TABLE VI

Case No.	Hb g./100 ml.	R.B.C. mil./c.mm.	M.C.V. μ^3	M.C.H.C. %	Retic. %	Treatment Day
10	{ 12.0 11.8	{ 4.2 4.4	88	32	0.1	Before treatment
3	{ 9.7 9.7	{ 3.3 3.4	109 109	27 27		14

nately, treatment in Case 10 had to be interrupted owing to the development of a cerebrovascular crisis after 10 days; treatment in Case 3 was continued for 15 days.

Hench *et al.* (1950), reviewing the effects of cortisone and A.C.T.H. in rheumatoid arthritis, noted that the concentration of haemoglobin and also the red blood count improved. Moreover, in Cushing's syndrome, in which there is an increased secretion of the gluco-corticoid hormones of the adrenal cortex, a polycythaemia is constantly found. The prompt response in Case 2 of both the haemoglobin and the red-cell count, and the presence of a reticulocytosis, suggest that cortisone may be capable of curing the anaemia of hypopituitarism. In view of this improvement it was particularly unfortunate that the patient terminated treatment prematurely. The response of the haemoglobin in Case 8 was again suggestive of the potency of cortisone in relieving the anaemia: the duration of treatment in this case is unfortunately too short to allow conclusions to be drawn.

The response of both the cases in which A.C.T.H. was given was disappointing; in neither case, however, was it possible to continue the administration for a very long time, and little change was observed clinically. The occurrence of cerebrovascular episodes in these patients makes it necessary to proceed cautiously with this substance, and in future it might be better to give small doses for a prolonged time.

Summary

Two types of anaemia are found in hypopituitarism—macrocytic hypochromic and normocytic hypochromic. The anaemia is usually of moderate severity.

The response to treatment with thyroid, testosterone, and iron is unsatisfactory, but cortisone seems to produce a prompt increase in the red-cell count and the haemoglobin concentration.

The cortisone and A.C.T.H. used in this work were a gift from Merck and Co. through the Medical Research Council. These substances were made available for this work through Professor H. L. Sheehan, to whom I am also indebted for much helpful advice.

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A SURVEY OF PULMONARY EMBOLISM IN A GENERAL HOSPITAL

BY

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A careful watch for pulmonary embolism in all departments of a general hospital combined with the free use of radiography showed thrombo-embolic disease of the lung to be the commonest of all serious acute pulmonary diseases. The radiological appearances having been discussed elsewhere (Short, 1951), the object of this communication is to present the clinical aspects of the condition and to stress its frequency.

Pulmonary embolism or pulmonary infarction was diagnosed in 113 patients admitted to Southmead General Hospital during the two and a half years ending March 31, 1950, and seven cases were seen elsewhere by me during the same period. I examined 85 of the 120 cases personally. The remainder were either rapidly fatal cases, or cases in which the diagnosis was not made before death or discharge from hospital. Necropsy revealed a certain number of unsuspected infarcts, and eight cases were diagnosed in retrospect by looking up the notes of all patients from the surgical and obstetrical wards who had chest radiographs taken post-operatively or in the puerperium. Besides the 120 definite cases presented here, a further 30 were seen in which the diagnosis of pulmonary infarction seemed probable but which are omitted because the evidence was inadequate or because it was impossible to exclude an alternative diagnosis.

Incidence

Table I analyses the cases according to the underlying disease. One-quarter were surgical (post-operative), one-sixth obstetrical, and the remainder (58%) medical. Of the medical cases, four-fifths were suffering from heart disease.

TABLE I.—Analysis of Cases According to Underlying Disease

	No.	Pulmonary Infarction	Pulmonary Embolism	Death	Necropsy
Medical ..	70	65	6*	45	41
Surgical ..	30	22	8	10	9
Obstetrical ..	20	19	2*	2	2
Total ..	120	106	16	57	52

* In two instances, pulmonary infarction was followed by massive pulmonary embolism.

Pulmonary embolism or infarction was diagnosed in 2.5% of all medical cases, 0.5% of all surgical cases, and 0.17% of all obstetrical cases. The incidence of pulmonary thrombo-embolism exceeded that of all other serious acute pulmonary diseases during this period, including lobar pneumonia (Table II).

TABLE II.—Hospital Admissions over Two and a Half Years of the Major Pulmonary Diseases (Excluding Tuberculosis)

Disease	No.
Primary pleural effusion ..	33
Primary carcinoma of lung ..	50
Lobar pneumonia ..	100*
Pulmonary embolism and infarction ..	113

* This figure from the hospital records may include some cases of bronchopneumonia and virus pneumonitis; it is probably too high.

In contrast with the reports of Farr and Spiegel (1929), de Takats et al. (1940), and Oschner (1945), and in agreement with the large review of Pilcher (1937), no seasonal variation was evident.

Medical Cases

Although pulmonary embolism is often more dramatic in surgical and obstetrical patients, it is more frequent in the medical wards and particularly in patients with heart disease (White, 1940; Carlotti et al., 1947).

Cases With Heart Disease

In addition to the 54 cases with heart disease admitted to the medical wards, two were admitted to the obstetrical wards on account of pregnancy and one to a surgical ward with retention of urine. Of these 57 cases, rheumatic heart disease accounted for a little less than half, and hypertensive and coronary disease for just under a quarter each.

Approximately 10% of all cases of heart disease admitted to hospital during this period were complicated by pulmonary embolism. The incidence was highest in rheumatic and coronary disease (15% in both groups) and lowest in hypertensive heart disease (5.6%). In half the cases of coronary disease, pulmonary infarction followed an episode of myocardial infarction. In four cases the interval between the two events was less than five days, and in none was it longer than a fortnight.

Pulmonary Congestion.—Judged by the presence of rales and radiographic evidence of marked hilar engorgement, pulmonary congestion was estimated to be severe in 76% of the cases with heart disease at the time of examination (Table III). A similar degree of pulmonary congestion was seen in only 4% of cases without heart disease, and in 37% it was considered to be absent altogether.

TABLE III.—Degree of Pulmonary Congestion in the 94 Cases in Which a Radiographic Examination was Made

	No.	Severe	Moderate	Absent
With heart disease ..	46	35	10	1
Without heart disease ..	48	2	28	18
Total ..	94	37	38	19

Arrhythmia.—Established auricular fibrillation was present prior to pulmonary embolism in 15 cases, a paroxysm of auricular fibrillation in 6, and auricular flutter in 2. The remaining 60% were in normal rhythm.

Thrombosis of Veins.—There were signs of deep femoral thrombosis in five cases, saphenous thrombophlebitis in six, and thrombosis of the brachial and cephalic veins in two. In addition, one patient was suffering from gangrene of the leg with presumptive venous thrombosis. In the remaining 43 cases there was no clinical evidence of venous thrombosis, though bilateral oedema of the legs due to congestive heart failure was present in 26 of them.

Recurrent Embolism.—There were several instances in which repeated pulmonary embolism led to a fatal issue. The following case history of a man aged 26 with rheumatic mitral stenosis illustrates this feature.

Haemoptysis, followed by a left-sided haemorrhagic pleural effusion, led to the diagnosis of the first pulmonary infarct in November, 1947. The second occurred in the following February and precipitated the development of congestive failure. The third episode did not occur until February, 1949, when left saphenous thrombophlebitis was followed by an attack of right-sided pleuritic pain. There was further infarction of the right lung in May of the same year, and in September he was admitted for the last time with three fresh infarcts.

Mortality.—Of the 57 cases of heart disease complicated by pulmonary infarction, 36 were fatal. In 14 cases death was a direct result of the pulmonary complication, and in

13 cases pulmonary infarction was an important factor in determining a fatal issue. The nine remaining deaths were due to cardiac failure, pulmonary infarction being incidental.

Cases Without Heart Disease

This group of 16 cases falls into three subgroups. The first consists of seven patients with long-standing saphenous varicosities, thrombophlebitis, and, in several cases, crural ulceration. The second is composed of six elderly patients (aged 59 to 70) suffering from a variety of chronic illnesses involving prolonged recumbency. The third consists of three patients, previously quite healthy, in whom pulmonary embolism occurred without obvious cause. The first and last of these subgroups require brief comment.

Whereas pulmonary embolism is often regarded as an uncommon complication of saphenous thrombophlebitis, the occurrence of seven cases in two and a half years suggests that its importance has been underestimated. Three of the cases were fatal—one from massive embolism, another from extensive infarction, and a third from chronic cor pulmonale following repeated embolism. In these cases the emboli arise not from the saphenous system but from the deep veins which become invaded by extension through the saphenous or popliteal openings (Wright, 1948), or which may have been the seat of previous thrombosis (Bauer, 1946).

The fact that pulmonary embolism may occur without warning in apparently healthy persons is emphasized by the three cases admitted to hospital with a diagnosis of pneumonia which had subsequently to be changed to pulmonary embolism. The history of the one fatal case will serve as a typical example.

A woman aged 49 gave a history of 13 days' left-sided pleuritic pain, cough, and fever. Sulphonamides had been administered for four days without benefit. Examination revealed a pleural rub at the left base with signs of consolidation. There was no history or evidence of thrombosis in the veins of the legs. Radiography showed a shadow at the left base and another small one at the right base. She made good progress, though there was no dramatic response to penicillin. A second radiograph, taken 11 days after admission, showed the left base virtually clear, though the diaphragm on that side was raised and there was also a small pleural adhesion at the right base. The following day the patient had a massive pulmonary embolism and died suddenly. At necropsy, the embolus was found in the main pulmonary artery and there was thrombus in the right popliteal vein.

Such cases, although not often fatal, are probably much commoner than is realized. In 1943 Homans reported 11 similar instances of thrombus developing silently in the deep veins of the leg in healthy persons whose first symptoms were those of pulmonary embolism or infarction.

Surgical Cases

Pulmonary embolism was diagnosed in 30 surgical cases, being responsible for death in eight. Adults of all ages were affected, but massive embolism was much more frequent in the elderly. Although only 27% of the patients were over 60, 62.5% of the instances of massive embolism were in this age group. Only one patient had heart disease. Eight had mild or moderate hypertension, but these showed no evidence of heart failure at the time of examination.

TABLE IV.—Surgical Cases—Operations Performed

Abdominal section (including partial gastrectomy 5, appendicectomy 5, hysterectomy 3) ..	20
Genito-urinary (including prostatectomy 2, suprapubic cystostomy 2) ..	5
Inguinal hernia ..	3
Miscellaneous:	
Bilateral compound fracture of tibia and fibula ..	1
Trendelenburg operation for varicose veins ..	1

Note.—In cases in which two operations were performed the major one is named. In three cases the appendix was removed at the close of the primary operation. In one case a herniotomy was performed after abdominal section. None of the five appendicectomies was straightforward, a gangrenous organ or an abscess being found on each occasion.

Type of Operation.—A negligible amount of cranial and thoracic surgery was performed at the Southmead General Hospital during this period, hence the finding (Table IV) that all the operations in this series were below the diaphragm is of no significance. It should also be mentioned that most of the gynaecological and fracture surgery was undertaken elsewhere. It has often been noted that cases in which infection is present and those in which the operation is long and difficult appear to be particular candidates for pulmonary embolism, and the present small series may be regarded as supporting these observations.

Thrombosis of Veins.—Thrombosis of the deep or superficial veins of the leg could be demonstrated in 50% of cases. There was clinical evidence of deep thrombosis in eight and of superficial thrombosis in three more. In four cases necropsy revealed thrombosis in the veins of the soleus muscle which had not been suspected during life. In two cases emboli appeared to arise from a leg in which saphenous phlebitis followed the use of this vein for transfusion.

Time of Embolism.—The majority of emboli occurred during the first and second post-operative weeks. In four cases there was a close relationship to first risings, as in the following examples:

A man aged 75 underwent retropubic prostatectomy. Three days later he got out of bed for the first time since the operation and had a fatal collapse 10 minutes later.

A man aged 74 underwent retropubic prostatectomy but remained in bed 12 days. On the twelfth day the house-surgeon urged him to start sitting out. Much against his will, he did so. After one and a half hours he complained of feeling faint and was helped back to bed, where he collapsed and died quickly.

In both instances the pulmonary artery was found to contain a long coiled thrombus which had originated in the lower limb.

Both mechanical and humoral factors may be operative in these cases. Chapman and Linton (1945) have shown that the act of straining at stool gives rise to violent fluctuations in venous pressure and flow in which any thrombus that may be present in the femoral veins tends to be dislodged. A similar mechanism probably comes into play in the effort of getting out of bed. Frequently the two events are combined, the first day out of bed being also the occasion of the first visit to the lavatory, though this was not specifically noted in the cases described above.

Macfarlane and Biggs (1946) have shown that fibrinolysis is activated by fear. This factor may be important (by causing detachment of thrombus) in those cases in which a patient is urged to sit out of bed against his inclinations and perhaps with considerable apprehension; or even if there is a dread of painful defaecation.

Obstetrical Cases

Considering the large number of deliveries, normal and abnormal, conducted in hospital, an incidence of pulmonary embolism of 0.17% is not high, a fact which is probably related to the low average age of the patients. Nevertheless there were two fatal cases in two and a half years, and a similar outcome was avoided in several others by only a small margin. The two factors which appeared to predispose to pulmonary embolism were age and any complication of pregnancy, delivery, or the puerperium. Of the cases, 55% were over 30, although only 30% of the women admitted to the obstetrical wards were in this age group. In other words, the incidence of pulmonary embolism in those under 30 was 1.1 per 1,000, whereas in those over 30 it was 3.1 per 1,000.

With one exception, pulmonary embolism was never seen in the absence of clinically obvious femoral venous thrombosis or some complication of pregnancy or delivery (Table V).

TABLE V.—Analysis of Obstetrical Cases

Case	Age	Femoral Thrombosis	Complication
6	37	+	Caesarean section
18	37	+	" "
38	31	+	" "
50	37	+	Toxaemia, hysterotomy
52	27	+	" "
57	24	+	" "
61	24	+	" "
62	20	+	Forceps delivery
65	33	+	Toxaemia, hysterotomy
71	35	+	" "
78	22	+	Peritonitis
79	32	+	Manual removal of placenta
82	42	+	" "
83	19	+	Evacuation of uterus
84	28	+	Rheumatic heart disease
88	35	+	" "
89	26	+	" "
97	20	+	Toxaemia
111	45	+	Rheumatic heart disease, caesarean section
147	39	+	Toxaemia, hysterotomy

Necropsy

Of the 57 deaths, 30 were a direct result of pulmonary embolism or infarction. A necropsy was performed in 52 cases, the presence of a pulmonary embolus or infarct being confirmed in all except four. In three of these serial radiography indicated that the infarct had resolved before death. In the fourth—a case of mitral stenosis and auricular fibrillation with good clinical and radiological evidence of two pulmonary infarcts between two and five months before death—the appearances were distorted by brown induration and pulmonary collapse secondary to long-standing pleural effusion.

In over half the necropsies there was evidence of more than one pulmonary infarct. Taking all evidence—clinical, radiological, and post-mortem—together, 52% of the 106 patients with pulmonary infarction gave evidence of two or more infarcts. Pleural effusion related to the pulmonary infarction was found in 11 cases, being blood-stained in five.

Origin.—In 29 of the necropsies a thorough search was made for the site of origin of the embolus. (This may necessitate dissection of the calf muscles and foot, which was prevented in some instances by restrictions.) Of these 29 cases, thrombus was found in the veins of the lower limb in 83%, in the heart in 17%, and elsewhere in 7% (Table VI). In two cases two potential origins were found. It is noteworthy that thrombus was found in the right heart chambers in only 5 of the 36 cases of heart disease—in each of which there had been long-standing auricular fibrillation—and in one of these an alternative origin was present in the femoral veins.

In 13 cases necropsy revealed thrombus in the femoral veins which had not been suspected during life. Three patients with chronic congestive failure were found to have thrombus in either the femoral or the profunda femoris vein. Thrombus was also found in the femoral vein in two cases of heart disease in which oedema of the legs had never been detected.

TABLE VI.—Source of Embolus Discovered at Necropsy—29 Cases

	No.	Leg	Heart	Elsewhere
Medical	22	18	5	1
Surgical	5	5	—	—
Obstetrical	2	1	—	1
Total	29	24	5	2

Note.—In two cases two potential origins were discovered.

Clinical Picture of Pulmonary Infarction

The non-resident medical staff see few cases of pulmonary embolism without infarction. Massive embolism occurs most often in the surgical and obstetrical wards, and the crisis is usually past before outside help can be obtained. Smaller emboli, on the other hand, are often overlooked. The patient may complain of transitory breathlessness or

faintness or momentary tightness in the chest. Physical examination generally reveals nothing abnormal, and radiography, too, is frequently negative, though an area of abnormal translucency may be found if sought for carefully (Westermarck, 1938). A minority of cases show an abnormal electrocardiogram.

Signs in the Chest

The physical signs in the chest in pulmonary infarction depend on three main factors which may be found either singly or in combination—namely, consolidation, pleurisy, and elevation of the diaphragm.

Shortly after infarction it was generally noted that the respiratory rate was raised and the movements of the chest were restricted. Auscultation sometimes revealed little abnormal. The commonest findings during the first 36 hours were diminished air entry and a few rales; less commonly there was a pleural rub. Later the percussion note might become moderately or markedly impaired and bronchial breathing be heard. In some cases there was tubular breathing without rales. Since the lower lobes are most often affected, the signs were most commonly found at the bases, posteriorly and laterally. Marked symptoms were sometimes produced by small infarcts with very localized signs.

Signs of pleural effusion were present in one-sixth of the cases, though radiology demonstrated the presence of hydrothorax in almost twice this number. In the absence of heart disease the amount of fluid was rarely great. Where an effusion of moderate size covered an area of infarction, the stony dullness to percussion associated with bronchial breathing was sometimes very striking.

Significant elevation of the diaphragm was demonstrated radiologically in 35% of cases. It was found in over 50% of cases without heart disease and was sometimes extreme. Clinically, this gave rise on the left side to a tympanitic percussion note at a higher level than usual, and in one case gastric resonance was found as high as the fourth intercostal space in the mid-axillary line. Marked elevation of the right dome produced signs simulating pleural effusion, and in three cases, in which the elevation was associated with pleural adhesion, it actually led to attempted paracentesis thoracis.

A radiographic examination is undoubtedly the most valuable aid to the bedside diagnosis of pulmonary infarction. A suggestive or confirmatory picture may be expected at some time in the course of the disease in almost every case (Short, 1951).

Tachycardia and Arrhythmia

Some degree of tachycardia is the rule in pulmonary infarction, and rates as high as 140 a minute are not uncommon. In the present series a regular rate exceeding 120 a minute was found in 19 cases (Table VII). In 18 the mechanism was simple sinus tachycardia, but in one case the electrocardiogram showed ventricular tachycardia. This latter patient had a myocarditis of uncertain aetiology and died within a fortnight.

TABLE VII.—*Tachycardia and Arrhythmia in Pulmonary Infarction*

	No.	Pre-existing Infarction				Following Infarction		
		A.F.	A.F.(P.)	Fl.	H.B.	S.T.	P.T.	A.F.(P.)
Medical ..	65	15	6*	2	—	11	1	3
Surgical ..	22	—	—	—	1	4	—	1
Obstetrical ..	19	—	—	—	—	3	—	1
Total ..	106	15	6*	2	1	18	1	5

A.F. = Auricular fibrillation. A.F.(P.) = Auricular fibrillation (paroxysmal). Fl. = Auricular flutter. H.B. = Heart-block (auriculo-ventricular). S.T. = Sinus tachycardia (over 120 a minute). P.T. = Paroxysmal tachycardia (ventricular).

* In three cases it was impossible to be certain whether the arrhythmia preceded or followed infarction.

Occasionally pulmonary embolism induces a paroxysm of auricular fibrillation. When auricular fibrillation is found in a case seen for the first time after pulmonary embolism it

is often impossible to tell whether the arrhythmia was present beforehand or not. Usually it may be assumed to have preceded the embolism; the reverse is much less common. The present series, however, includes five cases in which there was good evidence that auricular fibrillation was induced by pulmonary embolism. Four were suffering from heart disease; the history of the fifth, a surgical case, was as follows:

A man, aged 60 and hitherto healthy, was sent to a cardiologist on account of attacks of epigastric pain. No evidence of heart disease was found, though his blood pressure was 240/110. There was no cardiac enlargement, and the electrocardiogram was normal apart from occasional auricular extrasystoles. A barium-meal examination revealed a large gastric ulcer. Partial gastrectomy was performed in January 26, and seven days later he was observed to have thrombophlebitis of the right long saphenous vein, which had been used for transfusion during the operation. The same day, on his way back from the lavatory, he collapsed with pain in the chest and a feeling of faintness. The following day he expectorated some blood and complained of left-sided pleuritic pain. Diminished air entry and a few rales were audible at the left base, and, later, radiography showed a shadow in the left costophrenic angle. When first seen on the day of the pulmonary embolism the pulse was regular at 120 a minute. Next day the pulse was irregular and the electrocardiogram confirmed auricular fibrillation. The rhythm reverted to normal after digitalization and was still regular when the patient was last seen two years later.

Unexplained tachycardia or rapid auricular fibrillation not controlled by adequate doses of digitalis in a patient with heart disease should suggest three possible complications—namely, active carditis, thyrotoxicosis, and pulmonary infarction. The last-named is often a stealthy process in the presence of cardiac failure, and is easily overlooked.

Haemoptysis

If pulmonary infarction is not diagnosed in the absence of haemoptysis most cases will be missed, for this symptom was present in less than 40% of the total and in only 17% of those without heart disease. The amount of blood expectorated was usually small, though occasionally it was considerable and was continued for as long as a week.

Haemoptysis is a well-recognized symptom of heart disease, apart from pulmonary infarction, in patients with mitral stenosis or left ventricular failure. Nevertheless, persistent or recurrent haemoptysis in a patient with heart disease should always suggest pulmonary infarction.

Pleurisy

Next to haemoptysis, pleuritic pain is perhaps the most dramatic symptom of pulmonary infarction. Ninety per cent. of the surgical and obstetrical patients complained of it, though a pleural rub was heard in only a quarter of these (Table VIII). One-sixth of the cases developed signs of hydrothorax. In the majority the amount of fluid was small, rarely exceeding half a litre.

TABLE VIII.—*Incidence of Pleurisy in Pulmonary Infarction*

	No.	Pleuritic Pain	Pleural Rub	Pleural Effusion
Medical ..	65	30	14	15
Surgical ..	22	20	6	4
Obstetrical ..	19	17	4	3
Total ..	106	67	24	22

Note.—This table excludes cases with hydrothorax due to cardiac failure and those with small amounts of fluid not detected clinically.

In patients with heart disease pleuritic pain was rarer and effusion more common. Several of these patients presented with a large unilateral effusion. In such cases the fluid often showed a tendency to persist for months despite a good general response to digitalis and mersalyl.

There was an opportunity of inspecting the fluid, either by paracentesis or at necropsy, in 17 cases. It was haemorrhagic in eight. It is sometimes taught that an effusion resulting from pulmonary infarction is inevitably haemorrhagic, but in corroboration of the present findings it may be recalled that Spain and Moses (1946) found macroscopic blood in only 13 out of 47 effusions.

In one case an empyema resulted from secondary infection of an infarct followed by rupture of the abscess into the pleural cavity. In the remaining eight cases a yellow serous fluid was found. One specimen submitted for microscopy and culture was reported as sterile and containing an occasional lymphocyte. Such a fluid could easily be regarded as tuberculous in a case presenting without a characteristic history. A routine test for bile pigments was unfortunately not made. It has been suggested (Krause, 1945) that their presence in an effusion (presumably in the absence of jaundice) is diagnostic of pulmonary infarction.

Jaundice

Jaundice was observed in almost a third of the cases of heart disease complicated by pulmonary infarction. Half the patients were suffering from rheumatic heart disease. It was only once seen in a case of pulmonary infarction without heart disease, and in this instance the patient was found to have a chronic haemolytic anaemia.

Clinically, the depth of jaundice varied from a slight tinge to a deep yellow. Bile was present in the urine in one-third of the cases in which it was tested for. The serum bilirubin was estimated in 12 cases. In 11 the level was above 2 mg./100 ml., and in one it was 5 mg./100 ml. A raised serum bilirubin is probably present in most cases of severe passive congestion of the liver apart from pulmonary infarction (Kugel and Lichtman, 1933). Nevertheless, clinical jaundice is most frequently associated with pulmonary infarction.

Thirteen cases came to necropsy: cardiac cirrhosis of the liver was present in two, evidence of severe chronic venous congestion in seven, evidence of mild chronic venous congestion in one, and the liver appeared macroscopically normal in three. In six cases the volume of lung infarcted amounted to one lobe or more, in the remainder to half a lobe or less, and in one instance to no more than one-eighth of a lobe. In every case there was evidence of severe and long-standing pulmonary congestion.

Jaundice in heart disease complicated by pulmonary infarction has been considered to be mainly haemolytic owing to the destruction of red cells in the infarct. Kugel and Lichtman believed that infection was also an important factor in some cases. They explained its action partly on the basis of an enhanced activity of the reticulo-endothelial system causing an acceleration in the absorption of bilirubin from the infarct, and partly on a toxic action on the liver. Infection did not appear to play an important part in the aetiology of jaundice in the present series except in a single instance. The case with the smallest infarct and a liver which appeared normal was complicated by extensive lobar pneumonia.

During the period of two and a half years covered by this study transient jaundice was seen in three women with heart disease (not included in this series) in whom careful clinical and radiological examination revealed no definite evidence of pulmonary infarction. Two of these had mitral stenosis with normal rhythm, one of them being in congestive failure. The third had hypertensive heart disease, thyrotoxicosis, and auricular fibrillation with severe congestive failure, and the jaundice was at one time quite marked. In none of these cases was there any clinical evidence of disease of the biliary tract or gross hepatic pathology.

Although the development of jaundice in a case of heart disease should strongly suggest pulmonary infarction, such a lesion is not invariably present. Sherlock (1945) has shown that where the pressure in the great veins is markedly raised the resulting high pressure in the hepatic sinusoids may produce a mechanical blockage of the bile canaliculi

with consequent obstructive jaundice. In the third case, mentioned above, hepatic damage due to thyrotoxicosis (Youmans and Warfield, 1926) may have played a part.

Treatment

Provided there was no contraindication, all cases of deep femoral thrombosis were treated with dicoumarol, a low prothrombin index being maintained until the patient was active. To obtain an immediate anticoagulant effect heparin was usually given for the first 48 hours with the dicoumarol. No case so treated developed pulmonary embolism and no serious bleeding was encountered.

It was intended to treat similarly all cases of pulmonary embolism in which an early diagnosis was made. Actually, one-third of the cases in this series received a course of anticoagulant therapy. Although the number of treated cases and controls was insufficient for a statistical analysis, the beneficial effect was impressive. Purpura and haematuria were encountered in one case and purpura alone in another. Dicoumarol must be blamed for one death. A patient who had undergone partial gastrectomy developed pulmonary embolism on the seventh post-operative day. Dicoumarol therapy was begun at once, and after four days the prothrombin index was returned as 60%. He died suddenly the following day, and at necropsy 3 litres of blood was found in the peritoneal cavity. Greater familiarity with dicoumarol and the difficulties of the prothrombin estimation eliminated haemorrhagic complications entirely during the final year.

Femoral vein ligation was considered in three patients in whom repeated pulmonary embolism occurred over a period of several months, but was never actually performed. Two of them, who were suffering from advanced mitral disease, died. The third, a post-operative case, recovered on a prolonged course of dicoumarol. In retrospect, it is believed that the two cases with mitral stenosis might have been protected from further emboli by long-term dicoumarol therapy (Cosgriff, 1950).

Discussion

Pulmonary embolism accounts for between 5% and 7% of all post-operative and maternal deaths (McCartney, 1945). It is the direct cause of death in a similar proportion of cases of coronary thrombosis (Eppinger and Kennedy, 1938) and probably of rheumatic heart disease also. In addition there are the many deaths, particularly in patients with heart disease, in which pulmonary embolism is an important contributory factor. Furthermore, as other causes of death are being steadily reduced by the advances in surgery, obstetrics, anaesthesia, and post-operative care, the relative importance of pulmonary embolism is increasing. A survey of necropsies carried out at two general hospitals in Bristol between 1913 and 1948 (Short, unpublished) showed that massive pulmonary embolism was the principal cause of death in 4.5 per 1,000 necropsies in the five-year period 1913-17, 8.1 per 1,000 in 1929-33, and 16.8 per 1,000 in 1944-8.

During the past decade it has been increasingly realized that most pulmonary emboli are not massive and fatal, and that they concern physicians as least as much as surgeons and obstetricians. Indeed, the present study suggests that thrombo-embolic disease of the lung may have become the commonest of serious acute pulmonary lesions in general hospital practice.

There is reason to believe that in the surgical and obstetrical wards many pulmonary infarcts are misdiagnosed as pleurisy, pulmonary collapse, or pneumonia. In the medical wards many are overlooked, for the symptoms in patients suffering from cardiac failure are often far from striking. Pleuritic pain is often absent, and the elevation of temperature, pulse, and respiration rates may be slight. Furthermore, several of the symptoms and signs of pulmonary infarction are met with in heart disease in the absence of a focal lung lesion—for example, haemoptysis, basal rales,

and pleural effusion. Even radiography may be unreliable owing to the tendency of pulmonary congestion to obscure the infarct shadow. The diagnosis must continually be borne in mind and should be suggested particularly by the following signs: continuous or recurrent haemoptysis, unexplained tachycardia, jaundice, and a large unilateral effusion which persists or recurs despite a satisfactory general response to therapy.

Pulmonary embolism is common in patients bedridden from any cause, especially where dehydration or anaemia is present. It also occurs in patients with long-standing saphenous thrombophlebitis. Furthermore, it must be considered in the differential diagnosis of pneumonia, for femoral thrombosis is sometimes a silent process and the first symptom may be pulmonary.

Despite the warnings which have been sounded during the past decade, the general attitude towards femoral venous thrombosis and minor pulmonary emboli is still far too complacent. These events are by no means so benign as they are sometimes pictured, and as warnings of possible massive embolism they are of outstanding importance.

Bauer (1946) has declared that femoral thrombosis treated conservatively—that is, without anticoagulants—is followed in almost every case by chronic oedema, in 90% of cases by indurative lesions on the lower leg, and in 80%, sooner or later, by crural ulceration.

Pulmonary infarcts often resolve without serious consequences. Nevertheless, in the present series they accounted directly for the deaths of 15 patients and were an important contributory factor in 13 others. Pulmonary infarction almost led to a fatal issue in five otherwise healthy surgical and obstetrical subjects. One, a patient admitted for a Trendelenburg operation for varicose veins, had to be detained in hospital for four months and undergo a rib resection on account of an empyema which resulted from infection of a pulmonary infarct.

Every thrombo-embolic incident should be regarded as a warning of possible massive embolism. On the basis of collected reports, totalling over 4,000 cases, it has been shown (Cosgriff, 1947) that in the absence of anticoagulant therapy or venous ligation 20% to 30% of all patients with femoral venous thrombosis will develop a pulmonary embolus and 6% to 14% a fatal one. Of cases which have had one pulmonary embolus, 30% will have another and 18% a fatal one.

The importance of watching the legs of all post-operative and puerperal patients and those with recent myocardial infarction is still not appreciated. It is the early signs which are important—a raised skin temperature, local tenderness in the calf, and a positive Homans dorsiflexion sign. It is because this stage is overlooked that pulmonary embolism is regarded as unheralded. The frequency with which thrombus is found in the deep femoral veins (Carloti *et al.*, 1947) and the relative infrequency with which it is found in the right side of the heart, indicate that even in heart disease most pulmonary emboli arise in the legs.

Post-operative pulmonary infarction is often misdiagnosed as massive collapse, pneumonia, or pleurisy. While this paper was in preparation such a misdiagnosis had a tragic sequel. A patient underwent a nasal operation in another hospital. Eight days later she complained of pleuritic pain in the chest. A radiographic examination was requested and pleurisy was diagnosed. Five days later the patient collapsed and died suddenly from massive pulmonary embolism. The fatality was unexpected but not unheralded. Had the warning been recognized, the fatality might have been averted by anticoagulant therapy. A complaint of pleuritic pain within three weeks of operation or delivery should be regarded as indicating pulmonary infarction until this has been disproved.

There is considerable evidence that anticoagulant therapy reduces the incidence of pulmonary embolism in femoral thrombosis (Cosgriff, 1947) and myocardial infarction (Wright *et al.*, 1948; Tulloch and Gilchrist, 1950) and re-

duces the risk of further embolism when one has already occurred (Cosgriff, 1947). It has been demonstrated that heparin is capable of dissolving thrombus already formed—at least in experimental myocardial infarction (Solandt *et al.*, 1939)—but the fear that anticoagulants might loosen thrombus present in the femoral veins and so encourage embolism has proved to be unfounded. Where necessary, both heparin and dicoumarol may be given within eight hours of operation (Jorpes, 1946) and within 12 hours of delivery (Leissner, 1941).

In view of the apparent danger of thrombus becoming detached when the patient first gets out of bed after operation, anticoagulant therapy once started should be continued until the patient is active. Indeed, in cases in which the risk of embolism is great—for example, following prostatectomy—it would appear to be reasonable to employ anticoagulant therapy over this danger period even in the absence of other indications.

It is freely admitted that anticoagulants at present available are neither easy to control nor free from danger. They are, nevertheless, both reasonably effective and reasonably safe in experienced hands, and their use until something better is discovered is fully justified.

Although femoral vein ligation was not employed on any case in this series, experience suggests that it may have a small but definite sphere of usefulness in those cases in which repeated embolism occurs despite anticoagulant therapy or in which such therapy is contraindicated.

Summary

Pulmonary thrombo-embolism was diagnosed during a period of 30 months in 120 patients, of whom 113 were in the wards of a general hospital. The incidence of pulmonary thrombo-embolism in this hospital was higher than that of lobar pneumonia. Pulmonary embolism was directly responsible for 30 deaths, and pulmonary infarction was an important contributory factor in 13 more.

Fifty-eight per cent. of the cases were classed as medical, and 80% of these had heart disease. There were three instances (one fatal) of pulmonary embolism appearing without warning in apparently healthy subjects.

Among the 30 surgical cases (8 fatal) were 4 in which pulmonary embolism was precipitated by first rising.

Among the 20 obstetrical cases (2 fatal) pulmonary embolism was nearly three times as common in those over the age of 30 as in those under 30. Pulmonary embolism was only once seen in the absence of obvious femoral thrombosis or some complication of pregnancy or delivery.

Pleuritic pain and haemoptysis are the two most striking symptoms of pulmonary infarction. Pleuritic pain was noted in 65% of all cases and was present in fully 90% of the surgical and obstetrical cases. Haemoptysis was noted in less than 40% of all cases; the incidence falls to 17% if cases with heart disease are excluded.

The physical signs in the chest in pulmonary infarction depend on the presence and degree of three factors—namely, consolidation, pleurisy, and elevation of the diaphragm.

Signs of pleural effusion were present in 20% of cases. The fluid was blood-stained in 8 out of 17 cases in which it was inspected.

Jaundice was observed in almost one-third of the cases of heart disease complicated by pulmonary infarction.

A paroxysm of auricular fibrillation was precipitated by pulmonary infarction in five cases.

In several patients with congestive heart failure the symptoms were slight and the presence of pulmonary infarction was overlooked. In post-operative and puerperal patients the condition was often misdiagnosed as pleurisy, pulmonary collapse, or pneumonia.

The importance of paying serious attention to every case of femoral thrombosis and pulmonary embolism is reiterated, and measures of prophylaxis and therapy are briefly discussed.

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DEAFNESS WITH USE OF DIHYDROSTREPTOMYCIN IN TUBERCULOUS MENINGITIS

BY

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Attention has recently been drawn to the reduced success and increased deafness resulting from the use of dihydrostreptomycin instead of other forms of streptomycin in the treatment of tuberculous meningitis (Minkenhof, 1950; Biagi, 1951; Cathie and Garrow, 1951; Somner, 1951). My experience in Ayrshire Central Hospital, Irvine, and Belvidere Hospital, Glasgow, seems to confirm the latter finding, although the results, in terms of percentage recovery, have not been adversely affected. Deafness itself, however, is a most perplexing problem, especially since, in my experience, hearing-aids have been of no value to the patients developing it. Lip-reading tuition has been given during their stay in hospital and after dismissal, but this, of course, is a very poor substitute for normal hearing, although it does help them to enter into conversation.

For several months dihydrostreptomycin was suspected as being the cause of increased deafness complicating recovery from tuberculous meningitis—and indeed this was mentioned to representatives of Glaxo Laboratories, who have recently provided supplies of the calcium chloride complex to conduct a controlled

investigation on a series of new cases. Unfortunately the introduction of dihydrostreptomycin coincided with an intensification of intrathecal (but not intramuscular) streptomycin therapy, and the possibility that this may have been responsible for the increased incidence of deafness required to be first excluded. Accordingly, when this discovery of increased deafness was made in April of last year, the course of intrathecal streptomycin was reduced to one more closely resembling that previously used, the intramuscular regime being unaltered. It is too early to assess the ultimate results with this course. So far, it does not appear to have affected the recovery rate; but cases of deafness have already occurred. For comparison, this latter course is now being used, the calcium chloride complex being substituted for dihydrostreptomycin. It is hoped to publish later a report on the results.

The courses given and the results obtained are outlined below:

1. Results Prior to Use of Dihydrostreptomycin

The adult course in average cases extended over a period of six months, as follows:

Intramuscular Streptomycin	Intrathecal Streptomycin
2 g. daily in 2 doses for 3 months 1 g. daily for 1 month 1 g. on alternate days for 1 month 1 g. twice weekly for 2 weeks 1 g. weekly for 2 weeks	100 mg. daily for 2 weeks Rest for 1 week 100 mg. daily for 1 week 100 mg. on alternate days for 2 weeks 100 mg. weekly until end of 6 months

Of 26 patients treated, 13 died and 13 survived for periods varying from two to three and a half years. Only one of these became slightly deaf during treatment of a relapse. The deafness has not progressed.

2. Results Using Dihydrostreptomycin

A. *Intense Intrathecal Course.*—The adult course in average cases extended over a period of six months, as follows:

Intramuscular Dihydrostreptomycin	Intrathecal Dihydrostreptomycin
Exactly as above	100 mg. daily for 2 weeks 100 mg. on alternate days for 8 weeks 100 mg. weekly till end of 6 months <i>Para-aminosalicylic acid was given concurrently and for a further six months</i>

Of 51 patients treated 17 died and 34 survived for periods ranging from eight months to two years: 20 cases became deaf.

B. *Less Intense Intrathecal Course.*—The adult course in average cases extended over a period of six months as follows:

Intramuscular Dihydrostreptomycin	Intrathecal Dihydrostreptomycin
Exactly as above	100 mg. daily for 2 weeks 100 mg. on alternate days for 4 weeks 100 mg. weekly till end of 6 months <i>Para-aminosalicylic acid was given concurrently and for a further six months</i>

Fourteen patients received this course and were observed over a period varying from three and a half to seven months. So far, four have died. Of the survivors two are already becoming deaf.