

Review article

Granulomatous inflammation — a review

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SUMMARY The granulomatous inflammatory response is a special type of chronic inflammation characterised by often focal collections of macrophages, epithelioid cells and multinucleated giant cells. In this review the characteristics of these cells of the mononuclear phagocyte series are considered, with particular reference to the properties of epithelioid cells and the formation of multinucleated giant cells. The initiation and development of granulomatous inflammation is discussed, stressing the importance of persistence of the inciting agent and the complex role of the immune system, not only in the perpetuation of the granulomatous response but also in the development of necrosis and fibrosis.

The granulomatous inflammatory response is ubiquitous in pathology, being a manifestation of many infective, toxic, allergic, autoimmune and neoplastic diseases and also conditions of unknown aetiology. Schistosomiasis, tuberculosis and leprosy, all infective granulomatous diseases, together affect more than 200 million people worldwide, and granulomatous reactions to other irritants are a regular occurrence in everyday clinical histopathology. A knowledge of the basic pathophysiology of this distinctive tissue reaction is therefore of fundamental importance in the understanding of many disease processes.

Granulomatous inflammation is best defined as a special variety of chronic inflammation in which cells of the mononuclear phagocyte system are predominant and take the form of macrophages, epithelioid cells and multinucleated giant cells. In most instances these cells are aggregated into well demarcated focal lesions called granulomas, although a looser, more diffuse arrangement may be found. In addition there is usually an admixture of other cells, especially lymphocytes, plasma cells and fibroblasts.

Before considering the pathogenesis of granulomatous inflammation it is essential to review our knowledge of the three fundamental cells involved, namely the macrophage, the epithelioid cell and the multinucleated giant cell.

Macrophages and the mononuclear phagocyte system

The name "mononuclear phagocyte system" was proposed in 1969 to describe the group of highly phagocytic mononuclear cells and their precursors which are widely distributed in the body, related by morphology and function, and which originate from the bone marrow.¹ Macrophages, monocytes, promonocytes and their precursor monoblasts are included, as are Kupffer cells and microglia. Labelling studies with tritiated thymidine have shown that granuloma cells, including both epithelioid cells and multinucleated giant cells, are also of the same lineage²⁻⁵ and it is claimed that monocytes in tissue culture may develop into epithelioid cells and giant cells.⁶

The origin of tissue macrophages (histiocytes) from bone marrow precursors via circulating monocytes is now well established,⁷ the maturation process being accompanied by progressive morphological and functional changes which continue even when macrophages enter the tissues.⁸ The production of monocytes is under positive and negative feedback control, with peripheral macrophages and lymphocytes secreting factors that are both stimulatory and inhibitory to stem cell proliferation in the marrow.⁹ Recruitment and localisation of monocytes into inflammatory lesions is aided by two groups of substances. The emigration of monocytes from the circulation is promoted by chemotactic agents including microbial products, complement

components, fibrin degradation products and lymphokines while the immobilisation of macrophages within a lesion is aided by other lymphokines including migration inhibition and macrophage adhesion factors.^{10,11} Although immigration from the circulation seems to be by far the most important source of macrophages in the inflammatory reaction, local macrophage mitosis does occur.¹² However, perhaps due to chromosomal instability, this seems to be limited to very few divisions.¹³

Light microscopy of routine haematoxylin and eosin stained sections does not allow macrophages to be distinguished from other mononuclear cells in an inflammatory infiltrate unless they contain recognisable ingested material. Macrophages may be round, oval or spindle shaped in outline with a cytoplasm which varies from eosinophilic and finely granular to clear and vesicular. The nucleus has a smooth or sometimes indented membrane with marginated heterochromatin and usually a single nucleolus. On ultrastructural examination the cell membrane is irregular, being thrown into folds and processes. Cytoplasmic organelles vary greatly according to the functional activity of the cell⁸ and include endoplasmic reticulum (rough and smooth), mitochondria, Golgi complexes, microtubules, microfilaments and membrane bound vesicles, the latter including primary and secondary lysosomes and residual bodies. However, in the absence of obviously phagocytosed material there is no ultrastructural feature that is absolutely diagnostic for the macrophage.

Enzyme histochemistry is more valuable in the tissue identification of cells of the mononuclear phagocyte series, but suffers from the disadvantage of requiring specially prepared material. Macrophages typically contain non-specific esterases diffusely in the cytoplasm, and the presence of membrane bound lysosomal enzymes, especially acid phosphatase and lysozyme is also useful in their recognition. Furthermore, variations in the cytoplasmic distribution of peroxidase correspond to different stages in macrophage differentiation.¹⁴ 5-nucleotidase, leucine aminopeptidase and alkaline phosphodiesterase I are cell membrane-associated macrophage enzymes which have also been used as macrophage markers.¹⁵ Intracellular localisation of macrophage products, notably alpha-1-antitrypsin,¹⁶ also has a role in cell identification. However, it is the development of monoclonal antibodies to specific cell types that holds the most promise for the identification of mononuclear phagocyte cells.^{17,18} If the various stages of functional differentiation of these cells are to be recognised morphologically then immunohistology with specific monoclonal

antibodies, similar to those presently available for lymphocyte subsets¹⁹ is the most hopeful approach.

The ability to ingest a wide variety of substances into membrane bound vacuoles (endocytosis) is a distinctive but not unique property of mononuclear phagocytes. Two mechanisms are involved, pinocytosis and phagocytosis. Macrophages take up fluids and soluble proteins, immune complexes, hormones, lectins and other macromolecules by pinocytosis^{20,21} whereas larger particles are engulfed by phagocytosis. The process is initiated by interaction between a particle and a surface receptor which then triggers intracytoplasmic contractile proteins, including actin and myosin, to create membrane movement and pseudopodial ingestion.^{20,22-24} Macrophage surface receptors are of many types and specificity. Particles opsonised by immunoglobulin G and E interact with Fc receptors^{25,26} while those attached to the third component of complement bind to C3b receptors.²⁷ Both Fc and C3b receptors may also react with immune complexes while non-immunological receptors exist for lectins,²⁸ alternative pathway complement activators²⁹ and other particles.

Particulate ingestion is followed by phagosome-lysosome fusion allowing intracellular degradation and microbial killing. Digestion of particulate material and dead organisms is accomplished by lysosomal enzymes¹³ but killing of micro-organisms depends on other methods, in particular the production of superoxides, hydrogen peroxide and hydroxyl radicals³⁰ and other microbicidal substances. The process is aided by the presence of antibody, IgG for bacteria, IgE for metazoa.³¹

Intracellular killing of micro-organisms is greatly enhanced by the phenomenon of macrophage activation,³² a change which is accompanied by morphological⁸ and many other functional alterations including the secretion of a range of different substances, enhanced phagocytic capacity, and an ability to recognise and kill tumour cells.¹¹ Activation can be accomplished by immunoglobulins, immune complexes, activated complement components, lymphokines, and by non-immunological agents such as bacterial endotoxin.³³

Extracellular secretion by activated macrophages is now recognised as a most important function^{34,35} and some idea of the myriad of secretory products can be obtained from the Table. It can be seen that among the factors produced are those with essentially opposing effects, for example collagenase and fibrogenic substances, suggesting that there are very subtle controls over secretion which at present are almost a complete mystery. Nevertheless it is known that activation is not an "all or none" phenomenon, and that the function of activated macrophages can

*Secretory products of macrophages***Enzymes**

Neutral proteases—for example, collagenase, elastase, plasminogen activator, angiotensin converting enzyme, enzymes denaturing proteoglycans and myelin.
 Acid hydrolases—for example, phosphatases, sulphatases, proteases, ribonucleases.

Lysozyme**Esterases****Enzyme inhibitors**

Alpha-1-antitrypsin

Plasmin inhibitors

Complement components

C1, C2, C3, C4, C5

Properdin, Factors B, D

Oxygen metabolites

Superoxides, hydrogen peroxide, hydroxyl radical

Endogenous pyrogens**Bioactive lipids**

Prostaglandins, thromboxanes, leukotrienes

Platelet activators

Binding proteins

Transferrin, B₁₂ binding protein, fibronectin

Cyclic AMP**Factors stimulating proliferation of:**

Lymphocytes (T and B)

Myeloid precursors (colony stimulating factors)

Erythroid precursors

Fibroblasts

Small blood vessels

Factors inhibiting proliferation of:

Lymphocytes

Tumour cells

Viruses (interferon)

be varied according to the nature of the activating stimulus.³⁶ Furthermore there is increasing evidence that macrophages do not form a homogeneous group of cells, but that they are markedly heterogeneous, different populations having different characteristics and functions.^{37,38} The tumoricidal effect of activated macrophages is only poorly understood. It is likely that macrophage-tumour cell contact is necessary in some instances^{31,35,39} while macrophage secretions, especially peroxides, are important in others.⁴⁰

Macrophages have complex interactions with lymphoid cells at different phases of the immune response.⁴¹⁻⁴³ Induction of immunity probably requires the initial presentation of an antigen to T lymphocytes which can then initiate cell-mediated immunity or generate “helper” functions for antibody-producing B lymphocytes. Macrophages are responsible for this presentation, but only after they have endocytosed the antigen and “processed” it. Macrophage-T cell interaction is restricted to cells bearing surface HLA-DR (or Ia) molecules and hence is under the control of immune response genes. Cell-to-cell contact is usually necessary at the onset, but growth and differentiation factors which cause T cell proliferation and differentiation and which are secreted by macrophages (“monokines”) are also involved. Mention has already been made of the role of macrophages as effectors of the immune response. Lymphokines, antibodies and immune complexes cause macrophage chemotaxis and activation, allowing ingestion and final elimination of the antigen, a process that is enhanced by opsonisation with antibody and complement. It is clear, therefore, that macrophages have properties which make them highly suited to their central role in granulomatous inflammation which is the defence of the host from exogenous or endogenous irritants.

Epithelioid cells

Epithelioid cells are mononuclear cells with finely granular eosinophilic cytoplasm, vesicular nuclei, and indistinct cell boundaries which are usually found aggregated into clusters within certain granulomas. Their mononuclear phagocyte origin is not in doubt,^{2-5,44} but there remains controversy over the mechanisms by which epithelioid cells are formed, and in particular the role of cell-mediated immunity. Epithelioid cells have been considered to be a hallmark of delayed hypersensitivity granulomas,⁴⁵ a fact well illustrated in the pathology of leprosy, where epithelioid cells only occur with the appearance of cell-mediated immunity to the causative organism.⁴⁶ However there are now reports of epithelioid granuloma formation in congenitally athymic “nude” animals^{47,48} suggesting that T cell function is not essential. Furthermore, although lymphokines induce dramatic changes in macrophages *in vitro*, the changes are not quite those of epithelioid transformation.^{49,50}

Ultrastructural examination of epithelioid cells⁵¹⁻⁵⁵ reveals closely applied and often interdigitating cell membranes which, in the experience of most workers, lack any junctional specialisation. Nevertheless some authors⁵⁶ have illustrated desmosome and hemidesmosome-like structures. The nuclei are regular and ovoid with margined heterochromatin, and the complex cytoplasm contains numerous mitochondria and an active Golgi apparatus. Some epithelioid cells contain rough surfaced endoplasmic reticulum resembling that of plasma cells or fibroblasts⁵²⁻⁵⁴ (type A or plasmacytoid epithelioid cells) while others have numerous cytoplasmic single membrane-bound vesicles containing electron-lucent or weakly osmiophilic material (type B or vesicular epithelioid cells). There is now good evidence that these two

cytoplasmic appearances represent the two ends of a morphological spectrum, intermediate forms having rough endoplasmic reticulum and vesicles in varying proportions.⁵³⁻⁵⁷ The proportions of the different cell types vary in different granulomas according to the aetiology,⁵³ but generally speaking plasmacytoid epithelioid cells are predominant in the early phase of granulomatous inflammation while the vesicular cells become numerous at a later stage, suggesting that plasmacytoid cells mature with time into vesicular cells, presumably with a progressive modification of function.⁵⁷

One of the consistent features of the epithelioid cell is the virtual absence of recognisable endocytosed material, either on light or electron microscopy, suggesting that the cell is not actively phagocytic. Nevertheless, a common finding is the intracellular Schaumann body, a complex of crystalline calcium salts and conchoidal bodies probably derived from autophagocytic residual lysosomal bodies.⁵⁸⁻⁵⁹ Functional studies on epithelioid cells have, until recently, only been possible on "facsimile" epithelioid cells, that is, cells produced artificially from macrophages by experimental manipulation.⁶⁰⁻⁶² Although having many of the morphological features, these facsimiles are not identical to epithelioid cells and their authenticity has been questioned.⁶³ However, viable epithelioid cells have recently been isolated from granulomas produced *in vivo*, allowing functional studies to be made.⁶⁴ Both facsimile and isolated "true" epithelioid cells are, as would be expected from their morphology, poorly phagocytic, and there is a blanket inhibition of endocytosis by both immunological and non-immunological receptors. Moreover, there is evidence that the expression of surface immune receptors (Fc and C3b) is reduced in epithelioid cells compared with macrophages, although there is some dispute over the detailed changes.⁶⁴⁻⁶⁶ It appears therefore that the epithelioid cell is not specialised to interact with extracellular particulate matter. Nevertheless recent studies in sarcoidosis indicate that epithelioid cells express surface HLA-DR (Ia) antigens⁶⁷ and consequently have the potential to interact immunologically with activated T lymphocytes in their vicinity.⁴²

Electron microscopy suggests that epithelioid cells have important biosynthetic properties. Enzyme histochemistry has shown the presence of acid phosphatases, β -galactosidase, lysozyme and non-specific esterase, while ultrastructural cytochemistry has revealed a mucoglycoprotein, not yet further characterised, within the vesicles of type B cells.⁶⁸ Some of these vesicles have been seen to fuse with the plasmalemma, presumably discharging their

contents into the extracellular space.⁵⁶ Considerable attention has been given to the secretion of angiotensin-converting enzyme by epithelioid cells, not only to the immunocytochemical localisation of the enzyme⁶⁹ but also to the use of serum angiotensin-converting enzyme activities in the clinical diagnosis of granulomatous diseases.⁷⁰ The role of angiotensin-converting enzyme in the granuloma is highly speculative but there is preliminary evidence to suggest that it inhibits the migration of macrophages and leucocytes.⁷¹ Furthermore its secretion by the epithelioid cell can be controlled by T lymphocytes.⁷² It is highly likely that epithelioid cells secrete many more substances, similar to and in keeping with, macrophages. However, details are not known at present.

As secretory cells, epithelioid cells share features in common with activated macrophages. Indeed, some workers consider the two terms to be synonymous, but this is surely an oversimplification. Most reports of activated macrophages describe increasing phagocytic capacity and expression of surface receptors, but epithelioid cells exhibit the opposite. Nevertheless it is possible that epithelioid transformation could be a specialised type of macrophage activation, perhaps by a distinct subpopulation of mononuclear phagocytes. The lack of any evidence of phagocytosis, recent or past, in epithelioid cells raises the possibility that these cells do not arise from phagocytic tissue macrophages⁴⁴ but develop directly from monocytes entering the lesion which are already destined to mature into epithelioid cells.^{63,64} The factors which initiate this process, however, remain a complete mystery.

The epithelioid cell is, therefore, best regarded as a very specialised type of mononuclear phagocyte, immobilised in the granuloma, whose function has been diverted away from phagocytosis to extracellular secretion.

Multinucleated giant cells

Multinucleated giant cells are a regular feature of granulomatous inflammation. There is now overwhelming evidence that they are macrophage polykaryons, produced by the fusion of macrophages, rather than by nuclear mitosis without cytoplasmic division.^{2,5,6,73,74} Traditionally inflammatory giant cells have been divided into the Langhans (tuberculous) type, in which up to 20 nuclei are distributed centrally or around the periphery of the cell, and the foreign-body type with often very numerous haphazardly arranged nuclei throughout the cytoplasm. However it is now clear that there is no fundamental difference between these two cell types, and there is no diagnostic

significance. Both types are commonly found to coexist in the same lesion, transitional forms have been described, and studies in tissue culture have shown that foreign body type giant cells “mature” into Langhans type cells, probably by movements of the intracellular cytoskeleton.^{5 13}

Mechanisms whereby macrophages fuse to produce giant cells have been widely studied. Fusion induced by viruses occurs in many cell types throughout the body, including macrophages,²¹ but is of limited significance in the granulomatous environment. Three main ideas have been suggested for inflammatory giant cell formation. First, it was proposed that fusion may be an immune-mediated phenomenon, giant cell production being stimulated by lymphokines.^{75 76} However, the evidence for this has been questioned,⁷³ macrophage fusion occurs *in vitro* in the absence of immune factors and giant cell formation occurs equally well in normal and athymic mice.⁷⁷ The second suggestion is that fusion occurs between “young” macrophages and “older” cells, the latter having existed for some time in the granulomatous environment acquiring chromosomal abnormalities and changes in the macrophage surface.⁵ The recognition of the altered and abnormal cell surface by young macrophages is the stimulus for cell fusion, and the process is regarded as a means whereby altered, effete and senescent cells can be removed. However, other studies have failed to produce giant cells by altering macrophage surfaces *in vitro*, or by coculturing macrophages of different genetic makeup.⁷⁸ The third proposal is that giant cells form as a result of simultaneous attempted phagocytosis,⁷³ during which two macrophages attempt to ingest the same particle. The endosome margins of one macrophage, instead of fusing together around the particle, fuse with the endosome margins of a second macrophage, resulting in fusion of the two cells. There is considerable circumstantial and experimental evidence to support this theory, including the relatively poor phagocytic capacity of giant cells⁷⁹ which can be explained at least partly by the interiorisation of surface membrane receptors during the original fusion process.⁸⁰ Although ingested foreign material can frequently be found within giant cells this is not always the case, and this is one of the possible anomalies of the simultaneous endocytosis theory. The proponents of the idea suggest that this can be explained by the fact that the granulomatous environment itself produces endocytogenic material from endogenous macromolecules, independently of the initial irritant.^{56 73 80}

Ultrastructural examination of multinucleated giant cells from granulomas produced by foreign material provides some evidence to support the

simultaneous endocytosis theory, in that the cells often contain ingested material or the products of its degradation, residual bodies with myelin figures.⁸¹ Prominent microfilaments are also present, especially in the periphery of the cytoplasm and these sometimes fuse together to produce the star-shaped asteroid bodies seen on light microscopy.⁸² More centrally there is an active Golgi apparatus and numerous mitochondria, lysosomal bodies and some membrane-bound vesicles. The giant cells of epithelioid cell granulomas are different, however. They rarely contain microfilaments or any recognisable ingested material. Instead they have an ultrastructure similar to that of epithelioid cells^{51 53 83} and some authors have described giant cells with the cytoplasmic features of both type A and type B epithelioid cells.⁵⁵ The way by which these cells could be formed is a mystery—the poor phagocytic capacity of epithelioid cells⁶⁴ would make their fusion by simultaneous endocytosis very unlikely unless the cytoplasm did not develop its epithelioid appearance until after cell fusion had occurred. There is now some electron microscopical evidence to suggest that fusion of epithelioid-like cells may follow the development of specialised desmosome-like intercellular junctions between adjacent cells.^{56 84}

The functions of multinucleated giant cells are only speculative. While their formation in foreign body granulomas may be only an accident of simultaneous endocytosis the process does have the advantage of successfully interiorising particles which would otherwise be too large for endocytosis by a single cell. Moreover there is no reason to suspect that intracellular digestion by giant cells is inferior to that by mononuclear macrophages. The ultrastructure of giant cells, especially those in epithelioid granulomas, suggests that they too could have important biosynthetic and secretory functions similar to mononuclear epithelioid cells.

Pathogenesis of granulomas

Granuloma formation is usually regarded as a means of defending the host from persistent irritants of either exogenous or endogenous origin. The causative agent is walled off and sequestered by cells of macrophage lineage allowing it to be contained, if not destroyed altogether. Experimental models of granulomatous inflammation have provided much of our present knowledge of the pathogenesis of granulomas.⁸⁵ Such studies have shown that both the nature of the irritant and host factors are important in governing the type of reaction that is produced. All injected substances cause an initial influx of mononuclear cells by the phenomenon of

chemotaxis. However, what happens next depends on the resistance of the irritant to degradation by macrophages. If it is a soluble substance that is easily digested then the macrophages move away once degradation is complete.¹³ However if it is poorly soluble, persistent and undegradable a granuloma is formed. The exception to this rule is that soluble materials can produce granulomas if they combine with endogenous macromolecules to form insoluble, undegradable compounds, a mechanism considered important in granuloma formation by certain soluble metal salts such as beryllium.⁸⁵ Experimental granulomas can also be produced by soluble irritants complexed either with insoluble inert materials⁸⁶ or with antibodies to form insoluble immune complexes.⁸⁷

Why poorly soluble, undegradable material causes immobilisation of macrophages and their organisation into a granuloma is unknown, although in some instances, where there is involvement of the immune system, lymphocyte-produced MIFs undoubtedly have a role. The macrophages in the lesions are often activated, making them particularly suited to a degradative function, but in spite of this, granuloma-producing agents often persist within cells for a long time. Their resistance to degradation is quite unexplained in many cases, although sometimes there is evidence that the macrophage's armamentarium of lysosomal enzymes is inappropriate to denature the chemical structure of the irritant, such as the cell walls of certain bacteria.⁸⁸ Other irritants, such as some parasites, escape destruction by acquiring a coat of host antigens⁸⁹ or becoming sequestered within the macrophage cytoplasm, apparently safe from attack.⁹⁰ The latter sequestration is in part due to the failure of phagosomes to fuse with lysosomes, a feature of some mycobacterial infections.⁹¹

Observations that granulomas are of differing morphology and caused by a wide variety of irritants have led to numerous attempts to classify granulomatous inflammation, either to help in the diagnosis of granulomatous disease or to further the understanding of the granulomatous process. However, none has been very successful. On a pure morphological level, histopathologists have divided granulomas into "foreign body" and "epithelioid" types, depending primarily on the absence or presence of epithelioid cells. An inducing agent is often recognisable in foreign body granulomas while it is difficult or impossible to find in epithelioid lesions. Moreover the two lesions are said to contain either foreign body or Langhans type giant cells respectively. This classification is very unsatisfactory, however; the two types of giant cell are not distinct, as has been alluded to earlier, and in practice it is often

difficult to achieve agreement among different observers as to the presence or absence of epithelioid cells.

A second classification of granulomas is based on cell kinetics.^{13,92} Within any lesion there is a continuous turnover of macrophages, dying cells being replaced either by new recruits from the circulation or by local mitosis. However, there are striking variations in the turnover rate between different granulomas. "Low turnover" granulomas are those with little macrophage death, immigration or mitosis. They are typically produced by agents which, although poorly degradable, are relatively inert and non-toxic to the cells—for example, carrageenan, barium sulphate. The macrophages present are long lived and contain large amounts of the irritant.⁹³ Epithelioid cells are not found, and lymphoid cells are unusual, suggesting that immune mechanisms are of minor importance in their pathogenesis. These low turnover lesions correspond to foreign body granulomas. "High turnover" granulomas, on the other hand, are produced by irritants which are toxic to macrophages such as mycobacteria or silica. They are characterised by a high rate of recruitment and local division of macrophages to compensate for their relatively short life span and high death rate within the lesion.⁹⁴ The causative agent is present in only a small proportion of the cells and the lesions thus have some features in common with epithelioid granulomas. However, not all high turnover granulomas have epithelioid cells. Although a classification of granulomas by their cell kinetics is of considerable theoretical importance it is unfortunate that in clinical practice most lesions are of the high turnover type and contain macrophages in varying degrees of activation. There is some evidence of functional heterogeneity among the infiltrating macrophage population, not only between granulomas of different aetiology,⁶³ but also in different zones of the same granuloma.³⁸

The characteristics of a granuloma are not only dependent upon the properties of the causative irritant. Host factors are also of great importance, a fact well illustrated in the pathology of leprosy, where different individuals produce very different granulomatous reactions to the causative bacillus, with a spectrum of appearances between two extremes. At one end of the spectrum is lepromatous leprosy in which there are ill-defined collections of foamy macrophages containing large numbers of bacilli—features associated with foreign body granulomas. At the other end is tuberculoid leprosy with organised epithelioid granulomas in which bacilli are difficult to find. It is now clear that the most important factor governing the type of reaction

is the degree of immunological resistance to the organism developed by the host. Patients with high immunity develop tuberculoid reactions while those with low immunity have the lepromatous form.⁴⁶ Similar findings have been found in experimental zirconium granulomas in guinea pigs.^{95,96} A third classification of granulomas, therefore, is based on the immunological dependence of the lesions,⁹⁷ with granulomas being divided into immunological and non-immunological types. In view of the close interactions of lymphocytes and macrophages described earlier it is not surprising that both cell-mediated and antibody-mediated immunity have their role in the accumulation and differentiation of mononuclear phagocytes that is granuloma formation. Nowhere has this been studied more than in experimental schistosomiasis, where it is interesting that different species of the parasite apparently produce immunological granulomas by different means. The reaction to *Schistosoma mansoni* is largely a cell-mediated, T lymphocyte dependent reaction,^{85,98} whose progression is controlled by the balance of T cell subsets (helper and suppressor cells) and possibly by the antibody response to the parasite.^{99–101} *Schistosoma japonicum*, on the other hand, produces immunological granulomas by a method that appears to be independent of cell-mediated immunity, but whose initiation and control requires the presence of antibody.^{102,103} Cell-mediated immunity is also involved in the granulomatous reaction of tuberculosis and berylliosis,⁸⁵ while antibodies, especially when combined with antigen in the form of immune complexes, not only produce granulomas in the experimental model,⁸⁷ but are also probably implicated in the granulomatous reaction of extrinsic allergic alveolitis,¹⁰⁴ primary biliary cirrhosis,¹⁰⁵ and even in mycobacterial infections.¹⁰⁶ Recent studies using monoclonal antibodies to identify lymphocyte subtypes have highlighted the importance of cell mediated immunity in the genesis of epithelioid granulomas. In the granulomas of sarcoidosis⁶⁷ and tuberculoid leprosy,¹⁰⁷ the great majority of the lymphocytes present are T cells. Furthermore, helper T cells greatly outnumber suppressor/cytotoxic subsets, the ratio of helper to suppressor cells in sarcoidosis increasing with the clinical activity of the disease. Helper T cells in sarcoidosis are distributed uniformly throughout the granuloma⁶⁷ while in tuberculoid leprosy they are concentrated in a cuff around the central epithelioid cell zone.¹⁰⁷ The number of T lymphocytes in the non-epithelioid granulomas of lepromatous leprosy, on the other hand are small, the cells present being predominantly of the suppressor/cytotoxic subset.

In considering immune mechanisms in granuloma

formation it is also essential to take account of changes in the circulation. These have been studied recently in sarcoidosis where the high density of helper T cells at the site of granuloma formation is accompanied by a reduction in the proportion of helper cells in the circulation and an increase in the proportion of suppressor T cells.¹⁰⁸ Moreover there is evidence that the serum of many patients with sarcoidosis contains T cell suppressant factors, some of which are probably immune complexes.¹⁰⁹

The idea that immune mechanisms can initiate granulomatous inflammation has not gained universal acceptance. Epstein,^{63,110} while stressing the role of immune mechanisms in *amplifying* the granulomatous response, has cast doubt on the sole importance of immunity in the *initiation* of the reaction and has suggested the existence of a specific type of hypersensitivity leading to epithelioid granuloma formation which he terms granulomatous hypersensitivity. He states that the nature of this reaction is a mystery but suggests that it might be a specific function of the mononuclear phagocyte system. Other workers¹¹¹ have extended this idea by postulating that a specialised subgroup of mononuclear phagocyte cells can act as memory cells, being primed on first exposure to a granuloma-producing agent. Subsequent exposure is then followed by proliferation of these memory cells to produce epithelioid cells and giant cells. There is no good evidence to support this hypothesis, but in fact the concept of granulomatous hypersensitivity is very difficult to prove or disprove. However some support for its existence comes from the production of epithelioid granulomas in immune deficient animals and from the development of zirconium granulomas in man in the absence of demonstrable cell mediated immunity to this metal.¹¹² If granulomatous hypersensitivity occurs at all as an entity, its effects are greatly amplified by the conventional immune response.

Complications of granulomatous inflammation: necrosis and fibrosis

Granulomatous inflammation, like any inflammatory reaction, frequently results in tissue damage during the active phase and fibrosis during the healing process. It is not surprising, in view of the nature of some macrophage secretions (Table), that tissue necrosis is a frequent complication of some granulomas, especially towards the centre of lesions containing highly activated cells which are continually dying and releasing their toxic contents. Such necrosis may take the form of caseation and cavitation, as occurs classically in tuberculosis, or it may appear as a microabscess containing polymorphs. In

addition to autodigestion by macrophage enzymes, tissue necrosis may also be produced by the direct toxic action of a causative agent, especially in the case of infectious micro-organisms. There is also evidence that the process is augmented by the immune response, both by its cellular and humoral arms. Cavitation in tuberculous granulomas has been associated with strong delayed hypersensitivity to the tubercle bacillus.¹¹³ However recent studies with experimental mycobacterial infections in rats have shown that necrosis in granulomas is under much more subtle immunological influence.¹¹⁴ It has been suggested that the main stimulus to necrosis in this model is the formation of immune complexes between antibodies and excess antigen (mycobacteria) in the centre of the lesion. This situation develops when cell-mediated immunity, initially strong, begins to decline for unknown reasons, allowing the mycobacteria to proliferate, out of macrophage control. If cell-mediated immunity then improves again the number of bacilli diminishes and immune complexes will form in antibody excess causing epithelioid granuloma formation instead of necrosis.⁸⁷ Support for this theory has been obtained from experimental studies with mycobacteria coated with antibodies in differing proportions.¹⁰⁶ It may have important clinical relevance in the understanding of infective granulomatous diseases, particularly the "reactivation" of tuberculosis and the timing of BCG vaccination.¹¹⁴

Fibrosis is a common and important complication of granulomatous inflammation because it is often responsible for permanent tissue damage even after the causative agent has been eliminated. Thus hepatic and pulmonary fibrosis are important long-term complications of schistosomiasis and sarcoidosis respectively. However, until very recently, knowledge of how granulomas lead to fibrosis was very scanty. It is clear that permanent fibrosis is not inevitable—most pathologists have seen lung biopsies with florid granulomatous inflammation being followed by apparent complete resolution and some granulomas, such as those of lepromatous leprosy or carrageenan^{115 116} are associated with little fibrosis. Generally speaking, non-immunological, low turnover, foreign body type granulomas appear to stimulate the least amount of collagen production. Nevertheless, the granulomatous process can also be damped down by immunological mediators, particularly by suppressor T cells.⁹⁹⁻¹⁰¹

Experimental studies have illuminated many mechanisms whereby fibrosis within granulomas can be controlled by the secretions of endogenous cells. The degree of collagenisation is governed by the balance between collagen synthesis by activated

fibroblasts and collagen degradation, chiefly by neutral proteases. Macrophages have the potential to affect both sides of this balance. Their presence is highly desirable for successful wound healing¹¹⁷ and, when cultured under appropriate conditions they secrete substances which increase hydroxyproline production¹¹⁸ or stimulate proliferation in fibroblasts.¹¹⁹ Interleukin-1, a macrophage product which is closely related to endogenous pyrogen, is probably one such substance,¹²⁰ while fibronectin, a glycoprotein secreted by macrophages with important roles in cellular adhesion, is a chemotactic agent for fibroblasts.¹²¹ On the other hand, macrophage supernatants which inhibit collagen synthesis have been described,¹²² and collagenase secretion by activated macrophages is well established.³⁴ Lymphocytes also have the potential for affecting fibrosis by their secretion of lymphokines which can induce fibroblast migration, proliferation and collagen synthesis.^{123 124} Studies on whole granulomas have also found them to contain substances that induce fibroblast proliferation.^{125 126} They probably originate from macrophages or lymphoid cells. Moreover, a study of explanted granulomas of different types has found that collagen synthesis is most active in immunological granulomas and lowest in foreign body lesions,¹²⁷ corresponding with findings *in vivo* described above. This suggests that cell-mediated immunity is of considerable importance in controlling fibrogenesis but whether this is achieved by a direct action of lymphoid cell products, or by an indirect effect of macrophage activation is uncertain. Epithelioid cells have been suggested as having a role in fibrosis,⁴⁵ and while to date there is no direct evidence for this, the degree of fibrosis in mycobacterial granulomas does correlate with their content of epithelioid cells.¹²⁸

Conclusion

Granulomatous inflammation represents a distinctive tissue reaction to an irritant in which the central cell is the mononuclear phagocyte cell, but which can be modified by other phenomena, especially hypersensitivity. The last 25 years have seen tremendous improvement in our knowledge of cell biology, immunology and macrophage function but in spite of this many mysteries continue to surround the pathogenesis of organised granulomas and the function and significance of their two distinctive cell types, epithelioid cells and giant cells. Continued research into granulomatous inflammation is essential, not only for its theoretical value, but also for its important potential clinical implications. Better knowledge of the granulomatous process will both

help to elucidate the causes of so-called idiopathic granulomatous diseases, such as sarcoidosis, Crohn's disease or primary biliary cirrhosis, and also improve opportunities for therapeutic intervention. If the destructive properties of granulomas can be reduced while the beneficial functions are amplified, there will be immense scope for preventing the long-term complications, especially fibrosis, of many infective granulomatous diseases and for improving host defence, especially against neoplasia. Manipulations of this latter kind have already met with limited success with BCG immunotherapy for malignant diseases, and there is now early experimental evidence that cyclosporin A, a modulator of T lymphocyte function, could have a therapeutic role in the suppression of epithelioid granuloma formation.¹²⁹

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