Case Presentation at a Clinico-Pathological Conference*

CHAIRMAN: PROFESSOR C. J. UYS, *Department of Pathology, Groote Schuur Hospital and University of Cape Town*

CASE PRESENTED BY: O. L. MEYERS AND A. H. TIMME, *Departments of Medicine and Pathology, Groote Schuur Hospital and University of Cape Town*

A Bantu male, aged 40 years, was first admitted to Groote Schuur Hospital on 25 September 1970. He had a 1-month history of polyarthritis which commenced in both knees and spread to the ankles, shoulders, elbows, wrists and hands. There had been no preceding sore throat or pyrexial illness. One week before admission he had a non-productive cough and noted progressive generalized weakness and lethargy. An additional complaint at that time was dysuria and frequency of micturition, and he complained of a pain in his loins which radiated round to the groin while he passed urine. He worked as a labourer and there was no relevant illness in any member of his family.

On examination he was fully conscious, but in considerable pain. His temperature was 38·9°C, pulse rate 120/min—sinus and regular, and blood pressure 110/60 mmHg. There was no lymphadenopathy or clubbing and subcutaneous nodules were not noted. Marked soft tissue swelling was present and he complained of tenderness with limitation of movement of his elbows, knees, ankles, shoulders and of the small joints of the fingers of both hands. He had no conjunctivitis. Cardiovascular examination was normal. Examination of the chest showed dullness and decreased breath sounds at the right base, as well as bilateral basal crepitations. He was acutely tender in both renal angles and slightly tender in the right loin, but there was no evidence of peritoneal irritation.

The only abnormality detected in the central nervous system was a right pupil slightly larger than the left, but both were regular and reacted to light. There was no evidence of urethritis. The urine contained 2+ of protein. Occasional pus cells per high-power field were seen. His ESR was 102 mm in the first hour (Westergren); his haemoglobin 15 g/100 ml, and his white blood cell count 22 000/mm³, with 80% neutrophil polymorphonuclears. Subsequently the white cell count was noted to be 5 900 and 6 700/mm³, with 70% polymorphonuclears. The platelet count varied between 130 000 and 170 000/mm³. He was given 2 Disprin tablets every 4 hours and during the first 8 days there was gradual improvement, although there was a pyrexia of between 37·2 - 37·8°C throughout this time. On admission X-ray of the chest showed the heart to be enlarged in the transverse diameter with bilateral small pleural effusions. Other than slight congestion of the lung fields, there was no active pulmonary lesion. One month before admission his chest X-ray had been normal. X-rays of the knees, elbows, wrists, shoulders and ankle joints showed no bone or joint lesions. His blood urea was 26 mg/100 ml; serum electrolytes were normal; total bilirubin was less than 0·5 mg/100 ml; alkaline phosphatase 5·6 units; SGOT 29 units; serum albumin 4·4 g/100 ml and globulin 2·8 g/100 ml; and serum uric acid 2·8 mg/100 ml. The gonococcal complement fixation test was negative. Paul Bunnel, Widal, brucella and Weil-Felix agglutination tests were all negative and his serum complement was 227 C'H (normal 150 - 210). No lupus erythematosus cells were detected and his latex fixation test was initially weakly reactive, but later became strongly positive (5 October).

His ECG was within normal limits. There was no significant bacteriuria and urine culture was negative. His creatinine clearance on the 2 October was 35·5 ml/minute with a serum creatinine of 1·1 mg/100 ml. On the eighth hospital day his temperature rose to 38·3°C and the only additional physical signs of note were increased crepitations and rhonchi on the right side of the chest. The following morning his temperature had reached 38·9°C. At that time the haemoglobin estimation was 13·5 g/100 ml and the white blood cell count 6 600/mm³, with a normal differential count, but with 2% myelocytes. Repeat estimation of serum proteins showed 3·7 g/100 ml albumin and 3·0 g/100 ml globulin. The ECG showed T wave inversion in the left chest leads. Concurrently he also had a gallop rhythm although there were no other signs of cardiac failure. Blood cultures were negative and he was started on intravenous penicillin. A chest X-ray on 4 October showed the pleural effusion to be slightly increased with patchy consolidation in the right middle lobe. The heart was central but not enlarged. Two days later he became cyanosed, very short of breath and very drowsy. His pulse rate was 140/minute and he was in congestive cardiac failure. An X-ray of the chest showed a diffuse opacification of both lung fields and the heart appeared to be enlarged in its transverse diameter. His temperature reached 40·6°C and he started having generalized convulsions.

Cooling was attempted by physical means. He was given intravenous furosemide, magnesium sulphate and 150 ml of low-strength mannitol to reduce possible cerebral oedema. His convulsions were controlled but within 10 minutes he developed frank pulmonary oedema with production of copious quantities of frothy pink secretions from his chest. His blood pressure dropped transiently with insertion of a nasotracheal tube, but with the administration of oxygen at high flow rate his condition improved over the next hour. He was given intravenous hydrocortisone in large doses and started on intramuscular Colistin and genta-

*Held at Groote Schuur Hospital and Medical School, University of Cape Town, on 18 March 1971.

mycin. Chest X-rays, that afternoon and later in the evening, showed the lungs still to be densely opaque. An Astrup test showed a pH of 7·403, P_{CO_2} of 32 mmHg, standard bicarbonate of 21 mEq/litre, and base excess of −3·6. Serum enzymes were: SGOT 34, LDH 540, HBD 408 units. By the following morning, 7 October, he was improved but reduced breath sounds with numerous crepitations and rhonchi were apparent diffusely over the chest, and he was producing copious secretions which could not be adequately cleared through the nasotracheal tube. Tracheostomy was performed but by midday his level of consciousness had once more deteriorated. His blood pH had dropped to 7·17; the P_{CO_2} was 30 mmHg, the standard bicarbonate 12 mEq/litre and base excess −16. He was given intravenous sodium bicarbonate. By 1700 his blood pH had dropped to 6·97 with a P_{CO_2} of 37 and P_{O_2} of 48 mmHg. Shortly before this Astrup was done, he suddenly stopped breathing and had cardiac arrest. External cardiac massage was performed and intermittent positive pressure respiration commenced. He remained deeply unconscious and despite ventilation with 100% oxygen, his P_{O_2} was only 48 mmHg. By 1800 he was deeply unconscious, had generalized diminished tone with uniformly brisk reflexes and bilateral ankle clonus. His pupils were still of normal size and reacting, corneal reflexes were present and he had bilateral flexor plantar responses. In the evening he was transferred to the respiratory intensive care unit where he died the following morning.

DIFFERENTIAL DIAGNOSES

O. L. MEYERS, *Department of Medicine, University of Cape Town*

The protocol presented here is of a young Bantu male who had an illness characterized by joint and cardiac disease, and who finally died after a 6-week illness, from a combination of metabolic acidosis and hypoxia. From the information presented a consideration of the possible causes of the joint disease, which could also produce heart disease and this mode of death, must include a number of disease categories. I should think that we need not consider the causes of suppurative arthritis because of the diffuse nature of the joint disease and because of its relatively subacute prolonged nature. By the same reasoning, I think that tuberculosis is also not of primary concern here, unless we invoke the concept of tuberculous rheumatism, which probably does not exist.[1]

I believe from the evidence presented that we have to confine ourselves to diseases which have a multisystem nature. Could this man have suffered from rheumatic fever? The age of the patient is against this, but I think one very important feature which argues even more strongly against this diagnosis is that the arthritis of rheumatic fever tends to resolve within 1 - 3 weeks, whether or not treatment has been instituted. One would also have expected much more evidence of carditis when he was first seen, and certainly there was not much evidence of cardiac enlargement when viewed radiologically.

Rheumatoid arthritis of acute onset is also to be considered. The usual picture of joint involvement in rheumatoid arthritis is that of a subacute disease. However, acute onset of rheumatoid arthritis occurs in up to 20% of patients. The pattern of joint involvement too is not helpful, since a pattern of large joint disease at the onset of the arthritis occurs in about one third of patients with rheumatoid arthritis.[2] The development of a strongly positive rheumatoid factor would tend to suggest this diagnosis, but there are many other diseases which do the same, so that I do not think that this necessarily favours the diagnosis.

The one feature of this case which disturbs me is the emphasis on cardiac disease. Many lesions have been described in rheumatoid arthritis ranging from rheumatoid valvulitis to myocarditis, coronary arteritis and pericarditis. The discrepancy between the pathological descriptions and the clinical recognition of the cardiac disease is well known.[3,4] In the average case the rheumatoid arthritis is usually far advanced and readily recognizable; generally too, the disease has been present for some time. In the rare exception a cardiac granuloma may occur with minimal or no joint disease.[5] For these reasons I am reluctant to accept this man's illness as being explicable entirely on a rheumatoid basis.

The terminal cerebral disease, in my opinion, can be accounted for on a different basis. We are told that cardiac failure associated with drowsiness was present, which preceded the generalized convulsions. It seems to be quite likely that there was cerebral oedema present and that the combination of cerebral oedema and high temperature could have triggered the convulsions. I do not, however, think that cerebral oedema was responsible for all the problems subsequently encountered. For cerebral oedema to have produced the complete picture, I would have expected to have seen a progression of rostrocaudal involvement which did not seem to occur. The protocol tells us, however, that there was a metabolic acidosis at the time of the cardio-respiratory arrest and that this increased, despite treatment. It seemed very likely to me that the terminal cerebral involvement was therefore explicable either on the basis of combined cerebral oedema and metabolic acidosis or that it could have been on a metabolic upset alone. This kind of cerebral involvement, e.g. hemispheral dysfunction, followed by medullary involvement in the absence of a rostrocaudal progression of neurological deficit, is seen commonly in patients with cholaemia, where a metabolic cause for the cerebral disease is postulated.

There is, however, one feature in the last few days of this man's life which may be pertinent to the problem. On two occasions the P_{O_2} was found to be 48 mmHg. The first time was while he was receiving oxygen at high flow via a nasotracheal tube, and the second time was while he was being ventilated with 100% oxygen. I thought these two results a little puzzling in the context of this illness, particularly if one were to postulate that the pulmonary involvement was all due to oedema of cardiac origin. The other finding of interest was the presence of this hypoxia with no increase of the P_{CO_2}; this combination raises the possibility, in my mind, of a so-called alveolar-capillary block situation. The acceptance of the latter opens a

number of possibilities for consideration, which could all be grouped under the heading of the interstitial pneumonias or the diffuse interstitial fibrosing diseases.

Now to return to the original problem of joint disease, heart disease and possible pulmonary disease, we must again consider rheumatoid arthritis. While the diffuse pulmonary involvement in rheumatoid arthritis has been described by many persons, it is usually not such an acute disease.[6,7] However, one wonders about the relationship rheumatoid arthritis has to acute desquamative interstitial pneumonia, particularly when we recall a patient recently under the care of Dr Ferguson, who had severe rheumatoid arthritis and this type of pneumonic disease. The association of auto-antibodies with interstitial pulmonary fibrosis attests to the possible auto-immune aetiology of this group of disorders.[8,9] I considered the acute form of this disease described by Hamman and Rich, and was interested on reading their original paper, to see how prominently cardiac failure featured in the protocols presented.[10]

The two other diseases which need to be mentioned, are systemic lupus erythematosus and polyarteritis nodosa.

I can find little ancillary evidence to support the diagnosis of systemic lupus erythematosus, e.g. no LE cells were ever seen and there was no leucopenia; there is no record of an antinuclear factor being done.

Systemic lupus erythematosus is, however, a common disease in this hospital and presents in many guises. It could have produced this clinical picture, including the joint disease.

Polyarteritis nodosa too must merit consideration. The patient was a male, in the age group when polyarteritis nodosa commonly presents, and there was an initial leuco-

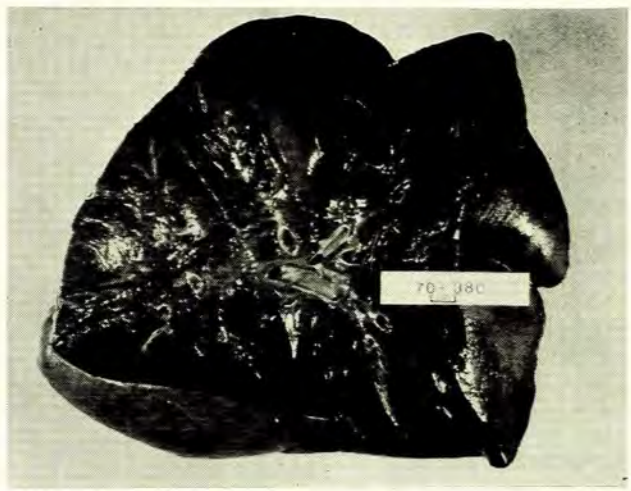

Fig. 1. Cut surface of the lung, showing the lobular areas of consolidation.

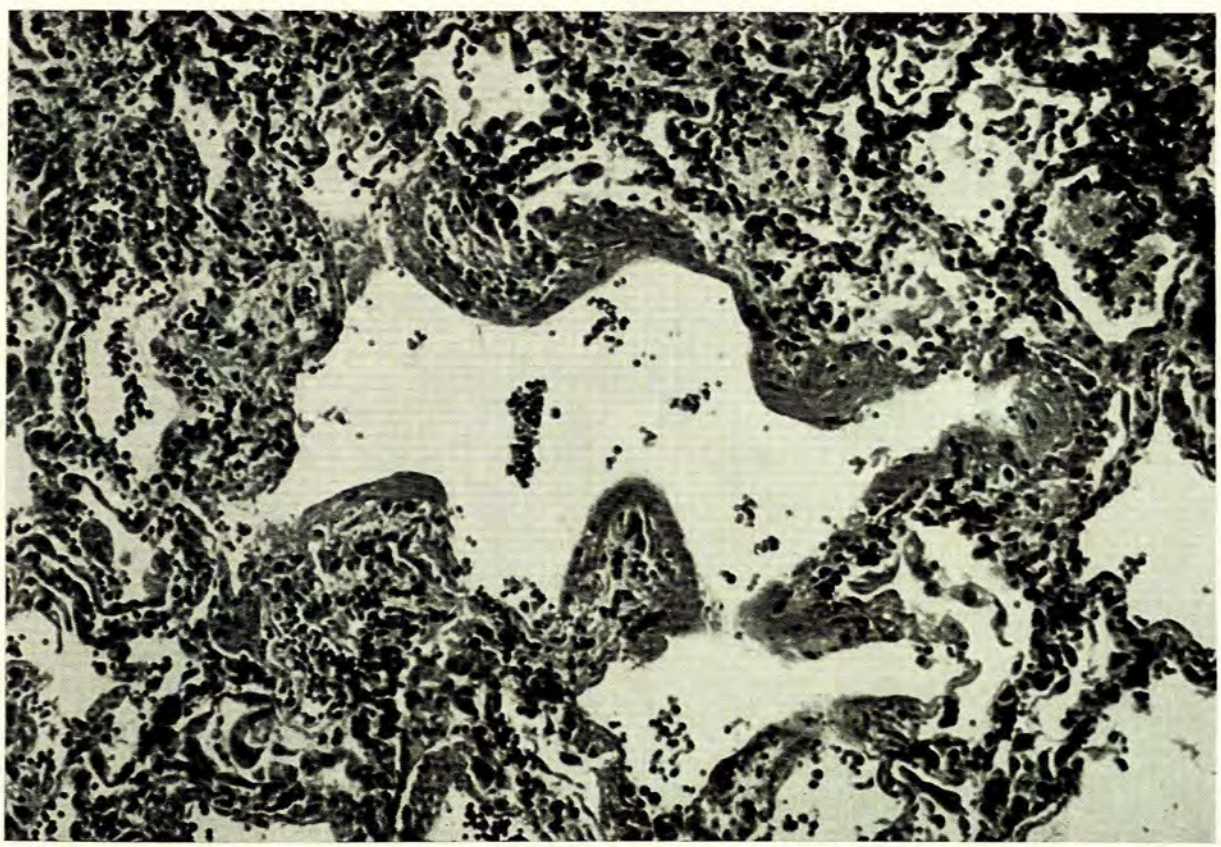

Fig. 2. Hyaline membrane lining alveolar ducts and alveoli (H. and E. × 120).

cytosis. Cardiac involvement in this disease is well recognized, but joint disease of rheumatoid arthritis-type is a relatively rare occurrence, though not unknown.[11] The arteritis of polyarteritis nodosa, too, is not unlike that seen in some patients with rheumatoid arthritis. I am, however, a little reluctant to accept this as an explanation of this man's disease.

For the record, I think that we can exclude from the discussion the usual viral infections which may produce joint and heart disease, because of the rather prolonged nature of the joint involvement. By the same token, mycoplasma infections need not be considered here.

Discussion

Dr L. Werbeloff (interpretation of X-rays): The first picture (25 September 1970) is essentially normal; there is no evidence of infiltration at the bases, but possibly there is a little thickening of the pleura. It is questionable whether the heart is enlarged. The second picture (4 October 1970) shows evidence of rapid deterioration. There are foci of disease and commencing pleural effusion. The heart appears a little bigger. The pictures taken later (6 October 1970) show little aeration of either lung and the appearances are those of 'stiff' lungs. I would say that the over-all appearances are those of pulmonary oedema.

Dr O. L. Meyers: In summary, at this stage, I would like to say that I believe this man had a system or auto-immune disease involving heart and joints, but it is not possible to categorize the disease on the evidence available.

We now come to a consideration of the terminal illness which was ushered in by more severe cardiac failure and punctuated by a high temperature and generalized convulsions.

I think that the attending physicians were thinking about cerebral oedema because they instituted the regimen of mannitol, magnesium sulphate and furosemide. I suppose, not unexpectedly, he was precipitated into severe pulmonary oedema, which dominated the clinical and radiological picture until his death. Deepening coma became a part of this clinical picture but, although there was a sudden cessation of the respiratory centre and a cardiac arrest, it would seem from the protocol that he still had intact pupillary reflexes, suggesting that this cerebral disease did not affect the whole brain stem.

In view of what has been postulated about this man's illness, a cerebral vasculitis at first seems a very likely possibility, but there are problems about accepting this. I would have expected to have seen at least some evidence of focal neurological signs if this were the case (except in the convulsions occurring in SLE and the rare leuco-encephalopathy which may occur in the collagen diseases where focal neurological deficits are not usually found).

In conclusion there are a number of other diseases which need to be mentioned only for exclusion. I do not

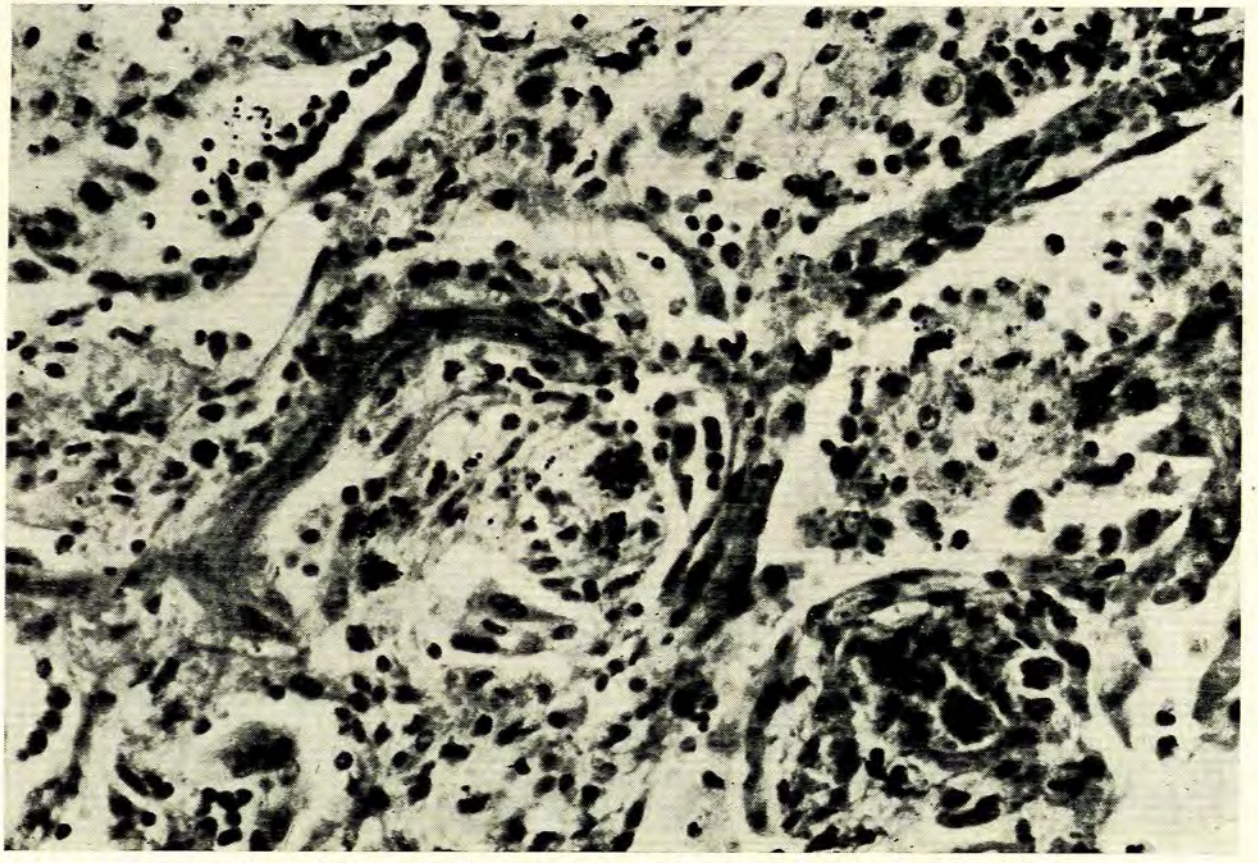

Fig. 3. Showing definition of collagen in alveolar walls (Van Gieson × 312).

think that this man had sarcoidosis, neither was there much to suggest subacute bacterial endocarditis, although murmurless bacterial endocarditis is known in clinical practice. A septicaemia illness also seems unlikely. I would therefore say that from the evidence presented here this man had:

(*ii*) diffuse collagen disease affecting joints, heart and lungs; and

(*ii*) terminal cerebral involvement due to a combination of cerebral oedema and metabolic acidosis.

CLINICAL DISCUSSION

Dr I. Huskisson: The latex test was weakly positive initially. This is against rheumatoid arthritis. In this condition it is more definitely positive from the outset when the lungs are involved.

Dr A. Ferguson: I disagree with the interpretation of the second X-ray. The appearances are those of pneumonic condition and not simply those of pulmonary oedema and the whole illness right from the beginning seemed like primary lung disease.

Professor S. Saunders: The low Po_2 is similar to a case discussed recently who had oxygen toxicity.

Dr A. Ferguson: There are many pathological processes which can have the same end-result. This is not oxygen toxicity.

POSTMORTEM FINDINGS

A. H. TIMME, *Department of Pathology, University of Cape Town*

Autopsy Findings

The body was that of an adult Bantu male. A tracheostomy wound was present but there were no external abnormalities of the joints and there was no clubbing. Both lungs (RL 1135 g, LL 973 g) were largely covered by a fibrinous pleurisy, occasional adhesions also being found at the left base. The cut surface of both lungs showed dry, ill-defined areas of greyish-white consolidation 1 - 3 cm in diameter throughout the lung parenchyma (Fig. 1). Occasional areas of lobular haemorrhage were seen. The pulmonary vessels were normal. The organs were slightly friable but there was no gross evidence of scarring. The hilar lymph nodes were slightly enlarged and contained a small focus of caseous tuberculosis. The heart (390 g) showed slight hypertrophy of the left ventricular wall which measured about 1·6 cm in thickness. The right ventricle also showed mild hypertrophy.

The liver (1 259 g) showed an accentuation of its lobular pattern with pallor of the centrilobular zones. The kidneys (295 g) were not remarkable. The left femur contained

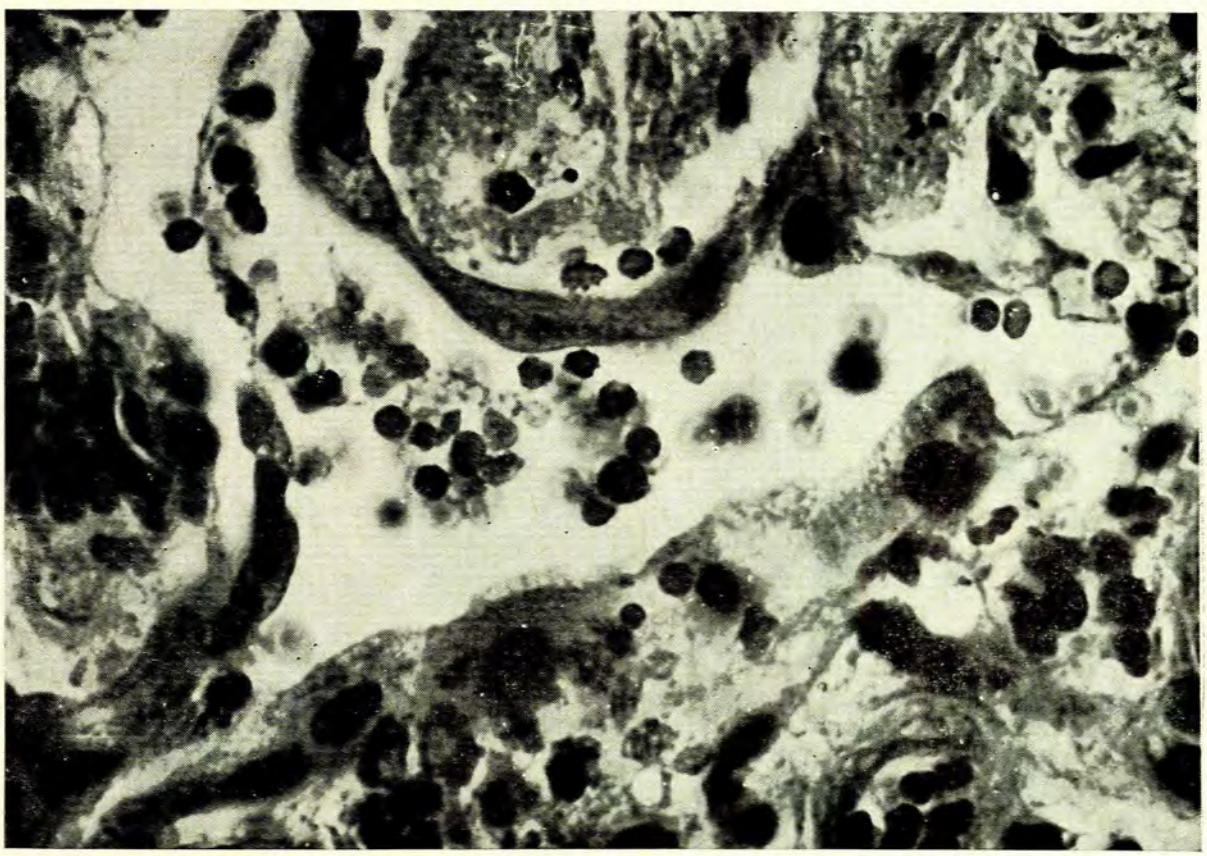

Fig. 4. The cells lining the alveoli. The cytoplasm is finely vacuolated and fine microvilli project from the luminal surface of some cells (H. and E. × 750).

slightly reactive marrow. The skull showed an old depressed fracture in the frontal area and underlying this there was an area of slight cerebral atrophy. The rest of the organs showed no abnormality.

Postmortem Lung Culture

No mycoplasma or viruses were isolated (Monkey kidney and Hela cells). Bacterial culture of the lung produced a moderate growth of *Klebsiella aerogenes*.

Microscopic Examination

In the lungs the picture varied somewhat in different areas. The most conspicuous feature was the presence of PAS-positive hyaline membranes lining the walls of numerous alveoli and alveolar ducts (Fig. 2). Areas of intra-alveolar haemorrhage and fibrinous exudate were present, but were never striking. The alveolar walls usually were thickened because of oedema and a limited cellular infiltration composed of mononuclear cells. The alveolar capillaries were congested. In general the alveolar reticulin pattern was unaltered, despite the above changes, but in a very few areas the reticulin was increased. In such foci there was a proliferation of fibroblastic cells and the laying down of limited amounts of collagen. Early organization of intra-alveolar exudate was also found (Fig. 3).

Many of the alveoli were lined by a continuous layer of swollen epithelial-like cells in which occasional mitotic figures could be found (Fig. 4). These cells had relatively large vesicular nuclei and an eosinophilic or finely vacuolated cytoplasm. Fine processes could be seen on the luminal surface of a few cells. Occasional alveoli contained moderate numbers of mononuclear histiocytes, some of which contained carbon pigment. Only a small percentage of cells in the alveoli (attached or free) contained PAS-positive granules, but frozen sections stained with Sudan Red demonstrated that a high percentage of cells lining the air spaces and those lying free in the lumen, contained globules of neutral lipid (Fig. 5). Electron-microscopy of formalin-fixed tissues confirmed that many of the alveolar lining cells were granular pneumocytes which contained the characteristic lamellar bodies in their cytoplasm.

Synovial villi of the wrist joint were prominent and their tips were covered by fibrin. The lining synovial cells were swollen. Immediately below the surface were numerous large macrophage-type cells with relatively small nuclei and finely vacuolated cytoplasm (Fig. 6). PAS and mucicarmine stains were negative. Other mononuclear cells were present in the stroma of the villi but plasma cells were absent. No haemosiderin was present.

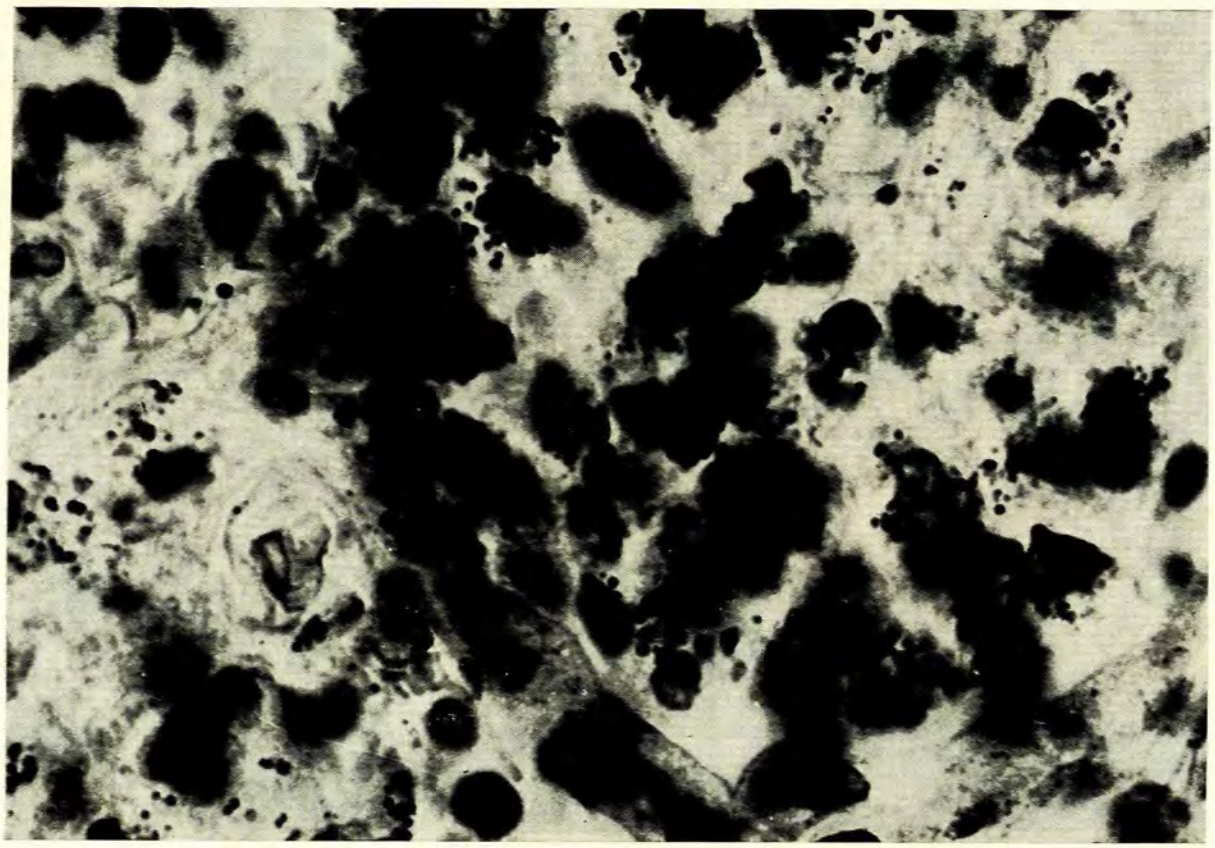

Fig. 5. Globules of neutral lipid are present in the cytoplasm of cells (Sudan Red × 750).

A very extensive, recent centrilobular necrosis was present in the liver.

Occasional scattered foci of cellular infiltration were noted within the fibrous septa of the psoas muscle. Cells present included lymphocytes and occasional large mononuclear cells. No vascular lesions were noted but a few degenerate muscle fibres were seen in relation to the cellular foci.

Comment

The changes in the lungs appear to be those of a 'fibrosing alveolitis' which is characterized in particular by hyaline membrane formation and enlargement and proliferation of the granular pneumocytes. Although similar features may be found in the lungs in many other conditions, e.g. uraemia, atypical pneumonia, rheumatic fever, it is possible to exclude such causes and one is left with the diagnosis of an acute variant of the Hamman-Rich syndrome (diffuse interstitial fibrosis).[10]

Cases of fibrosing alveolitis with such a short history are uncommon and where such cases have been autopsied it appears that the lung changes may be more advanced than anticipated.[10] In this case the lesions in the lung are mostly fairly acute with very little evidence of fibrosis. An unusual feature is the abundance of lipid droplets in the free and attached alveolar cells.[12]

The nature of the 'arthritis' is uncertain. The material in the foamy macrophages could not be characterized histochemically, but unfortunately frozen sections were not available. There is, however, no resemblance to the lesions seen in rheumatoid arthritis.

The liver necrosis appears to have been a terminal event. Cases of fibrosing alveolitis with hepatic involvement have been described but the histological changes have been of a more chronic nature.[13] Anoxia may have been a factor but the autopsy did not disclose changes in other organs which may show anoxic degeneration, e.g. pituitary and brain. The lesions in the muscle are not distinctive.

GENERAL DISCUSSION

Dr Meyers: I am surprised that Dr Timme says there is nothing to see in the heart. There are so many indications of severe cardiac disease.

Professor Uys: Dr Timme, you will agree that although no cardiac abnormalities were demonstrated, this does not rule out the presence of cardiac disease. It is well known that in certain instances there may be gross cardiac dysfunction and yet little demonstrable abnormality at autopsy.

Professor Saunders: The terminal illness took 12 days in which time very dense lungs and high temperatures were demonstrated. There was a marked degree of liver

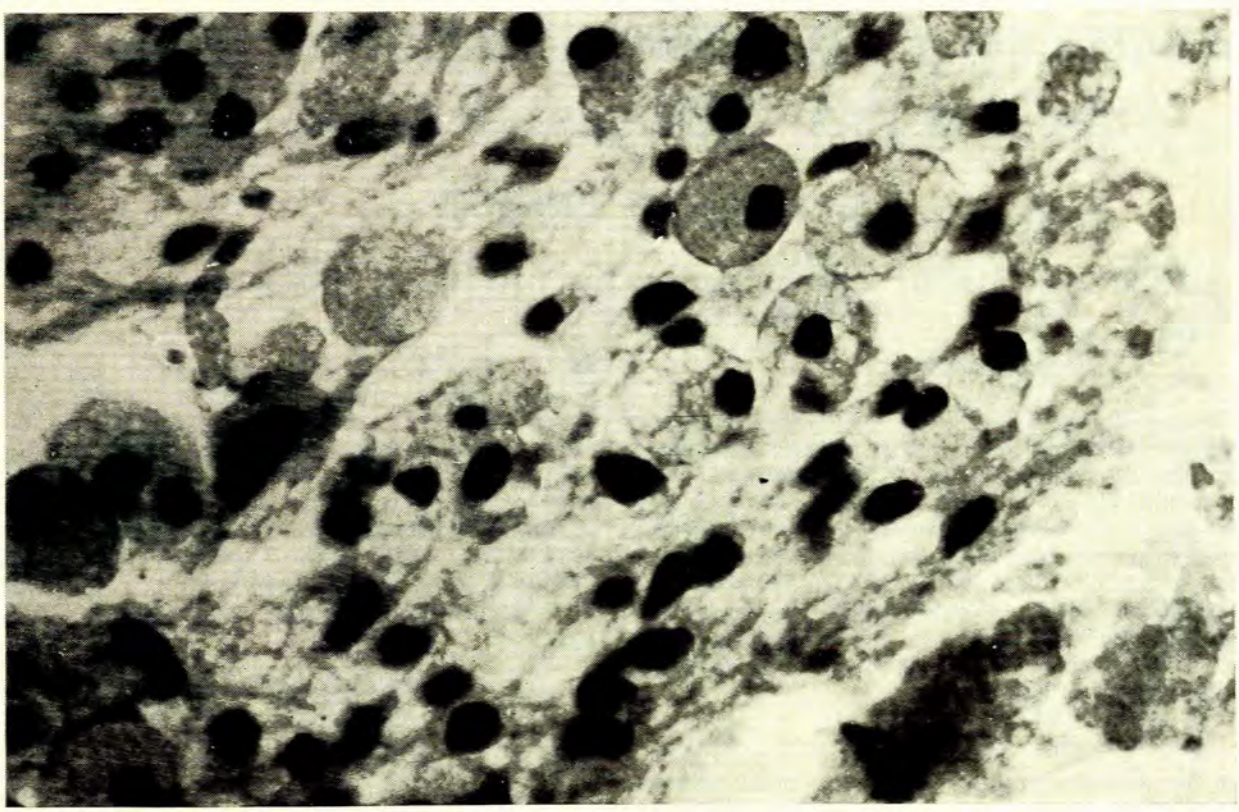

Fig. 6. Synovial membrane of wrist joint showing the large cells with foamy cytoplasm (H. and E. × 700).

cell necrosis at autopsy, and yet the SGOT was only moderately raised. This is very surprising but does occur. Is there any possible explanation for the liver cell necrosis?

Dr Timme: There is no adequate explanation. The necrosis appears to be very recent. It may be of several hours' duration and is unlikely to have occurred more than 2 days before death. I do not think that it is a component of the general disease process.

Professor Uys: I am also of the opinion that the liver necrosis was of very recent onset and not more than 24 hours' duration. While the necrosis is of a more severe degree than that usually associated with anoxia, I think it must be attributed to this factor. A man in the terminal stages of cardiac failure with a severe pneumonic lesion must have been subjected to an extreme degree of anoxia.

Dr Huskisson: This man had a significantly reduced creatinine clearance, and yet there is no evidence of renal disease. What is the explanation for this?

Dr Meyers: I think this figure quoted may have been unreliable. Indeed, the initial symptomology referable to the kidneys may have been unreliable and no significance is attached to it.

Dr Milner: Can you still exclude the possibility of this being a viral infection?

Dr Timme: This can positively be excluded.

ANATOMICAL DIAGNOSIS

A. H. TIMME

1. Hyperacute fibrosing alveolitis of intrinsic type.
2. 'Arthritis' of undetermined type.

REFERENCES

1. Ghormley, R. K. and Deacon, A. D. (1936): Amer. J. Roentgenol., **35**, 740.
2. Empire Rheumatism Council (1950): Ann. Rheum. Dis., **9**, suppl.
3. Liebowitz, W. B. (1963): Ann. Intern. Med., **58**, 102.
4. Sokoloff, L. (1964): Mod. Conc. Cardiov. Dis., **33**, 847.
5. Good, A. E., Lang, K., Olson, J. R. and Frishette, W. A. (1970): Arth. Rheum., **13**, 166.
6. Edge, J. R. and Richards, A. G. (1957): Thorax, **12**, 352.
7. Scadding, J. (1969): Proc. Roy. Soc. Med., **62**, 227.
8. Turner-Warwick, M. and Doniach, D. (1965): Brit. Med. J., **1**, 886.
9. MacKay, I. R. and Ritchie, B. (1965): Thorax, **20**, 200.
10. Hamman, L. and Rich, A. (1944): Bull. Johns Hopk. Hosp., **74**, 177.
11. Richardson, J. S. (1963): *Connective Tissue Disorders*, p. 116. Oxford: Blackwell Scientific Publications.
12. Liebow, A. A., Steer, A. and Billingsley, J. G. (1965): Amer. J. Med., **39**, 369.
13. Turner-Warwick, M. (1968): Quart. J. Med., **37**, 133.