Clinicopathological Conference

A Case of Idiopathic Cavitation of Lung

DEMONSTRATED AT THE POSTGRADUATE MEDICAL SCHOOL OF LONDON

Clinical History

Professor J. G. SCADDING: The patient (Case No. 163450; P.M. No. 10765) was a single woman aged 53 years at the time of death. She had been employed as a clerk in the Post Office, and had been incapacitated since the age of 50 years. Her father had died aged 54 years of "chronic bronchitis," but her family history was otherwise irrelevant. In 1953, at the age of 42 years, she was in bed for five weeks with "bronchitis." After this she noticed a cough with scanty mucoid sputum and tiredness, and she lost 3 kg. in weight. In March 1954 she attended out-patients at Brompton Hospital, where it was noted that she was thin, and that there were rales over the upper part of the right lung and over most of the left lung. A chest radiograph showed mottled shadows above both clavicles. Tomograms showed no evidence of cavitation, and three sputum cultures for tubercle bacilli were negative.

In June 1954, after sudden pain in the right side of the chest, she was admitted to Hammersmith Hospital and found to have a right-sided spontaneous pneumothorax with some upper lobe adhesions (Fig. 1). The intrapleural pressure was $0+10$ cm.H_2O, changing to $-10+2$ after removal of 900 ml. of gas. The lung thereafter re-expanded. A Mantoux test with 1:100 Old Tuberculin was negative. Further sputa were examined with negative results for tubercle bacilli.

Over the next few years her winter cough continued, and in January 1957 she was admitted to another hospital with "bronchitis and pneumonia." She had noticed gradually increasing breathlessness on exertion, worse in foggy weather.

In December 1957 she was readmitted to Hammersmith Hospital with an acute upper respiratory infection, fever, purulent sputum, and soreness behind the sternum. She was found to be thin, pale, tachypnoeic, and with a fever up to 104° F. There were rhonchi and rales all over both lungs, especially in front.

Investigations

Radiologically the upper zone opacities were denser, and the hilar shadows elevated and prominent. Tomograms showed some apical bullae; the hilar shadows were distorted with no evidence of lymph-node enlargement. The Mantoux test 1:100 was again negative. Sputum on admission contained pneumococci; many specimens were all negative on culture for tubercle bacilli. The total leucocyte count was 4,000/c.mm., 54% neutrophils. Scalene node biopsy showed moderate sinus reaction only. Indirect maximum breathing capacity was 32 l./min., and did not increase after isoprenaline; CO transfer factor (steady state method) 12–13 ml./min./mm.Hg; total lung capacity 4.39 l.; residual volume 2.62 l. On treatment with tetracycline her temperature settled in three days, and the sputum became mucoid, 20–50 ml. daily.

After this she continued at work until December 1958, when she had another attack of "bronchitis," treated with penicillin. In January 1959 she developed another acute illness, with pain in both sides of the chest and breathlessness, which was treated with penicillin and tetracycline. When she was admitted for investigation the sole symptom was breathlessness; she could manage only one flight of stairs without stopping. The Mantoux test was again negative, 1:100. The sputum, which was mucoid, was negative for tubercle bacilli on culture. *X*-ray of the chest now showed several large and many small cavities in a contracted right upper lobe (Fig. 2), and the left upper lobe was similarly but much less extensively affected. She was treated with 6 mega units of penicillin daily for two weeks on the hypothesis that progressive changes in the upper parts of the lungs might be an unusual variant of chronic suppuration in the lungs, or in some other way related to pyogenic bacterial infections. There was some subjective improvement. The E.S.R. fell from 40 mm. to 16 mm. and sputum volume from 50 ml. to 10 ml., but there was little radiological improvement.

Lung Function

There had been further deterioration in the ventilatory capacity since December 1957: F.V.C. 0.9 l.; $F.E.V._1$ 0.6 l.; and V.C. 1.7 l.; after bronchodilator, F.V.C. 1.4 l.; $F.E.V._1$ 0.7 l.; and V.C. 2.0 l. Followed up in out-patients, she continued to suffer recurrent episodes of increased cough, wheezing, and breathlessness, and could not continue at work after June 1960.

In October 1960 the mixed venous P_{CO_2} was 54 mm. and peak expiratory flow rate 70 l./min.

In June 1961 she was readmitted with a left spontaneous pneumothorax, extremely breathless but afebrile. Intercostal catheter underwater drainage was instituted with prompt relief;

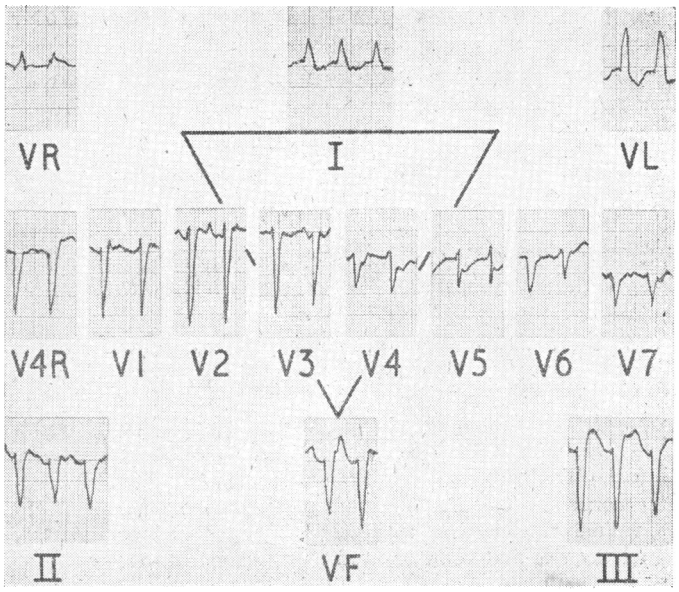

FIG. 4.—Electrocardiogram taken on final admission (11 February 1964).

the initial intrapleural pressure was +5 +15. In view of her extreme breathlessness and the evidence of airway obstruction, prednisolone 40 mg. daily was given, but with no improvement symptomatically or objectively ($F.E.V._1$ before prednisolone 0.40 l., after 0.45 l.). Prednisolone was therefore withdrawn.

In January 1962 she had another left spontaneous pneumothorax, treated with intercostal tube drainage again with prompt re-expansion. Over the next two years dyspnoea remained severe—a radiograph taken at this time is shown in Fig. 3. From time to time there was some oedema, improved by diuretics. In October 1963 the mixed venous P_{CO_2} was 53 mm. and the $F.E.V._1$ 0.44 l. In February 1964 she was admitted for the last time because of very severe dyspnoea, mental confusion, and oedema. Physical and radiological signs were unchanged; mixed venous P_{CO_2} 70 mm., blood urea 84 mg./100 ml. She was treated with bronchodilators, oxygen, diuretics, and digoxin, but slowly deteriorated, the P_{CO_2} rising to 91 mm. She developed a supraventricular tachycardia (Fig. 4) and died five days after admission.

Clinical Diagnosis

No firm clinical diagnosis was reached. She had evidence of generalized airways obstruction with only mild recurrent bronchitis, unexplained fibrosis and cavitation in the upper lobes, and probable emphysema in the lower lobes, causing progressive respiratory failure. Pulmonary tuberculosis, chronic pyogenic infection of the upper lobes, pulmonary histiocytosis X, and even polyarteritis nodosa had been considered during life, but rejected. We therefore awaited the morbid anatomical findings with even more interest than usual.

Dr. E. J. MORAN CAMPBELL: Just three points: we considered tracheostomy and other heroic measures, but decided they were not justifiable on humanitarian grounds; secondly, it is possibly my fault that emphysema is down as a diagnosis—it is always nice to have a radiologist who sees less in *x*-rays than one does oneself, and, thirdly, I would just like to question the term "progressive respiratory failure." I would say that the feature of this lady was that she had terminal respiratory failure, not progressive respiratory failure.

Professor SCADDING: Perhaps I should have said progressive lung disease with respiratory insufficiency and terminal respiratory failure.

Dr. C. M. FLETCHER: Could I just ask—was she ever cyanosed, or did she appear to be chronically hypoxic?

Dr. MORAN CAMPBELL: Not when I saw her. Was she blue when she had the pneumothorax?

Professor SCADDING: Not notably. We did not do an arterial oxygen saturation.

Post-mortem Findings

Dr. B. E. HEARD: On external examination this was a thin body with rigor mortis. Post-mortem lividity was present posteriorly.

The *heart* weighed 291 g. The pericardium was normal with no effusion. The left atrium was normal and also the left ventricle (15 mm.). The right atrium was slightly hypertrophied, and the right ventricle was hypertrophied (6 mm.). All valves were normal in circumference, and the cusps were normal. The coronary arteries showed minimal atherosclerosis. The aorta showed a number of plaques in the thoracic and abdominal regions, but they were not ulcerated or calcified. Other arteries and veins showed no specific features.

Lungs

The larynx, vocal cords, and trachea were normal. Both pleural sacs were obliterated by dense fibrous adhesions, which were especially thick over the apices. The *lungs* (combined weight 1,080 g.) were perfused with formalin. The right lung showed extensive destruction of the apical and posterior segments of the right upper lobe, the anterior part of the middle lobe, and the apical segment of the lower lobe (Fig. 5). Large cavities with bluish-white fibrous walls were present. They were crossed by strands of surviving pulmonary arteries and accompanying bronchi (Fig. 6). The bronchi supplying the cavities were patent and could be probed. The bronchi were sometimes distorted and bronchiectatic and there was centrilobular emphysema (Fig. 7). Accompanying arteries showed marked intimal fibrosis. Histologically the cavities were lined by a thin layer of dense, inactive-looking fibrous tissue with no epithelial lining; outside this was a zone of collapsed fibrous lung containing dust pigment, in which were found distorted, often dilated bronchioles and partially or completely obliterated pulmonary arteries (Fig. 8). Only a very occasional small focus of lymphocytes could be seen. Elastic stains showed large quantities of elastin in irregular masses running through the fibrosed area; the configuration of the elastic fibres often indicated an origin from the obliterated pulmonary vessels, but presumably some of it was from alveolar walls (Fig. 9). There was no evidence of active inflammation in the walls of the cavities.

The rest of the lung showed numerous scattered foci of distensive and destructive centrilobular emphysema (Fig. 7). Histologically bronchiolar narrowing was occasionally seen with associated small scars. The bronchi showed dilatation of mucous ducts, but the mucous glands were normal. The left lung was taken for other research purposes.

The tongue, oesophagus, stomach, and duodenum were normal, but there was a small congenital diverticulum of the jejunum, 1 cm. across (on the mesenteric border). The rest of the alimentary tract was normal.

Liver

The *liver* (1,145 g.) showed cough furrows, and histologically there was centrilobular congestion. Amyloid stain was negative. Gall bladder, bile ducts, and pancreas were normal.

A nodular *thyroid* weighed 28 g. *Adrenals* weighed 5 g. each and appeared normal. Pituitary and parathyroids were normal. The *spleen* (107 g.) was firm and Malpighian follicles were visible. Gross and microscopical tests for amyloid were negative. Vertebral bone-marrow and lymph nodes were normal.

The *kidneys* were normal in size (right 120 g., left 132 g.). Calices were normal. Histologically a few glomeruli were replaced by fibrous tissue and a few others showed slight thickening of Bowman's capsule, but mostly there were no abnormalities. The uterus contained several myomata, about 2 cm. diameter.

The *brain* (1,245 g.) appeared normal macroscopically and most of the sections were normal; but the cerebellum showed a great reduction in the number of Purkinje cells presumed due to hypoxia (Fig. 10).

Pathologist's Diagnosis

(1) Healed cavitation of the lungs of unknown origin, dense pleural adhesions, and centrilobular emphysema.

(2) Right ventricular hypertrophy.

(3) Mild venous congestion of the liver and cough furrows.

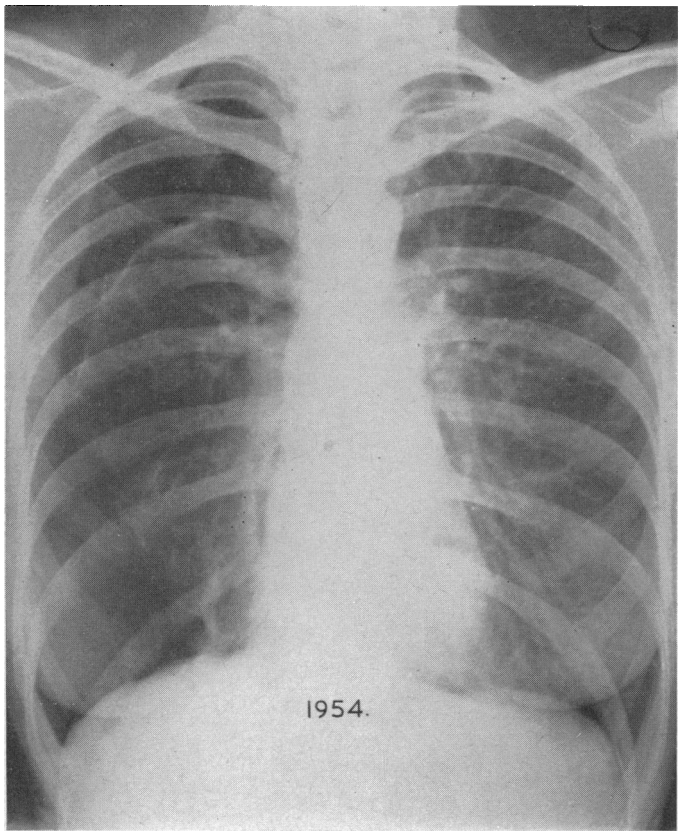

FIG. 1.—Radiograph (1954). Right-sided pneumothorax and apical adhesions. Left lung clear.

FIG. 2.—Tomograph (4 March 1959) of the right upper zone showing cystic changes throughout the right upper lobe.

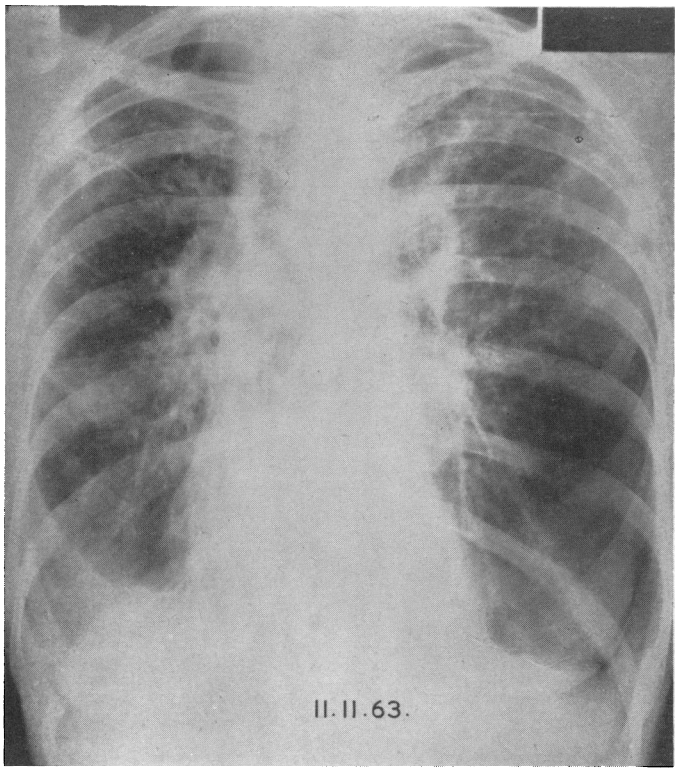

FIG. 3.—Postero-anterior radiograph (11 November 1963) showing widespread pulmonary fibrosis, particularly in the right lung and left upper zone, with displacement of the mediastinum to the right.

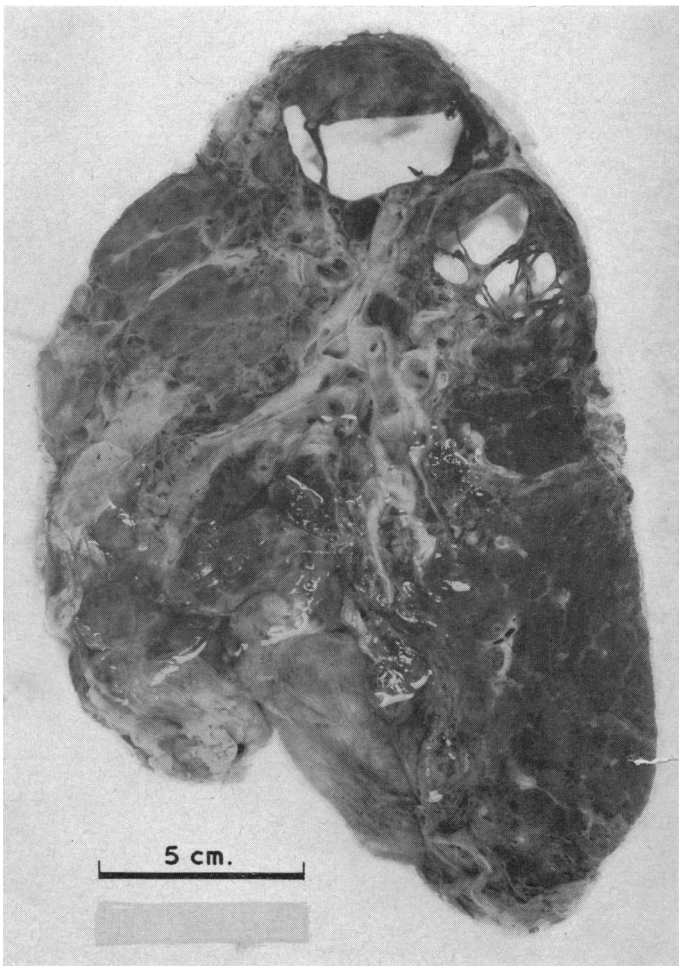

FIG. 5.—Slice of right lung showing destruction and cavitation of the apical and posterior segments of the upper lobe, the anterior parts of the middle lobe, and the apical segment of the lower lobe (pressure fixation).

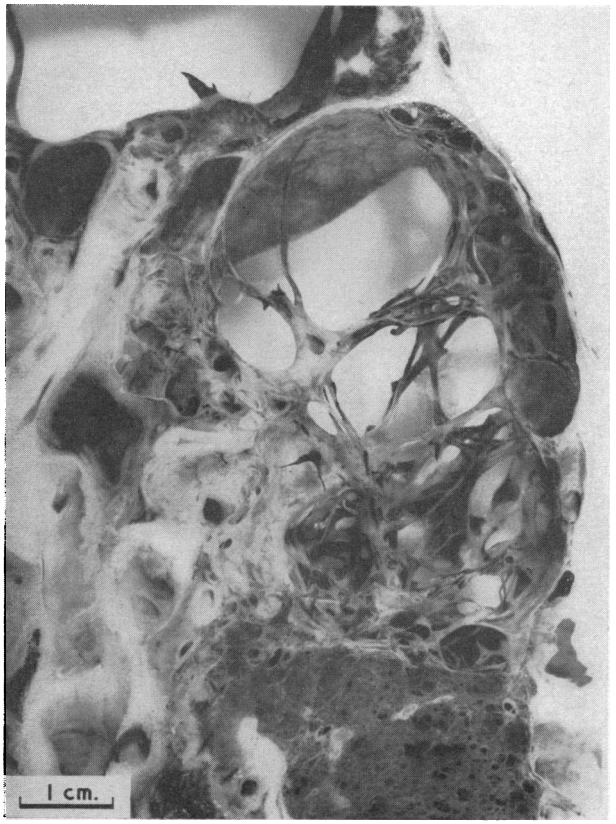

FIG. 6

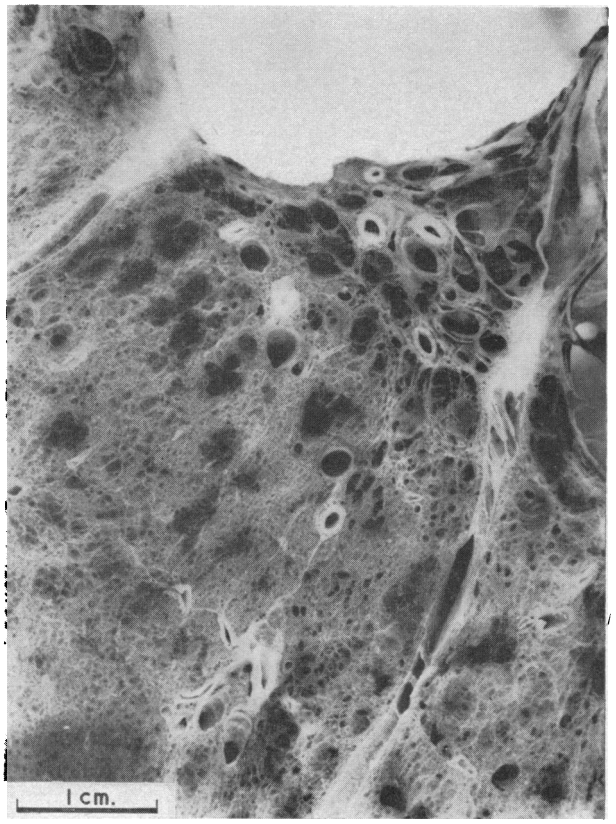

FIG. 7

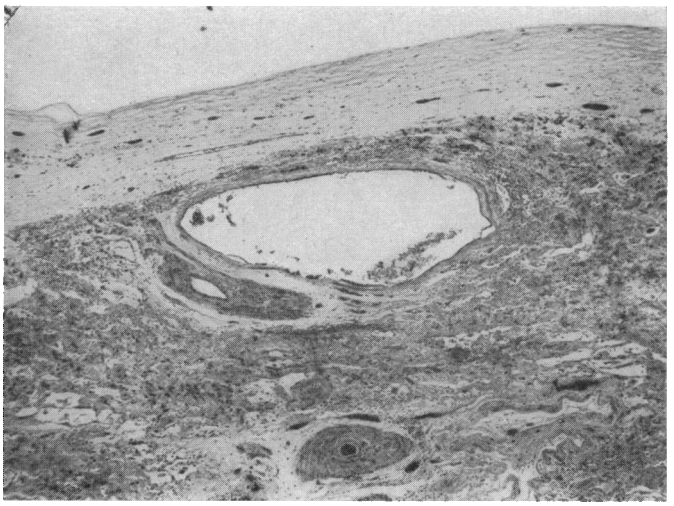

FIG. 8

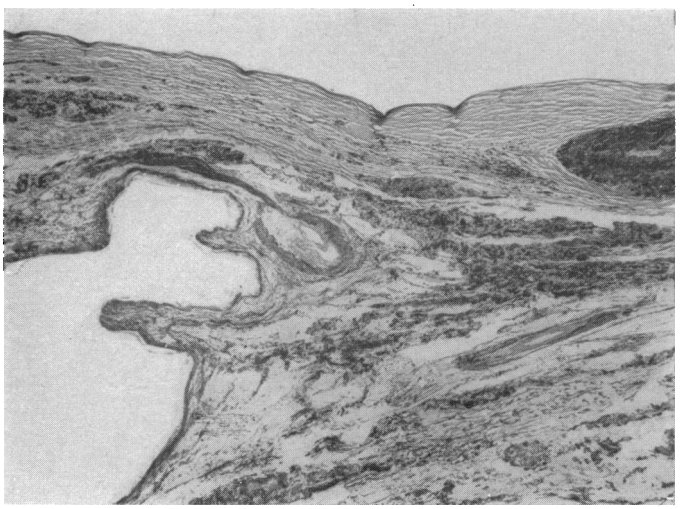

FIG. 9

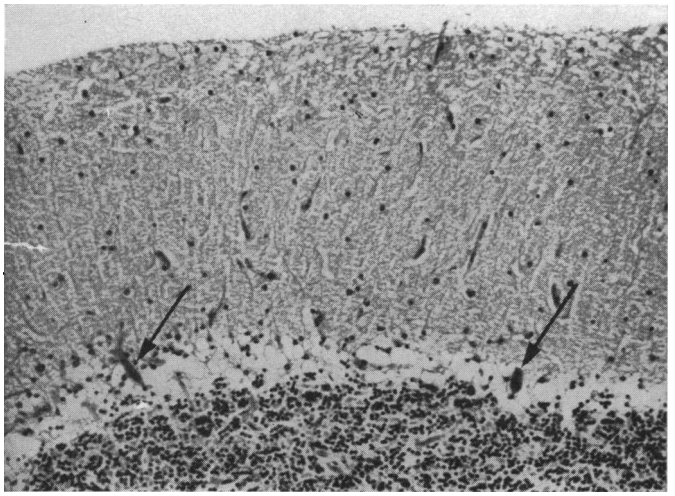

FIG. 10

FIG. 6.—Higher magnification of the apical segment of the lower lobe showing cavities crossed by strands composed of pulmonary arteries and bronchi, the latter often communicating with the cavity (pressure fixation, barium sulphate impregnation).

FIG. 7.—Foci of destructive centrilobular emphysema near a cavity (pressure fixation, barium sulphate impregnation).

FIG. 8.—Section of wall of cavity showing thick fibrous layer (pale staining), collapsed fibrosed adjacent lung, a dilated bronchiole (centre), thickened pulmonary arteries, and only a small number of inflammatory cells. (H. and E. ×30.)

FIG. 9.—Section of wall of cavity (stained for elastic tissue (black)). There are irregular clumps of elastic fibres representing collapsed lung, and a thickened pulmonary artery (upper right quadrant). Above and to the right of the dilated bronchiole is a pulmonary artery with two lumina suggesting recanalization of a thrombus. (Elastic van Gieson. ×30.)

FIG. 10.—Section of cerebellum showing very scanty Purkinje cells (arrows) due to hypoxia. (H. and E. ×115.)

(4) Diverticulum of the jejunum.
(5) Uterine fibroids.
(6) Partial loss of Purkinje cells due to hypoxia.

Discussion

Professor SCADDING: It is very difficult to sum up this case, because both clinically and pathologically we are left without a recognized category into which to put it; and that always makes a summary difficult. It seems clear that she had a respiratory disease characterized clinically by airways obstruction, which was prominent in her case; she had relatively minor chronic bronchitic symptoms, though the recurrent attacks of bronchitis added seriously to her disability when she had them. We had evidence that several of these attacks were at least partly associated with bacterial infection; but how far they contributed to the progression of her respiratory disease must, I think, remain doubtful. Certainly the case did not have the features that we associate with the patients who start with chronic bronchitis and go downhill with deteriorations associated with recurrent respiratory infections, so that explanation of the progression of her disease cannot be sustained.

The most striking feature was the progression—which we could follow radiologically—of the curious process going on in the upper parts of the lungs, particularly on the right side. What seemed to be happening was that the lobe was steadily contracting while large air-containing spaces were developing inside it.

During my account of the clinical aspects I put before you the possibilities which we considered to account for that, none of them being satisfactory. When we come to the morbid anatomical findings we are still in the same situation—that it remains very difficult to explain how this curious contraction with fibrosis and the formation of large air-containing spaces with featureless walls developed.

Another Case

I have under my observation at the moment another patient in whom exactly the same inexplicable process seems to be taking place. She also started with this picture of a respiratory disease with prominent airways obstruction; and over the years of observation the upper lobes have steadily contracted until they appear to consist only of fibrous strands with air-containing spaces between them. All our searches for the usual causes of such events have been unsuccessful. It makes me wonder whether there is not some process that we have not yet elucidated going on in these cases to account for their curious features.

May I ask Dr. Heard a question or two? I was interested in the scarring which he mentioned beside the terminal bronchioles. What did he think was the origin of those two little nodules of scarring he showed beside terminal bronchioles and obstructing the entrances to respiratory bronchioles?

Dr. HEARD: I think those were inflammatory in origin.

Professor SCADDING: Those could, then, be attributed to bacterial infection?

Dr. HEARD: Yes, they are the type of lesion that Reid[1] has described in chronic bronchitis.

Definition of Cavities

Professor SCADDING: Another point I would like to make concerns "bullae," "cysts," and "cavities." I customarily use the term "cavities" to refer to an air-containing space in the lung which has no epithelial lining but is lined by granulation or even just fibrous tissue. If that is accepted we can call the air-containing spaces in this case "cavities," I presume. By "cysts" and "bullae" I usually mean air-containing spaces with epithelial linings of different types. "Cysts" have an epithelium derived from bronchi or bronchioles, and "bullae" look as if they originated from alveolar tissue; or, more generally, from the respiratory part of the broncho-pulmonary tree beyond the terminal bronchiole. Is that a reasonable usage?

Dr. HEARD: We looked this up in medical dictionaries before the meeting but had no satisfaction at all on the difference.

Professor SCADDING: I find the only thing to do with words is to instruct them firmly what they are going to mean before you use them.

Dr. MORAN CAMPBELL: I would like to make three points: first, the morbid structure and function fit with each other. The physiological features were of a reduced lung volume, with gross disturbance of ventilation–blood-flow relationships, as indicated by the absence of hypoxaemia and the fact that the diffusing capacity was fairly maintained. Secondly, I would emphasize that the useful conventional distinction between restrictive and obstructive ventilatory limitation must not be pushed too far. When the airway to a large part of the lung is progressively narrowed until very little ventilation is possible the spirometric findings change from an obstructive pattern to the restrictive pattern characteristic of loss of ventilated lung. Thirdly, despite the lung disease, the pulmonary vascular disease, and the load on the right ventricle as witnessed by the hypertrophy, she became oedematous only towards the end of her life when the P_{CO_2} rose.

Professor GOODWIN: You were implying that the oedema had nothing to do with the cardiac failure.

Dr. MORAN CAMPBELL: Whatever the interpretation, she is one of these patterns who, despite pulmonary hypertension, only develop oedema terminally.

Electrocardiograms

Professor GOODWIN: This would fit very well—the patients in whom the P_{CO_2} has been high for a long time commonly get considerable right heart hypertrophy, pulmonary hypertension, and right heart failure.

I wonder if I could comment on the electrocardiogram? The almost terminal electrocardiogram shows the pattern which we have come to recognize as indicative of airways obstruction with elevation of P_{CO_2}. The earlier electrocardiograms did not show this pattern; they were practically normal, and that fits in with the previous estimation of the P_{CO_2}. There is right axis deviation; the frontal QRS vector force is directed to the right; there is striking enlargement of the P wave in lead II indicating right atrial enlargement, and the axis of the P wave is also directed towards the right. Caird and Stanfield (1962)[2] worked on this at this school some years ago. It is important that the P wave is largest in lead II, and that there is a deep S wave in V_4 with a still dominant R wave in V_5. Had this patient lived longer and the P_{CO_2} been elevated longer I am sure we would have seen the quite classical pattern of deep S wave in V_5.

Some of these changes have been produced experimentally by breathing out against resistance and simulating airways obstruction. Some of them are due to right ventricular hypertrophy, as we have seen here; some of the changes, notably the deep S waves in the left praecordium, are due to some rotational changes produced by changes in the lung and the effect of the heart position on the vector forces in the

horizontal plane. The second point about this graph is that it suggests that the serum potassium may have been low at the time. I don't know if we have any estimation of serum potassium at this date. This does bear on the arrhythmia, because ectopic rhythms are common in patients with this sort of lung failure. This is commonly due to the fact that they have in the past been treated extensively with diuretics, and tend to have a low potassium ; although this would not seem to be the case in this patient.

Dr. MORAN CAMPBELL: Whether or not you call this condition cor pulmonale I would not use digitalis, although I might use diuretics if the oedema became serious.

Cor Pulmonale

Professor GOODWIN: We must qualify the use of the term "cor pulmonale." One type is due to this sort of lung disease and another to pulmonary embolism, which gives an entirely different picture. The only point I wanted to make was that terminal supraventricular arrhythmias are quite common in this disease, and are not infrequently connected with potassium loss due to diuretics and the effects of digitalis. Another explanation, of course, could be the effect of lung disease in producing right ventricular hypertension and right atrial enlargement.

Dr. P. STRADLING: There are some points of interest in relation to a case that Dr. Heard and I showed here in 1962.[3] He also had a long (ten-year) illness ; he had multiple attacks of spontaneous pneumothorax but these preceded his illness rather than punctuated it. He had progressive destructive pulmonary disease, the cause of which remained undetermined both during life and after death. There were minimal radiographic shadows in the upper zones in 1954 which had extended steadily during the next two years, when we ill-advisedly did a thoracotomy on the left side in an attempt to obtain a diagnosis in a young man: he was only 31 at this time and was going downhill steadily.

Thoracotomy did not help at all ; no diagnosis was obtained and the condition progressed relentlessly. Gross pulmonary destruction and cavitation developed on both sides. He died undiagnosed from a terminal pneumonia. But there are differences: my patient was made very much more comfortable by prednisone, together with tetracycline, and the infection was largely controlled by this means. He also had persistent severe pain on the left, whereas this patient had no pain except when she had a pneumothorax. She had steadily increasing dyspnoea, whereas he was not markedly dyspnoeic until towards the end. The heart in the present case was enlarged, as we have heard, but my patient's heart was not enlarged ; in fact it was smaller than average. I imagine that the conditions are probably different in view of the points I have made, but there are some very interesting similarities.

Sir JOHN MCMICHAEL: Was that case published ?

Dr. STRADLING: Yes, sir.[3]

Causes of Airway Obstruction

Dr. C. M. FLETCHER: I would like to ask Dr. Heard about this bronchial narrowing that he said he thought might have caused airway obstruction—my impression was that he demonstrated this in the destroyed part of the lung: was there in fact any evidence of any abnormality in the structure of the bronchi in the part of the lung the patient was using, which was presumably the almost completely normal lower lobe ?

Dr. HEARD: The photograph I showed was of a relatively good part of the lung, but mild centrilobular emphysema was present in other areas. The extent of the centrilobular emphysema in the lung slice suggested that bronchiolar narrowing may be quite extensive, but we would need to carry out more histological work to be more precise.

Sir JOHN MCMICHAEL: In one section my recollection was that you had an airway, bronchus, or bronchiole, obviously narrowed, which led into a dilated duct. There were two nodules of fibrous tissue around and I was not quite sure whether this was regarded as some inflammatory process narrowing the bronchiole.

Dr. HEARD: I think what happened initially was that there was an area of inflammatory change and this damaged the bronchiole wall, and scarring arose possibly partly from organized alveolar exudate.

Sir JOHN MCMICHAEL: Well, that is extremely interesting. We are faced with a disease which hasn't yet acquired a label—I don't suppose we can get very much further. Have you something further to say, Dr. Heard ?

Dr. HEARD: Anderson and Foraker[4] have done some very important work on the bronchiolar obstruction which is complementary to the bronchiolar scarring I have just mentioned. They measured the area of the lumen of a bronchiole and the area of the wall and they also measured the amount of alveolar tissue around the bronchiole. It was done photographically and by drawing the projected photograph. In the normal lung the bronchioles were held out all the way around by intact alveolar walls. In the emphysematous lung, on the other hand, bronchioles had often contracted down from lack of alveolar wall support. Anderson and Foraker concluded that a lot of the airways obstruction in emphysema is the result of bronchiolar narrowing because of loss of support by the alveolar walls.

We are grateful to Dr. J. P. Shillingford and Dr. B. Heard for assistance in preparing this report, and to Mr. W. Brackenbury for the photomicrographs.

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