

WEGENER'S GRANULOMATOSIS

BY

P. O. LEGGAT AND E. W. WALTON

From Walkergate Hospital and Department of Pathology, Durham University

(RECEIVED FOR PUBLICATION AUGUST 3, 1955)

In recent years there has been an increasing number of reports, mostly in journals of pathology, of the association of giant cell granulomatous lesions of the upper air passages or respiratory tract with diffuse necrotizing angitis and glomerulonephritis. The first published case was one of two cases described by Klinger in 1931 under the title "Borderline Cases of Periarteritis Nodosa," but it was Wegener, who, in describing three cases briefly in 1937 and in detail in 1939, realized that they represented a group separable by the nature of the tissue reaction from the more usual forms of polyarteritis nodosa. Recently, Fahey, Leonard, Churg, and Godman (1954) have summarized the findings in 22 previously reported cases and described seven new cases. The purpose of this article is, in describing the clinical features of four new cases, to support the view that Wegener's granulomatosis is a separate, well-defined syndrome of increasingly frequent occurrence, and to indicate the features rendering such a diagnosis possible.

CASE REPORTS

CASE 1.—A married woman aged 42 years first became ill with a right-sided pleurisy in March, 1954. This resolved completely after domiciliary treatment with sulphonamide for one week. On recovery the patient was referred to a chest clinic where, although she felt quite well, a chest radiograph revealed a large homogeneous shadow in the lateral segment of the middle lobe of the right lung (Fig. 1). Within the next month, re-examination showed several similar rounded shadows in the left lower lobe, and she was admitted to hospital in May for further investigation. A Mantoux test (1 in 10,000 O.T.) was positive, but repeated examination of sputum and gastric washings for tubercle bacilli, with culture and guinea-pig inoculation, were negative, as were attempts to isolate fungi from the sputum; indeed, the only pathogenic micro-organism isolated at any stage was a coagulase-positive staphylococcus. The Wassermann reaction and a histoplasmin skin test (0.1 ml. 1 in 100) were negative. Secondary neoplastic deposits were suspected, and, owing to the absence of any obvious primary lesion, an exploratory thoracotomy was performed on June 28. The left lower lobe contained several rounded, greyish yellow, apparently

necrotic, subpleural areas measuring up to 5 cm. in diameter. The histological report on a portion removed was indicative of tuberculosis. Accordingly, treatment with streptomycin 1 g. and sodium para-aminosalicylate (sodium P.A.S.) 18 g. daily was begun and continued until discharge from hospital three weeks later, at which time the patient was comparatively well, though complaining of intermittent anosmia.

On August 18 she was admitted to the Walkergate Hospital with a persistent productive cough accompanied by a considerable amount of purulent sputum. She was toxic and ill, with fever up to 103° F. The blood picture was within normal limits. Radiologically there had been considerable extension of the lesion on the right side, which still appeared as a rounded mass, though there was now a small pleural effusion in addition to the lung lesion. There was also a fresh homogeneous nodular lesion in the left upper lobe (Fig. 2). Streptomycin and P.A.S. were given again in the same dosage as before. This was followed by an immediate and progressive improvement in her clinical and radiological condition. Her temperature began to settle and there was considerable resolution of the lesion in the right lung. On October 2, in the middle of the seventh week of the second period of streptomycin treatment, she developed a sensitivity reaction, with fever and diffuse skin rash, and the treatment with streptomycin and P.A.S. was discontinued. This reaction was associated with a slight blood eosinophilia, the eosinophils constituting 10% of a total leucocyte count of 6,850 per c.mm. Although the rash associated with the sensitivity reaction faded rapidly, it was three weeks before the temperature returned to its previous level, and fleeting diffuse arthralgia with oedema of the dorsum of the hands persisted. The anosmia had become more persistent, and examination revealed ulceration of the nasal septal mucosa with involvement of the cartilage. A biopsy of the nasal mucosa was reported as "non-specific granulation tissue." In early November an attempt at desensitization to streptomycin produced four days after the daily dose had reached 1 g., a further fairly severe sensitivity reaction. In addition to the polyarthritis and rash, the patient developed a mild peripheral neuritis of the hands with sensory changes but no motor involvement. Albuminuria and microscopic haematuria developed and persisted, the urine also containing many granular casts. From November 12 to December 7, isoniazid, 200 mg., and oxytetracycline, 4 g., daily were given, but in December it was

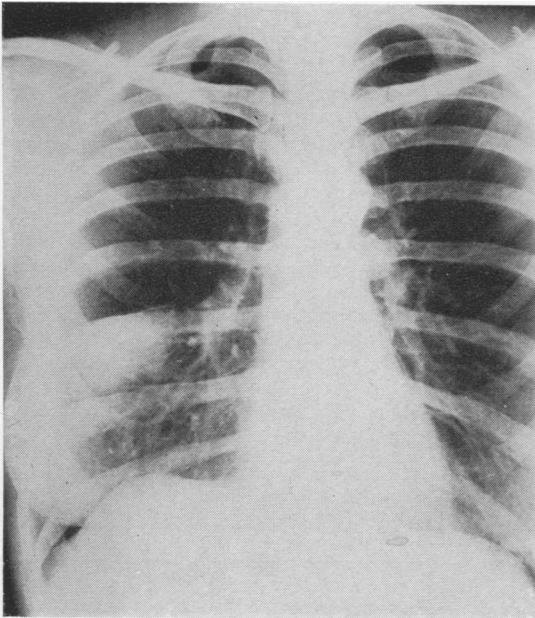


FIG. 1.—Case 1. In March, 1954, homogeneous shadow is seen in the lateral segment of the right middle lobe.

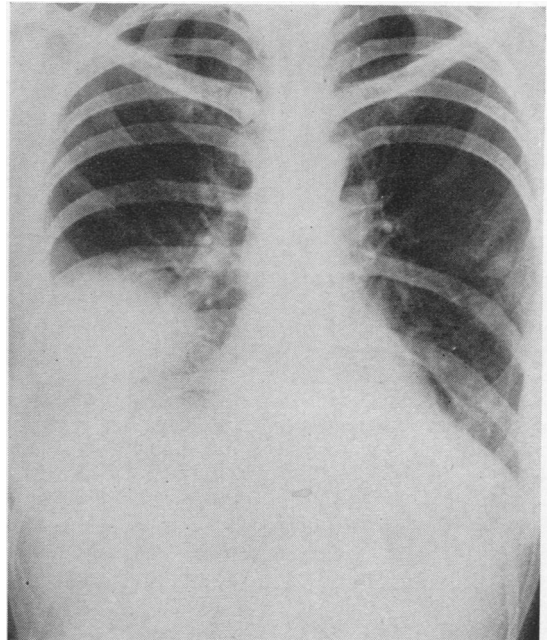


FIG. 2.—Case 1. By August, 1954, the lesion in the right lung had extended considerably. There is a homogeneous nodule in the third interspace on the left side.

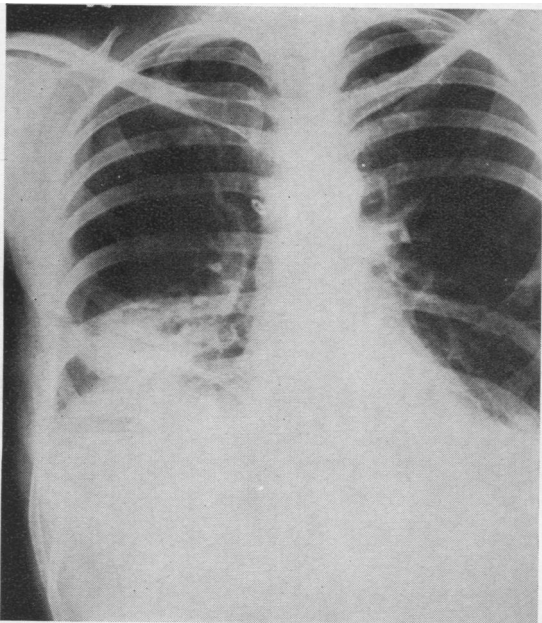


FIG. 3.—Case 1: In Dec., 1954, the lesion on the right side has undergone considerable resolution. The lesion on the left has broken down.

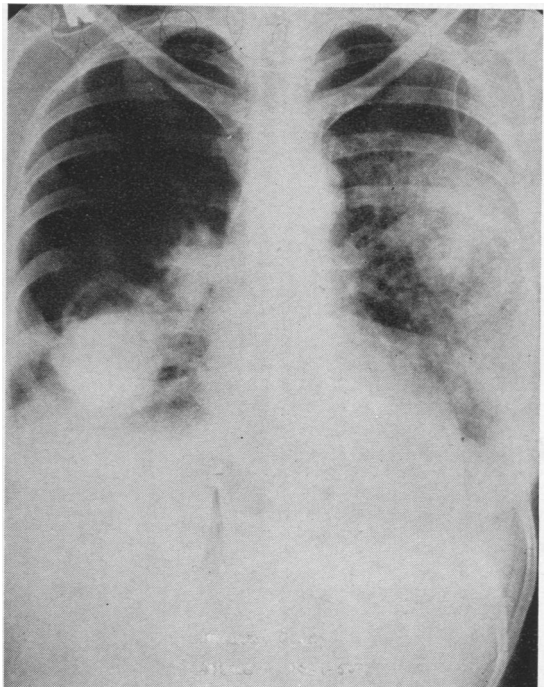


FIG. 4.—Case 1: In Jan., 1955, the right lesion has broken down extensively with multiple abscess cavities and extensive pneumonic changes throughout the left lung.

obvious that her condition was deteriorating. The lesions in both right and left lungs had developed cavities, and that in the right lung was increasing in size (Fig. 3). Desensitization to streptomycin was again attempted; but this provoked within 10 days (on December 29) a very violent reaction accompanied by a haemorrhagic rash on the elbows and the knees, polyarthritis, episcleritis, ulceration of the buccal mucosa and tongue, and slight bilateral deafness. Meanwhile, in the lungs there was progressive involvement of the right middle lobe and the left lung. Severe anaemia and haemoptysis developed, the haemoglobin falling to 5.8 g.%. A blood transfusion of two pints (1.1 litres) was given. Though treatment with sodium salicylate and penicillin produced some improvement in the sensitivity response, least marked in the dermal lesions, her condition slowly deteriorated. Finally she developed a left bronchopneumonia together with very extensive cavitation in the right lung in which all the basal segments of the right lower lobe were now involved as well as the middle lobe (Fig. 4). She died in peripheral circulatory failure on January 14, 1955, 10 months after the start of her illness. At no stage did the blood

pressure rise above 135 mm. Hg systolic and 85 mm. diastolic. The clinical course is summarized in Fig. 5.

Pathology.—A review of the biopsy sections from the lung and from the nasal mucosa showed the typical features of Wegener's granulomatosis, giant-cell granulomata being present in each specimen.

At necropsy the following lesions were found: granulomatous ulcerative rhinitis, laryngitis, tracheitis and bronchitis; multiple rounded, necrotizing giant cell granulomatous masses, largely coalescing, in the right lung and left lower lobe (Figs. 6 and 7), and bilateral non-specific bronchopneumonia; necrotizing giant-cell granulomata in the capsule and the trabeculae of the spleen and in the dermal papillae; widespread focal fibrinoid necrosis in the renal glomerular tufts with necrotizing angitis, both acute and healed, affecting the arteries and the veins of the spleen, kidney, pancreas, uterus, voluntary muscle, perirenal adipose tissue, and the bronchial circulation of the lungs (Fig. 8).

CASE 2.—A woman aged 34 years was admitted to the Royal Victoria Infirmary, Newcastle, on December 28, 1949, with a history of deafness and nasal obstruction

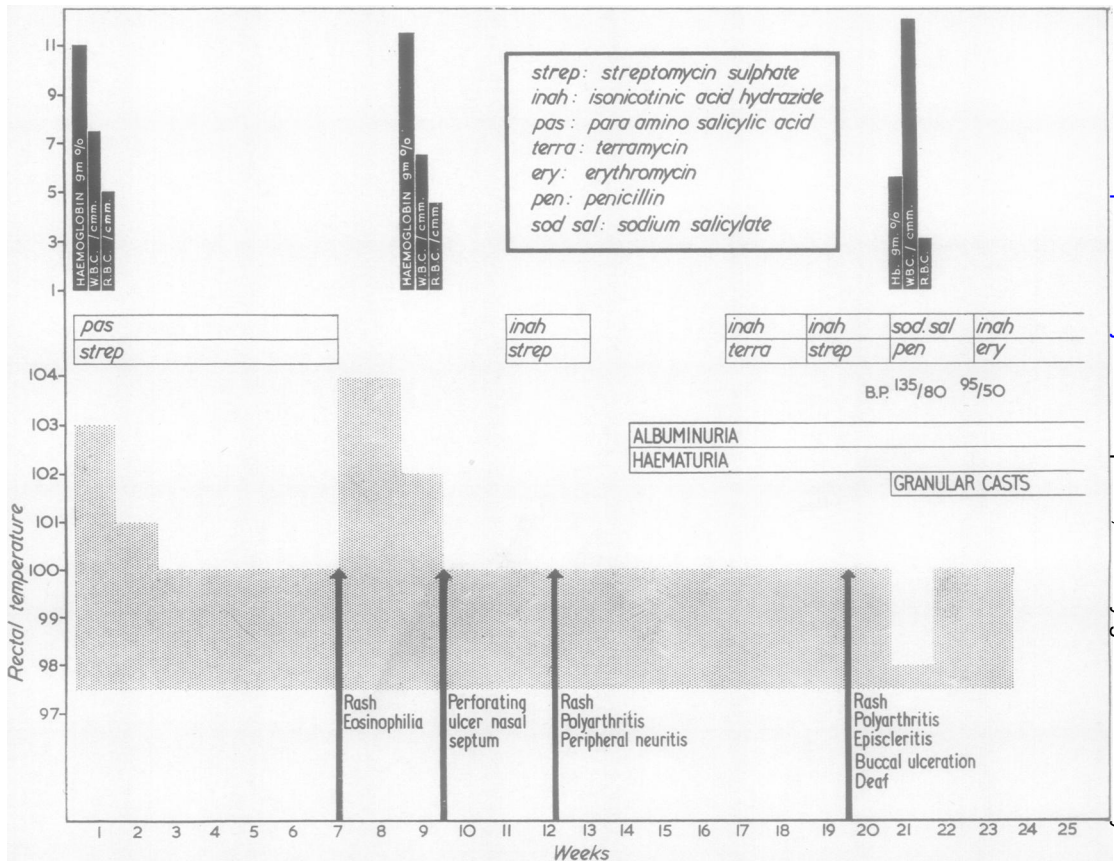


FIG. 5.—Summary of clinical course of Case 1. The temperature is expressed as the mean of the maximum daily readings over each period of one week.

Thorax: first published as 10.1136/hx.11.2.94 on 1 June 1956. Downloaded from http://thorax.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

She had been well until eight weeks previously when she complained of stiffness and swelling of the knees and the ankles, followed after two weeks by a mild tonsillitis. A few days before admission she developed a dry stuffy nose, bilateral conjunctivitis, and became deaf with continuous ringing in the ears. On examination she was very deaf and had evidence of bilateral scleritis. In addition, the nasal mucosa was intensely red and ulcerated, with thick pus in both nostrils. She was dyspnoeic and febrile up to 100° F. The blood pressure was 160/110 mm. Hg. The heart was not enlarged and the sounds were normal. There was no evidence of joint swelling, but nodules similar to rheumatic nodules were present over the elbow joints. Radiologically, the skull showed opacity of both maxillary antra, sphenoidal and ethmoidal air cells. There was a moderate leucocytosis, 16,800 per c.mm., with 80% neutrophils but no eosinophils. The urine contained numerous pus cells and a trace of albumin. A clinical diagnosis of subacute rheumatism was made and treatment was begun with penicillin and sodium



FIG. 6

FIG. 6.—Right lung ($\times \frac{1}{2}$), showing the confluent areas of necrosis in each lobe (Case 1).

FIG. 7.—Granuloma with numerous multinucleate giant cells and lung zone of necrosis (Case 1). Haematoxylin and eosin, $\times 180$.

FIG. 8.—Arteriole showing fibrinoid degeneration of one segment of the wall, and adventitial granuloma formation (Case 1). Weigert's elastica and Van Gieson, $\times 90$.

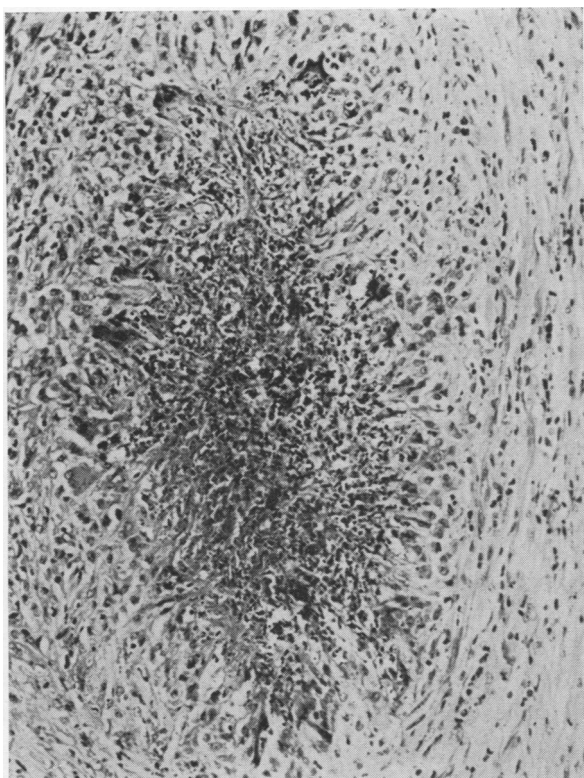


FIG. 7



FIG. 8

salicylate, 40 gr. four hourly. For 10 days there was little change in her condition, but the salicylate therapy had to be discontinued owing to early salicylate intoxication. Subsequently her general condition improved, though the conjunctivitis and rhinitis remained and a painless right otorrhoea developed. After six weeks of febrile illness, she suddenly became worse. The temperature, never very high, became subnormal, the pulse rapid, and the nasal obstruction more marked. Clinically there was evidence of diffuse bronchitis with stridor and no signs of consolidation. At this point she developed raised purplish red lesions on the dorsum of the hands which later became vesicles. The albuminuria became more marked, and seven weeks after admission she died suddenly. The only pathogens isolated from the sputum and the nasal swabs were *Streptococcus pyogenes* and *Staphylococcus aureus*. Culture and guinea-pig inoculation for tubercle bacilli and blood culture were repeatedly negative.

Pathology.—The following is a summary of the necropsy findings:

Granulomatous sinusitis and necrotizing giant cell ulcerative glossitis, tracheitis and bronchitis; multiple circumscribed giant cell granulomatous masses in all lobes of both lungs, with central cavitation in some, and bilateral non-specific bronchopneumonia; necrotizing giant-cell granulomata in the capsule and trabeculae of the spleen and the dermal papillae, and multiple splenic infarcts; focal fibrinoid necrosis of renal glomerular tufts with numerous periglomerular giant cell granulomata; and acute necrotizing arteritis of spleen, skin, kidney, and myocardium.

CASE 3.—A man aged 33 years was admitted to Carlisle Royal Infirmary on November 26, 1948. A "boil" had developed in the left ear two weeks previously; this later began to discharge and he became deaf on this side. A few days before admission he noted that the right nostril was blocked. On examination he was found to have a large granulomatous mass projecting from the posterior aspect of the left aural canal. There was another granulomatous mass, which bled easily, covering the floor of the right nostril, and radiologically appeared to extend into the right antrum. He was running a slight fever up to 99.4° F. The Wassermann and Kahn reactions were both negative. On December 23 a circular opacity of uniform density was noted in the mid zone of the left lung. The E.S.R. was raised to 66 mm. in the first hour. On December 25 a blood count showed slight anaemia with a mild polymorph leucocytosis: R.B.C. 4,470,000 per c.mm., W.B.C. 12,100 per c.mm. (neutrophils 71%, eosinophils 3%, lymphocytes 12%, monocytes 4%). Penicillin therapy produced a fall in temperature, though his general condition did not improve, and the swelling of the right side of the face, previously present, increased. On January 9, 1949, peripheral oedema was noted for the first time, in addition to a purpuric vesicular rash over the upper part of the right side of the face. These purpuric spots had purulent centres. On January 16 his sputum became blood stained, and ulceration of the pharyngeal mucosa was noted. Culture of the sputum

at this stage yielded *Staphylococcus aureus*. There was now a moderate polymorph leucocytosis and a slight eosinophilia, the leucocyte count being 21,000 per c.mm. (neutrophils 86%, eosinophils 4%). On January 20 the patient developed a haemorrhagic left pleural effusion of moderate size, but culture and guinea-pig inoculation of the pleural fluid were negative for tubercle bacilli. Meanwhile the haemorrhagic vesicular rash had spread to involve the pinnae, hands, elbows, and knees. These lesions were particularly obvious on the elbows.

The patient died on January 21, nine weeks after the onset of his illness.

Pathology.—At necropsy the chief findings are as follows: giant cell granulomatous ulceration of the left aural canal, both nostrils, palate, and pharynx; suppurative parotitis, sinusitis and otitis media; ulceration of the trachea and bronchi and multiple rounded necrotizing giant cell granulomata in both lungs, with central cavitation in the largest; focal fibrinoid necrosis of renal glomerular tufts with scattered periglomerular giant cell granulomata, infarct of the spleen and acute necrotizing arteritis of the kidney and ileum.

CASE 4.—A man aged 39 years first became ill in February, 1943, with diffuse limb pains, headache, soreness and swelling of the gums, and a slight non-productive cough. On admission to Carlisle City General Hospital three weeks later he was weak and febrile, but, apart from a small ulcer on the left upper alveolar margin, there was little apparent on clinical examination. After a few days he developed epistaxis and tender erythematous swellings of the alveolar margin of the right upper jaw and the bridge of the nose. Radiography of the maxillary antra showed some opacity but no evidence of tumour. *Strep. haemolyticus*, *Strep. viridans*, pneumococci, and *Staphylococcus aureus* were isolated from the alveolar ulcer and the sputum. Two weeks after admission conjunctivitis and a vesicular rash on the neck and face appeared. The ulceration of the upper jaw spread rapidly, involving the palate, and signs of consolidation with pleural friction appeared at both lung bases; the temperature and pulse rose to 102.4° F. and 120 per minute respectively. A blood culture and the Wassermann reaction were negative, and a blood count showed haemoglobin 76%, leucocytes 15,200 per c.mm., with 88% neutrophils and no eosinophilia. Despite treatment with sulphathiazole (2 g. then 1 g. every four hours) he rapidly deteriorated, with oliguria and a subnormal temperature, and died on April 6, 1943, nearly seven weeks after the onset of the illness. Culture and guinea-pig inoculation of sputum for tubercle bacilli were negative.

Pathology.—The following is a summary of the findings: necrotizing giant cell granulomatous ulceration of the sinuses, nose, soft palate, gums and mouth; scanty small giant cell granulomata in both lungs and bilateral suppurative bronchopneumonia; acute axillary lymphadenitis and acute (? uraemic) ulceration of ileum; multiple infarcts and focal fibrinoid necrosis of glomerular tufts in the kidneys, and acute necrotizing arteritis of kidney, ileum, and lymph nodes.

DISCUSSION

Each of the described cases demonstrated the characteristic morbid anatomical lesions of Wegener's granulomatosis (Godman and Churg, 1954) with, in each case, giant cell granulomatous ulceration of the upper air passages (nasal cavity, maxillary sinuses, oral cavity, and palate), necrotizing giant cell granulomata in the lungs and bronchi (Figs. 6 and 7), diffuse necrotizing arteritis (Fig. 8), and a well-marked renal lesion consisting of focal fibrinoid degeneration and thrombosis of loops of the glomerular tufts with, frequently, epithelial crescent formation, and periglomerular granulomata in Cases 2 and 3.

Though variations in the individual clinical picture occur, it is apparent, from a comparison of the four described cases with those reviewed by Fahey and others (1954), that the natural history of the disease follows one broad pattern. There is no particular sex preponderance, but the disease is commonest in the fourth and fifth decades. The first symptoms are usually referable to some part of the respiratory tract, most frequently nasal obstruction and purulent nasal discharge, at times blood-stained: deafness and aural pain may occur, and at times be accompanied by discharge, due, in some cases, to granulomatous involvement of the external auditory canal (Case 3) and in others to a non-specific subacute otitis media secondary to inefficient drainage of the middle ear (Johnsson, 1948). Painful swollen joints, haemoptysis, epistaxis, chest pain usually of a pleuritic nature, fever, productive cough with purulent sputum, wasting, orchitis, weight loss, and the silent development of saddle nose, have all been noted on occasion as presenting symptoms, but are less common.

As the disease progresses, the pulmonary lesions extend and may break down into multiple cavities, whilst symptoms and signs indicating involvement of other organs appear. Haemorrhagic, often vesicular, skin lesions develop, which in Cases 1 and 3 were mainly confined to the extensor surfaces of the elbows and knees, and the dorsum of the hands. Sometimes, as in Case 1, there is evidence of a peripheral neuritis (McCallum, 1954). Albuminuria as evidence of renal damage occurs fairly late in the course of the illness, but, having appeared, it is progressive, and is often accompanied by either microscopic or macroscopic haematuria (Case 1). After a brief duration, usually of less than six months, the disease inevitably terminates fatally, usually in uraemia: thus, of the 29 cases reviewed by Fahey and others (1954), 15 showed evidence of severe uraemia before death.

With regard to the differential diagnosis, the radiological picture of the lungs must be distinguished from that due to pulmonary tuberculosis, especially breaking down tuberculomata, carcinoma of lung, coccidioidomycosis of lung, histoplasmosis, blastomycosis, and pyogenic lung abscess. The lesions of sarcoidosis may sometimes be concentrated in those sites affected by Wegener's granulomatosis (Fahey and others, 1954), but the granuloma of sarcoidosis is non-necrotizing, and necrotizing glomerulitis has not been recorded in this disease. In classical periarteritis nodosa, pulmonary lesions with secondary abscess cavity formations are stated not to occur (Bergstrand, 1946). The case described by Sandler, Matthews, and Bornstein (1950) under the title "Pulmonary Cavitation due to Polyarteritis" may well be one of Wegener's granulomatosis, and has been attributed to this group by some authors (Fienberg, 1953).

The local lesion of the upper air passages closely resembles malignant granuloma of the nose. In this condition the granulomatous process usually remains confined to the midline facial tissues (Williams, 1949), though some authors would include Wegener's granulomatosis in this group (Friedmann, 1955).

No effective treatment for the condition has yet been discovered, though nitrogen mustard intravenously in one case produced temporary relief, and a combination of cortisone, A.C.T.H., and antibiotic therapy prolonged the life of one patient for 39 months (Fahey and others, 1954). Sulphonamides, penicillin, triethylene melamine, and radiotherapy have all been tried and found to be ineffective. In Case 1, streptomycin and P.A.S. therapy was followed by quite a definite clinical and radiological improvement, though only of a temporary nature. The improvement was probably due mainly to the control of secondary infection in the breaking down pulmonary lesions.

Although in the later stages the widespread vasculitis causes symptoms referable to many organs, in the early stages the lesions are confined to the respiratory tract, with, at times, involvement of the ears. In view of the peculiar distribution of the lesions in this early phase, it should be possible to make a diagnosis on clinical grounds. The clinical diagnosis can be confirmed by the examination of biopsy material from the nose or from the ears. In some cases the initial and the major lesion is in the lungs (Case 1). In this type of case, material for biopsy could be obtained only by formal thoracotomy. Renal and skin lesions develop late in the illness, though if the latter are present they

would provide suitable biopsy material to establish a diagnosis.

The aetiology of the condition is, as yet, unknown. In the reported cases, no specific infecting agent was isolated and relevant tissue sections in each case, stained by Gram and Ziehl-Neelsen, failed to reveal any micro-organisms. Evidence, based on the clinical and pathological data of Case 1, that the disease is, at least in part, one of hypersensitivity, has been presented elsewhere (Walton and Leggat, 1956).

SUMMARY

The clinical course and morbid anatomical findings are described in four cases of Wegener's granulomatosis. The treatment and the differential diagnosis are discussed. It is considered that the early stages of the condition have a constant recognizable clinical picture which facilitates diagnosis.

The authors are grateful for permission to publish Case 3 to Dr. T. C. Studdert and similarly for Case 2 to Dr. A. G. Ogilvie; for necropsy reports in Case 1 to Dr. C. Jobling and in Cases 3 and 4 to Dr. J. S. Faulds and for valuable advice to Professor J. B. Duguid.

REFERENCES

- Bergstrand, H. (1946). *J. Path. Bact.*, **58**, 399.
 Fahey, J. L., Leonard, E., Churg, J., and Godman, G. (1954). *Amer. J. Med.*, **17**, 168.
 Fienberg, R. (1953). *Amer. J. clin. Path.*, **23**, 413.
 Friedmann, I. (1955). *J. Laryng.*, **49**, 331.
 Godman, G. C., and Churg, J. (1954). *A.M.A. Arch. Path.*, **58**, 533.
 Johnsson, S. (1948). *Acta path. microbiol., scand.*, **25**, 573.
 Klinger, H. (1931). *Frankfurt. Z. Path.*, **42**, 455.
 McCallum, A. G. (1954). *J. Laryng.*, **68**, 560.
 Sandler, B. P., Matthews, J. H., and Bornstein, S. (1950). *J. Amer. med. Ass.*, **144**, 754.
 Walton, E. W., and Leggat, P. O. (1956). *J. clin. Path.*, **9**, 31.
 Wegener, F. (1937). *Verh. dtsh. path. Ges.*, 1936, **29**, 207.
 — (1939). *Beitr. path. Anat.*, **102**, 36.
 Williams, H. L. (1949). *Ann. Otol. (St. Louis)*, **58**, 1013.