventilation, increased dead space, and impaired perfusion/ventilation relationships. These abnormalities were most striking in patients with massive pulmonary-artery occlusion. The hyperventilation was a notable feature in some patients, and was thought to be due to an abnormal respiratory "drive" resulting from abnormal ventilation and perfusion in parts of the lungs. Further work is planned on this aspect of the disorder.

Pathology

The pathological findings have been briefly mentioned in Tables I and II and described in more detail in the case reports of the patients who died. A full study of the gross pathology, histology, and post-mortem pulmonary angiography will be published elsewhere (Harrison, 1963).

Prognosis and Incidence of Obliterative Pulmonary Hypertension

In idiopathic hypertension the prognosis is uniformly bad, and this is also true for thrombo-embolic pulmonary hypertension, for once symptoms develop the course is usually unfavourable (Owen *et al.*, 1953). A few patients with established thrombo-embolism have recovered, however. Two were reported by Wood (1956) and one by Dexter (1957), although in the last patient, while clinical improvement occurred, the pulmonary vascular resistance did not fall. Our own patient (Case 16)

is perhaps the most dramatic example of recovery of thrombo-embolic pulmonary hypertension with treatment.

Our own series bears out the ill-omen of the disorder, for 11 of the 19 patients died of the disease, despite long-term anticoagulant therapy in 12. Patients 1, 2, and 3 had phenindione for from five months to four years without obvious benefit.

Incidence.—The incidence of obliterative pulmonary hypertension is extremely difficult to assess. The relatively high incidence of thrombo-embolism in hospital patients is recognized, and it may be that thrombosis in pelvic and calf veins occurs not uncommonly during surgical operations (*Lancet*, 1960). Sharnoff (1959) studied blood coagulability in patients undergoing extensive surgery and noted an abrupt rise in platelet count, and shortening of clotting-time within a few hours of the start of the operation. Both these factors tended to return to normal a few hours later, although in some patients a second thrombotic phase developed in the first post-operative week. It is possible, therefore, that many patients during and after operations may have unrecognized thrombosis which may lead to thrombo-embolism which could progress insidiously until the pulmonary vascular bed has become irrevocably obstructed. It is therefore important to consider the diagnosis in patients with unexplained dyspnoea, chest pain, calf tenderness, haemoptysis, or vague ill-health after surgical procedures, and to follow up patients who have had pulmonary infarction.

Treatment

The experience of others and the findings in our own cases suggest that the only treatment likely to be of benefit is anticoagulant therapy, and that this applies equally to primary idiopathic pulmonary hypertension and thrombo-embolic pulmonary hypertension. Sevitt and Gallagher (1959) and Honey and Truelove (1957) have shown that phenindione effectively prevents venous thrombosis and pulmonary emboli.

The failure of anticoagulant therapy in all our treated patients save one was probably due to late diagnosis and treatment. In our view it is vital to make an early diagnosis and initiate treatment at once. We believe also that frank pulmonary embolism in otherwise healthy people should be treated for three to six months rather than the customary three weeks, and that careful watch should be kept on such patients for several years after the event to detect the onset of pulmonary hypertension and prevent the sudden occurrence of further vascular occlusion.

A point of considerable interest was the high incidence of reactions to phenindione, which occurred in three of the seven patients so treated, an incidence greatly in excess of the 3.6% noted among 522 patients by Stafford (1961) (*Lancet*, 1962).

SUMMARY

Nineteen patients with obliterative pulmonary hypertension without underlying heart disease are described and divided into two groups according to the presence of signs of pulmonary embolism or thrombosis.

The first group, consisting of 11 patients, presented with dyspnoea, symptoms suggestive of pulmonary infarction, and pulmonary hypertension. A source for embolism was present in the calf veins in six patients,

in the right ventricle in one, and in the pelvis in one. No source was found in three. Obstruction to major pulmonary arteries was proved by angiocardiology or necropsy in four. Obstruction to microscopic pulmonary arteries only was found at necropsy in two others.

Cardiac catheterization revealed severe pulmonary hypertension and an elevated pulmonary vascular resistance. Respiratory-function tests showed a characteristic pattern consisting of normal airways resistance, but reduced forced expiratory volume at 1 second; hyperventilation; ventilation-perfusion imbalance; and reduced arterial oxygen saturation at rest, falling on effort, and increasing to normal on 100% oxygen. Electrocardiography showed T-wave inversion in right and central precordial leads.

The second group of eight patients presented with dyspnoea, syncope or chest pain, and pulmonary hypertension. There was no history of pulmonary infarction and no apparent source for embolism. Clinically the condition was indistinguishable from idiopathic pulmonary hypertension, but in three of four necropsies the smallest pulmonary arteries were found to be occluded by thrombus. Angiography in life showed large main pulmonary arteries and tortuous branches, but no obvious obstruction. Pulmonary arteriography after death showed reduction in the normal number of tiny background arteries. Cardiac catheterization revealed a high pulmonary vascular resistance, and the electrocardiogram showed T-wave inversion as in the first group.

The results indicated that thrombosis may insidiously involve any part of the pulmonary arterial tree, commonly causing obstruction to major branches when a source for emboli is evident, such as in the lower limb veins or pelvis, but often occluding the arterioles only in the absence of an obvious source of embolism.

Thrombo-embolic pulmonary vascular disease should be suspected in any patient with unexplained haemoptysis, dyspnoea, or pulmonary hypertension. Hyperventilation with arterial desaturation on effort in the absence of underlying cardiac or pulmonary disease is particularly suspicious of involvement of the large pulmonary arteries.

The prognosis is poor, for 11 patients died of the disease, and treatment is unsatisfactory once severe pulmonary hypertension has developed, for much of the pulmonary vascular bed has by then been obliterated. Early diagnosis is essential, and prolonged anticoagulant therapy offers some prospect of success.

Pulmonary arteriography is the most informative single investigation, but clinical examination, the electrocardiogram, and respiratory-function tests offer important clues.

The pathogenesis of pulmonary thrombosis and embolism, the anomalies of respiratory function, and the various manifestations of the disease are discussed.

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Over 20 architectural firms have agreed to join working groups with architects of the Ministry of Health and of regional hospital boards to design component parts of hospitals for repetitive use. Eight working groups have been formed. Each group will deal with one or more classes of component, such as doors, sanitary fittings, storage, structural floors and frames, external cladding, etc. This development is the outcome of a recent conference at the Royal Institute of British Architects. A similar group has been set up in Scotland and one is being formed in Northern Ireland.