WEGENER'S GRANULOMATOSIS

BY

E. W. WALTON AND P. O. LEGGAT

From the Royal Victoria Infirmary, Newcastle-upon-Tyne

(RECEIVED FOR PUBLICATION MAY 27, 1955)

There have been few published reports of the association of giant cell granulomata of the upper respiratory tract with diffuse necrotizing angiitis and glomerulonephritis. The first published case was one of two cases described by Klinger in 1931 under the title, "Borderline Cases of Periarthritis Nodosa." Wegener, who reported three cases briefly in 1937 and in detail in 1939, postulated that they represented a pathological entity separable by the nature of the tissue reaction from the more usual forms of polyarteritis nodosa. He was impressed by the predominance in his cases of nasal and paranasal lesions and accordingly named the condition "rhinogenous granulomatosis." Recently Fahey, Leonard, Churg, and Godman (1954) summarized the findings in 22 reported cases and described seven new cases. The pathological findings in these seven cases were separately reported by Godman and Churg (1954), who were of the opinion that the "remarkable similarity of the pathological changes in all of the cases makes it probable that we are dealing with a separate and peculiar syndrome." They considered the syndrome to be characterized by three pathological features: (1) necrotizing granulomatous lesions in the upper air passages (nose, paranasal sinuses, nasopharynx, glottis, or adjacent regions) or in the lower respiratory tract (trachea, bronchi, lungs) or in both; (2) generalized focal necrotizing angiitis, involving both arteries and veins, almost always in the lungs, and more or less widely disseminated in other sites; (3) glomerulitis, characterized by necrosis (and thrombosis) of loops or lobes of the capillary tuft, capsular adhesion, and evolution as a granulomatous lesion.

The disease affects both sexes and all age groups, though most frequently in the fourth and fifth decades. The majority of cases have been in persons of previously good health and without any history of asthma, allergy, or sulphonamide therapy. Though one case reported by Fahey *et al.* was kept alive for 39 months by the use of cortisone and antibiotics, the prognosis is uniformly bad, a fatal outcome almost always resulting in less than six months. All of the only four

cases reported in detail in this country which fulfil the above criteria of Wegener's syndrome (Howells and Friedmann, 1950; Stratton, Price, and Skelton, two cases, 1953; McCallum, 1954) presented with symptoms referable to nasal ulceration or sinusitis. In other cases the presenting symptoms have been cough, continued fever with chest pain and shortness of breath, peripheral neuritis, and deafness.

We have studied a patient with this syndrome whose illness began as pleurisy, was mistakenly diagnosed as tuberculosis as a result of lung biopsy, and who developed a generalized hypersensitivity reaction, apparently to streptomycin, on three occasions. The following is an account of the clinical history, pathological features, and some aspects of the pathogenesis.

Case Report

E. A., a married woman aged 42 years, first became ill with a right-sided pleurisy in March, 1954. This resolved completely following domiciliary treatment with sulphonamide for one week. On recovery she 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. 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) 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 and P.A.S. 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 readmitted to hospital, having developed a high fever with a persistent productive cough. Treatment with streptomycin and P.A.S. was begun again, but on October 2 she developed a sensitivity reaction with fever and a diffuse skin rash, apparently due to streptomycin: this reaction was associated with a slight blood eosinophilia (leucocytes 6,850 per ml. and eosinophils 10%). 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 persistent and more marked, and examination revealed ulceration of the nasal septal mucosa with involvement of the cartilage. A biopsy of nasal mucosa was reported as "non-specific granulation tissue." In early November an attempt at desensitization to streptomycin produced, within a week, a further fairly severe sensitivity reaction. In addition to polyarthritis and rash, she 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 numerous granular casts. As a course of isoniazid and terramycin failed to benefit the patient, it was decided to make a further attempt at desensitization to streptomycin. This, however, within 10 days, provoked (on December 29) a very violent reaction accompanied by a haemorrhagic vesicular rash on the elbows and knees, polyarthritis, episcleritis, ulceration of the buccal mucosa and tongue, and slight bilateral deafness. Meanwhile, the lung picture had deteriorated, with progressive involvement of the right middle lobe and left lung, and severe anaemia had developed, the haemoglobin falling to 5.8 g.%, this necessitating a blood transfusion of 2 pints (1.14 litres). 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 bronchopneumonia and 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. Hg diastolic.

Pathological Findings

Nasal Biopsy.—Re-examination after death showed that the biopsy material consisted of dense, non-specific granulation tissue diffusely infiltrated by polymorphonuclear leucocytes, scanty eosinophil leucocytes, and occasional giant cells with granular eosinophilic cytoplasm and numerous peripheral nuclei; there were no areas of necrosis. The vessels appeared normal.

Lung Biopsy (Figs. 1–5).—On re-examination of the biopsy material, the two nodular lesions present consisted of granulation tissue containing multiple areas of necrosis, often confluent. In some areas, necrosis was complete with obliteration of the normal structure, loss of elastica stain-

ing, and fragmentation of the argyrophilic reticulin fibres. Some of these necrotic areas could be demonstrated to be of peribronchiolar origin by identifying in them surviving fragments of bronchiolar walls and epithelium. The granulation tissue round the necrotic areas was relatively avascular and infiltrated by polymorphonuclear leucocytes, plasma cells and lymphocytes, with infrequent eosinophil leucocytes. Giant cells (Figs. 2 and 3) were numerous and striking, varying greatly in size with from two to 20 nuclei, and of both Langhan's and foreign body type. The latter (Fig. 2) had foamy cytoplasm and were accompanied by numerous large macrophages. At the periphery of the lesions, solitary, more recent granulomata (Fig. 3) were found, and the granulation tissue passed slowly into recognizable lung tissue. Here the alveolar walls were thickened (Fig. 4), fibrosed, and infiltrated by lymphocytes and plasma cells, the alveoli being reduced in size, lined with enlarged cuboidal septal cells, and filled with foamy macrophages.

In the surrounding, more normal lung, several subsidiary nodules were present and consisted of peribronchiolar areas of early pneumonitis, similar to the more advanced lesion found at the edge

FIG. 1.—Lung biopsy, haematoxylin and eosin, $\times 10$. Necrotic area showing a central bronchiole.

FIG. 2.—Lung biopsy, haematoxylin and eosin, $\times 230$. Granulation tissue and foreign body giant cells with foamy cytoplasm.

FIG. 3.—Lung biopsy, haematoxylin and eosin, $\times 180$. Granuloma with numerous multinucleate giant cells.

FIG. 4.—Lung biopsy, reticulin, $\times 410$. Thickening of alveolar walls at the edge of a necrotic area.

FIG. 5.—Lung biopsy, reticulin, $\times 130$. Respiratory bronchiole showing organization of bronchiolar exudate to produce obstruction.

of the main necrotic areas. Many of these bronchioles of both terminal and respiratory type showed a non-specific bronchiolitis, the bronchiolar exudate frequently organizing to produce bronchiolar occlusion (Fig. 5).

The lung vessels showed a degree of change comparable with the intensity of the local inflammatory reaction. Thus the arterioles near the edge of the granulomatous areas showed endarteritis, often more striking in the side of the vessel nearest the granuloma. The internal elastic laminae of these vessels were intact, and serial sections revealed no zones of fibrinoid degeneration.

Necropsy.—The body was wasted. A warty pustular rash was present on the dorsum of both hands, on the elbows and knees. The skull, cranial sinuses, brain, and meninges were normal. One or two small shallow ulcers were present in the buccal mucous membrane and on the lateral border of the tongue.

Chest.—The trachea and main bronchi showed numerous irregular shallow, "moth-eaten" ulcers with greyish necrotic bases and measuring up to 2 cm. in diameter. Both lungs were very heavy, fibrous pleural adhesions being present over the left lower and right middle lobes, with elsewhere a patchy fibrinous pleurisy. A large, roughly rectangular greyish area of consolidation, measuring $9 \times 4 \times 4$ cm., extended laterally from the hilum of the right lung into the middle and upper part of the lower lobes. Two similar subpleural rounded areas, each 4 cm. in diameter, were present in the left lower lobe. Elsewhere the lung showed diffuse, often confluent, consolidation; the only normal lung tissue was found in both upper lobes. Several of the major right pulmonary arteries contained ante-mortem thrombi. One right hilar lymph node showed numerous calcified flecks suggestive of healed tuberculosis. The heart appeared normal apart from dilatation of the ventricles.

Abdomen.—The spleen was enlarged and soft, the Malpighian bodies being rather prominent. Both kidneys were enlarged, the cortex pale and swollen, with scattered petechial haemorrhages in both the capsular and cut surfaces. No infarcts were present in spleen or kidneys. Numerous mural leiomyomata were present in the uterus, the largest 2 cm. in diameter. The other organs and great vessels were normal.

Lungs.—Similar changes to those in the biopsy were found, save that the areas of necrosis were more extensive. Foamy macrophages were again prominent at the edges of the necrotic

areas; their cytoplasm contained numerous droplets of doubly refractile lipoid which gave a positive Schultz reaction for cholesterol. Most of the parenchyma of the lower lobes showed a fibrinous pneumonia with occasional scattered granulomata unrelated to vessels. The upper lobes showed oedema only. The trachea and main bronchi showed diffuse ulceration: in parts the submucosa was replaced by granulomatous tissue with occasional giant cells, which in some bronchi had eroded the cartilage to pass into the surrounding lung parenchyma. The vascular changes were also comparable with those in the biopsy specimen. In addition, many vessels, both arteries and veins, were occluded by recent ante-mortem thrombus. Necrotizing angitis was not observed apart from the areas of necrosis, though one or two bronchial arterioles did show segmental scars in their walls with segmental loss of the internal elastic lamina, probably indicative of a healed lesion of this type.

Kidneys.—There was a widespread bilateral diffuse glomerular lesion apparently affecting all the glomeruli and characterized by focal fibrinoid necrosis of the loops of the glomerular tufts with proliferation of the tuft epithelium and frequent epithelial crescent formation (Fig. 6). Polymorphonuclear infiltration was not marked. In many glomeruli the lesion was at a more chronic phase with fibrosis of the affected areas and marked periglomerular scarring. Many of the tubules were dilated and contained hyaline and granular casts, whilst there was a diffuse leucocytic interstitial infiltration. Necrotizing angitis affecting small vessels, including several afferent arterioles, was present in both kidneys.

Spleen.—The striking feature was the large number of solitary granulomata similar to those in the lung (Fig. 7). They were spherical, oval, or fusiform, depending on the place of section, and serial sections showed the majority to be of trabecular site and unconnected with arterioles. Similar lesions, but fewer, were present in the lymph follicles accompanied by necrotizing arteriolitis of the follicular arterioles. The capsule showed diffuse oedema, patchy fibrinous degeneration of collagen, and occasional small granulomata. Eosinophils were infrequent in the lesions.

Skin.—Diffuse, though patchy, fibrinoid degeneration of the collagen was seen in the papillary layer of the dermis, with occasional granulomata consisting of epithelioid cells, fibroblasts, and multinucleate giant cells of the Langhans type. Some of these had ulcerated through the epidermis

FIG. 6.—Kidney, P.A.S., $\times 230$. Glomerulus with fibrinoid degeneration of glomerular tufts.

FIG. 7.—Spleen, haematoxylin and eosin, $\times 130$. Trabecular granuloma showing several giant cells and central necrosis.

FIG. 8.—Spleen, haematoxylin and eosin, $\times 130$. Pulp arteriole at a bifurcation, one limb showing acute fibrinoid degeneration.

FIG. 9.—Pancreas, elastica, $\times 80$. Small artery showing segmental loss of the internal elastic lamina and fibrosis of the media, with recanalization by multiple channels of the occluding thrombus.

to form the pustular lesions visible macroscopically. The dermal vessels showed perivascular round-cell infiltration only.

Vessels.—Lesions affecting both arteries and veins, and of varying ages, were present in the spleen, kidney, pancreas, uterus, a uterine leiomyoma, voluntary muscle, and the periadrenal adipose tissue. Only vessels of up to 0.5 cm. in diameter were involved: the lesions often occurred near a bifurcation, were focal, merging at each end into normal vessel, and often segmental, affecting only a portion of the vessel wall in any one section. The acute stages (Fig. 8) were typified by fibrinoid necrosis of the vessel wall, thrombosis and perivascular, sometimes intramural, infiltration by polymorphonuclear leucocytes. Granulomata, usually perivascular but occasionally intramural, with occasional multinucleate giant cells, were often found. The characteristics of the healed stage (Fig. 9) were recanalization by multiple channels of the occluded vessels, perivascular fibrosis and, most impressive of all, segmental fibrosis of the media of arterioles with loss of the internal elastic lamina. Aneurysms were not observed.

No abnormality of either the vessels or the parenchyma was found in the liver, heart, adrenal, thyroid, or in a hilar lymph node. The sternal marrow was mildly hypoplastic and showed a slight eosinophilia.

Post-mortem Bacteriology.—Culture of bronchial exudate yielded only staphylococci and contaminants. Culture and guinea-pig inoculation of lung tissue were negative for tubercle bacilli. Sections of lung, skin, kidney, and spleen stained by Gram and Ziehl-Neelsen revealed no microorganisms.

Discussion

The case described features the unusual association of two types of lesions: necrotizing giant cell granulomata, most frequent in the respiratory tract but also in the skin and spleen, and widespread necrotizing angitis similar to polyarteritis nodosa. These lesions, together with glomerulonephritis, constitute, as defined by Godman and Churg, the pathological entity of Wegener's granulomatosis. The only characteristic lesions not seen to advantage in this case are periglomerular granulomata in the kidney; in nine of the 28 necropsied cases admitted to their series by Godman and Churg, renal granulomata were, however, not demonstrated. The main interest in this case lies in the light the clinical course throws upon the pathogenesis of the condition.

The concept that we have developed is as follows: (1) An initial lesion either of the nose and paranasal sinuses or of the lungs: the aetiology of this lesion is uncertain, though infection and allergy have been postulated. (2) A generalized hypersensitivity reaction occurring during immunization to bacterial or tissue breakdown products, or, as in this case, as a result of drug therapy, and producing the disseminated angitis and granulomata and the glomerulonephritis.

In our case, as in those reported by, among others, Fahey *et al.*, Ahlström, Liedholm, and Truedsson (1953) and Fienberg (1953a), the clinical course gives clear evidence of the priority of the respiratory tract lesions in the natural history of the disease. Evidence of involvement of other organs, as evinced by peripheral neuritis, albuminuria, polyarthritis, etc., only appeared in our case during or subsequent to the development of successive hypersensitivity reactions to streptomycin.

The nature of the respiratory tract lesions has been the subject of much discussion. Some authors, notably Wegener (1939), considered the lung lesions to be infarcts resulting from primary vascular disease. The opportunity afforded by lung biopsy to examine the lesions in this case at an early stage has produced striking evidence of the peribronchial distribution of the granulomatous foci, the vessels, as had previously been suggested by Johnsson (1948) and by Fienberg (1953a), being apparently affected secondarily to the antecedent inflammatory foci. Yet, as in our patient, in whom particular attention was paid to the possibility of a tuberculous or mycotic infection, no specific aetiological agent has ever been identified (Weinberg, 1946; Fienberg, 1953a) and the exact nature of the respiratory tract lesions remains uncertain. Many authors, notably Fienberg (1953b), have suggested that the respiratory tract lesions are due to allergy. He compared the findings in his two cases with those in six cases of the "cholesterol pneumonitis" recently described by Sniffen and his associates (Robbins and Sniffen, 1949; Waddell, Sniffen, and Sweet, 1949). He observed that ulceration and obstruction of bronchioles, thickening of the alveolar walls, and cholesterol-containing macrophages were common to both groups, and concluded that the primary disorder in both was "ulceration and obstruction of smaller bronchi, caused by a hypersensitivity reaction . . . and that this represents an Arthus phenomenon localized in the bronchial tree." Similar features were present in our case. In addition, in order to explain the constant concentration of the primary lesions in the respiratory

tract, Godman and Churg have suggested that two factors ought to be considered: first that this site is the "primary locus of attack of a noxious agent, probably microbial, which is present locally in highest concentration for the longest duration," secondly that the respiratory tissues are the most highly sensitized, forming "the first most susceptible shock tissues."

There can be little doubt that the disseminated lesions in this case occurred as a direct result of hypersensitivity reactions to streptomycin. Reactions of this type, manifesting with fever, eosinophilia, stomatitis, and skin rashes (Söderholm, 1950), are fairly common in streptomycin therapy (Crofton, 1953a and b). Moreover, each of the three characteristic lesions of Wegener's syndrome have been observed in hypersensitivity states and produced experimentally by hyperergic antigen-antibody reactions. Thus granulomata consisting of histiocytes and epithelioid cells, with sometimes giant cells and central areas of necrosis, have been produced by subcutaneous injection of shock antigen into specifically sensitized guinea-pigs (Goddard, 1947), whilst granulomata and necrosis are frequent histological features in many allergic diseases (Bohrod, 1947).

The presence of vascular lesions in both clinical and experimental hypersensitivity states is well known, being first demonstrated by Boughton in 1916. The classical experiments of Rich and Gregory (1943), who produced "typical diffuse polyarteritis nodosa by establishing in rabbits a condition analogous to serum sickness in man," have been repeated by many other workers. It is common knowledge that necrotizing arteritis may occur in hypersensitivity reactions to many drugs, especially to sulphonamides, in serum sickness (Clark and Kaplan, 1937) and in severe asthma (Churg and Strauss, 1951), though, so far as is known, never in a reaction to streptomycin. Pagel (1951), in discussing the pathogenesis of polyarteritis, suggests that the changes are "indicative of a tissue response to a variety of stimuli rather than one agent . . . a multiplicity of aetiological agents may produce periarteritis nodosa and the related conditions, the common pathogenic factor being antigenic hypersensitivity." On the other hand, similar lesions have been produced in rats by inducing experimental hypertension (Cromartie, 1943; Smith, Zeek, and McGuire, 1944; Smith and Zeek, 1947). That glomerulonephritis, "acceptably similar to the lesions . . . of glomerulonephritis in man" (Kobernick, 1952), has been frequently produced during sensitization of animals to nephrotoxic or other foreign sera is well known ;

prominent among such reports are those by Seegal and Loeb (1946) and Cavelti and Cavelti (1945). The lesions in our case were strikingly similar to those of the rapidly progressive type 1 glomerulonephritis (Ellis, 1942) which is a common feature in polyarteritis nodosa (Davson, Ball, and Platt, 1948). Considering these facts in conjunction with the clinical history, it appears beyond reasonable doubt that the disseminated lesions found at necropsy were a direct result of the hypersensitivity reactions to streptomycin.

Summary

A case is described which, at necropsy, presented the unusual association of necrotizing angitis with necrotizing giant cell granulomatous lesions of the respiratory tract and glomerulonephritis. The name Wegener's granulomatosis has recently been applied to this syndrome.

A lung biopsy at an early stage of the illness was thought at first to be indicative of tuberculosis, and during the resulting streptomycin therapy three successive hypersensitive reactions, each succeeding one more violent than the previous one, occurred.

It is concluded that the disseminated lesions characteristic of Wegener's granulomatosis are a result of hypersensitivity.

We should like to thank Professor J. B. Duguid and Dr. I. Rannie for their advice.

REFERENCES

- Ahlström, C. G., Liedholm, K., and Truedsson, E. (1953). *Acta med. scand.*, **144**, 323.
 Bohrod, M. G. (1947). *Amer. J. Med.*, **3**, 511.
 Boughton, T. H. (1916). *J. Immunol.*, **1**, 105.
 — (1917). *Ibid.*, **2**, 501.
 Cavelti, P. A., and Cavelti, E. S. (1945). *Arch. Path. (Chicago)*, **40**, 158.
 Churg, J., and Strauss, L. (1951). *Amer. J. Path.*, **27**, 277.
 Clark, E., and Kaplan, B. I. (1937). *Arch. Path. (Chicago)*, **24**, 458.
 Crofton, J. W. (1953a). *Brit. med. J.*, **2**, 1014.
 — (1953b). *Proc. roy. Soc. Med.*, **46**, 584.
 Cromartie, W. J. (1943). *Amer. J. med. Sci.*, **206**, 66.
 Davson, J., Ball, J., and Platt, R. (1948). *Quart. J. Med.*, **17**, 175.
 Ellis, A. (1942). *Lancet*, **1**, 72.
 Fahey, J. H., Leonard, E., Churg, J., and Godman, G. (1954). *Amer. J. Med.*, **17**, 168.
 Fienberg, R. (1953a). *Amer. J. clin. Path.*, **23**, 413.
 — (1953b). *Amer. J. Path.*, **29**, 913.
 Friedmann, I. (1955). *J. Laryng.*, **69**, 331.
 Goddard, J. W. (1947). *Amer. J. Path.*, **23**, 943.
 Godman, G. C., and Churg, J. (1954). *Arch. Path.*, (Chicago), **58**, 533.
 Howells, G. H., and Friedmann, I. (1950). *Journal of Clinical Pathology*, **3**, 220.
 Johnsson, S. (1948). *Acta path. microbiol. scand.*, **25**, 573.
 Klinger, H. (1931). *Frankfurt. Z. Path.*, **42**, 455.
 Kobernick, S. D. (1952). *Amer. J. med. Sci.*, **224**, 329.
 McCallum, A. G. (1954). *J. Laryng.*, **68**, 560.
 Pagel, W. (1951). *Journal of Clinical Pathology*, **4**, 137.
 Rich, A. R., and Gregory, J. E. (1943). *Bull. Johns Hopk. Hosp.*, **72**, 65.
 Robbins, L. L., and Sniffen, R. C. (1949). *Radiology*, **53**, 187.
 Seegal, B. C., and Loeb, E. N. (1946). *J. exp. Med.*, **84**, 211.
 Smith, C. C., and Zeek, P. M. (1947). *Amer. J. Path.*, **23**, 147.
 — and McGuire, J. (1944). *Ibid.*, **20**, 721.
 Söderholm, B. (1950). *Acta allerg. (Kbh.)*, **5**, 329.
 Stratton, H. M. S., Price, T. M. L., and Skelton, M. O. (1953). *Brit. med. J.*, **1**, 127.
 Waddell, W. R., Sniffen, R. C., and Sweet, R. H. (1949). *J. thorac. Surg.*, **18**, 707.
 Wegener, F. (1937). *Verh. dtsch. path. Ges.*, 1936, **29**, 202.
 — (1939). *Beitr. path. Anat.*, **102**, 36.
 Weinberg, T. (1946). *Amer. J. clin. Path.*, **16**, 784.