A clinicopathological classification of granulomatous disorders

D Geraint James

Abstract

Granulomatous disorders comprise a large family sharing the histological denominator of granuloma formation. Granulomas may be confluent or discrete; the degree of necrosis is variable; the cell components differ; and the presence or absence of Schaumann bodies and of calcification are distinctive. A clinicopathological synthesis provides the most secure foundation.

Granuloma formation

A granuloma is a focal, compact collection of inflammatory cells, mononuclear cells predominating, usually as a result of the persistence of a non-degradable product and of active cell mediated hypersensitivity. There is a complex interplay between invading organism or prolonged antigenaemia, macrophage activity, a Th1 cell response, B cell overactivity, a vast array of biological mediators. Differential diagnosis and management demand a skilful interpretation of clinical findings and pathological evidence. They are classified into infections, vasculitis, immunological aberration, leucocyte oxidase deficiency, hypersensitivity, chemicals, and neoplasia.

Keywords: granuloma; Th1 cell; cytokines; neoplasia

Figure 1 The cytokine network (IFN-γ = interferon gamma; IL = interleukin; MHC = major histocompatibility complex; TNF = tumour necrosis factor).
when Th2 seems to override Th1 influences. There is anergy and apoptosis, which may be reversed by CD28 agonists.

Immunohistochemistry has revealed a continuing role for fibronectin, collagen, integrin receptors, and transforming growth factors in that slippery road from a healthy granulomatous response to irreversible and unchangeable fibrosis.

Classification
This large family of granulomatous disorders comprise infections, vasculitis, immunological upsets, leucocyte oxidase defect, hypersensitivity, chemicals, and neoplasia (table 1). Differential diagnosis and management demand a skilful interpretation of clinical findings and histology (table 2).

(1) INFECTIONS
Infections are the commonest causes of disseminated granulomatous disease (table 2). Some experts regard an infection as the root cause of all such disorders but that it still remains undetected in some; over the past decade advances in molecular diagnostic techniques have allowed identification of causal organisms that were previously unrecognised. For instance, cat scratch disease is due to Bartonella henselae and Whipple's disease due to Tropheryma whippeli. Infective causes are suspected but not yet established for sarcoidosis, Crohn's disease, primary biliary cirrhosis, Kikuchi's disease, Langerhans' granulomatosis, and chronic granulomatous disease of childhood. The aetiology, course, prognosis, and treatment of granulomatous infections have been reviewed elsewhere. The present review draws attention to some which currently give rise to diagnostic confusion.

Mycobacterial infections
This large family of mycobacteria is responsible for granulomatous disorders of many different systems (table 3). The invading organism is met by a vigorous cell mediated hypersensitivity reaction involving macrophages, Th1 lymphocytes, and their cytokines. The polymerase chain reaction (PCR) has uncovered mycobacterial DNA in sarcoid tissue and mycobacterial RNA has been extracted from sarcoid spleen by liquid phase DNA/RNA hybridisation giving rise to false speculations concerning the aetiology of sarcoidosis.

Swimming pool (fish tank) mycobacterial granuloma
Mycobacterium marinum causes swimming pool (fish tank) granuloma. Although the primary...
Beware also of sea urchin granuloma of the feet in bathers and fishermen stepping on sea urchins.

**Buruli ulcer**

Mycobacterium ulcerans is the cause of chronic, relatively painless, cutaneous Buruli ulcers. The disease is most prevalent in Africa and Australia. The organism causes extensive undermined ulcers on the extensor surface of the extremities. The centres of the ulcers are necrotic, and the edges are undermined; the organisms are usually found at the periphery, where granulation tissue is most extensive. While it is relatively easy to diagnose Buruli skin ulcers on the basis of clinical features and histological findings, microbiological identification of the causal mycobacteria may sometimes be quite difficult, requiring long periods of culture. Newer techniques such as gas phase chromatography are becoming useful for identification of the acid-fast bacilli in low count subcultures.

**Granulomatous mycoses**

Granulomatous fungal infections mimic sarcoidosis worldwide. It is important to recognise or exclude fungi localised to one system or disseminated; in particular, granulomatous fungal meningitis needs to be distinguished from sarcoidosis by all available techniques (table 4).

**Whipple’s disease**

George Hoyt Whipple’s single case report described a 37 year old medical missionary who presented with fever, polyarthritis, and steatorrhoea. It is a chronic multisystem granulomatous disorder affecting middle aged white males, presenting with fever, polyarthri-

## Table 4 Granulomatous mycoses

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Clinical diagnosis</th>
<th>Immunopathology</th>
<th>Method of diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocardia sp</td>
<td>Actinomycosis</td>
<td>Pneumonia, granuloma</td>
<td>Microscopy, culture</td>
<td>Penicillin, minocycline</td>
</tr>
<tr>
<td>Actinomyces sp</td>
<td></td>
<td>Fibrosis</td>
<td>Culture</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td>Coccidioides immitis</td>
<td>Coccidioidomycosis</td>
<td>Bronchopneumonia</td>
<td>Culture, CFT</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic granuloma</td>
<td>ELISA</td>
<td>Fluconazole</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>Cryptococcosis</td>
<td>Pneumonia, infarction, abscess, granuloma fibrosis</td>
<td>Tube precipitin, microscopy, culture</td>
<td>Fluconazole, Amphotericin B, flucytosine</td>
</tr>
<tr>
<td>Candida sp</td>
<td>Candidiasis</td>
<td>Abscess, granuloma</td>
<td>Microscopy, culture</td>
<td>Nystatin, Amphotericin B</td>
</tr>
<tr>
<td>Moniliasis</td>
<td></td>
<td>Necrosis, granuloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporothrix schenckii</td>
<td></td>
<td>Granuloma, histiocytosis</td>
<td>Microscopy, culture, culture</td>
<td>Amphotericin B, Amphotericin B</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td></td>
<td>Pneumonia, histiocytosis</td>
<td>Microscopy, culture, culture</td>
<td>Amphotericin B, Amphotericin B</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>Aspergillosis</td>
<td>Necrotising granuloma</td>
<td>Microscopy, culture, culture</td>
<td>Amphotericin B, Itraconazole</td>
</tr>
<tr>
<td>Paracoccidioides brasilense</td>
<td></td>
<td>Bronchopneumonia, pulmonary cavities, exudate → granuloma</td>
<td>CFT, culture, Sputum</td>
<td>Amphotericin B, flucytosine</td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>Blastomycosis</td>
<td>Microabscess, pneumonia</td>
<td>CFT, culture</td>
<td>Sulphadiazine, Amphotericin Itraconazole</td>
</tr>
<tr>
<td>Phialophora sp</td>
<td>Chromoblastomycosis</td>
<td>Cutaneous granuloma</td>
<td>Culture</td>
<td>Flucytosine</td>
</tr>
<tr>
<td>Madurella sp</td>
<td>Mycetoma</td>
<td>Subcutaneous granuloma</td>
<td>Plants in pus</td>
<td>Ketoconazole, Itraconazole, Dapsone</td>
</tr>
</tbody>
</table>

CFT = complement fixation test. ELISA = enzyme linked immunosorbent assay.
megaly and generalised lymphadenopathy. Biopsy of lymph node, liver, or small intestine reveals foci of PAS staining foamy macrophages in all sites. The PAS positive material within these histiocytes corresponds with lysosomes containing bacilliform bodies. Electron microscopy reveals rod shaped bacilli, termed Whipple bacilli or T whipelli or Whipple associated bacterial organism. The nucleic acids extracted from an endoscopic biopsy specimen of the proximal small bowel of a patient with Whipple’s disease has been subjected to nucleotide sequencing and amplification by the PCR. The resulting PCR product from the bacterial 16S ribosomal DNA was then the subject of a computer database search for the rRNA sequences most similar to it. It showed that Whipple bacilli were most likely to belong to the family of Gram positive bacteria of the rhodococcus, streptomyces and arthrobacter genera, and more weakly related to mycobacteria. PCR primers for T whipelli now provide a helpful diagnostic technique.

Cat scratch disease
Cat scratch disease or fever is also known as benign lymphoreticular or regional granulomatous lymphadenitis. It only occurs in humans, especially those who are scratched or bitten by kittens and then develop regional lymphadenitis proximal to the site of injury. Primary involvement is that of the lymph nodes, which first show lymphoid hyperplasia. Later, scattered granulomas with central areas of necrosis coalesce to form abscesses. B henselae is the responsible Gram negative bacillus. It is identified by PCR hybridisation and indirect fluorescent antibody assay.

The histopathological features of cat scratch disease are not diagnostic and may be mistaken for tularemia, lymphogranuloma venereum, syphilis, brucellosis, atypical mycobacterial infections, fungal infections, and toxoplasmosis. Warthin-Starkey silver staining is used to detect B henselae, which may be present in the early phase of the disease. A skin test antigen has been made from lymph node pus. It is inoculated intradermally, and the degree of induration and erythema is measured at 48 hours.

The cat scratch antigen skin test is positive in about 90% of patients who are clinically suspected of having the disease. This test will become redundant when techniques for amplifying specific nucleotide sequences with PCR come into general use. There is no well recognized response to antibiotics, and recovery usually occurs without treatment.

Kikuchi’s disease
This disorder was described in 1972 by a Japanese pathologist and is characterised by lymphadenitis showing focal reticulum cell hyperplasia, nuclear debris, and phagocytosis. Clinically there is localised tender cervical lymphadenopathy with an upper respiratory prodrome. Most cases occur in women under the age of 30 years. Kikuchi’s disease occurs world wide and has been often confused with toxoplasmosis, cat scratch disease, tuberculo-

sis, infectious mononucleosis, and non-Hodgkin’s lymphoma. A viral aetiology is strongly suspected on the basis of clinical features, although serological and ultrastructural studies have not yet identified an infectious agent.

(2) Vasculitis
The family of vasculitic granulomatoses comprise Wegener’s granulomatosis, necrotising sarcoidal granulomatosis, Churg-Strauss syndrome, lymphomatoid granulomatosis, polyarteritis nodosa, broncho-centric granulomatosis, giant cell arteritis, and systemic lupus erythematosus. They may occasionally be confused with sarcoidosis and hypersensitivity pneumonitis (extrinsic allergic alveolitis), so a careful clinicopathological synthesis is essential (table 5).

Granulomatous vasculitis is a small group of systemic disorders of unknown cause and obscure pathogenesis. It has long been considered that both humoral and cellular immune mechanisms are involved, and a cascade of cytokines may influence their course. The future management may indeed depend upon manipulation of this cytokine network.

(3) ImmunoLogical aberrations
The causal agent or antigenic insult remains unrecognised in many granulomatous disorders so they are clumsily lumped together as a group in which an immunological upset plays a major part. They are waiting for the cause to be found or the immune process better understood. Within this category are sarcoidosis, primary biliary cirrhosis, hepatic granulomatous disease, Langerhans’ granulomatosis, orofacial granulomatosis, Peyronie’s disease, Blau’s syndrome, hypogammaglobulinaemia, and immune complex disease.

Sarcoidosis
Sarcoidosis is a multisystem disorder of unknown cause(s) most commonly affecting young adults, and frequently presenting with hilar lymphadenopathy, pulmonary infiltration, ocular and skin lesions. The diagnosis is established most securely when well recognised clinicoradiographic findings are supported by histological evidence of widespread epithelioid granulomas in more than one system. Multisystem sarcoidosis must be differentiated from local sarcoid tissue reactions. There is imbalance of CDT4:CD8 subsets, an influx of Th1 helper cells to sites of activity, hyperactivity of B cells, and circulation of immune complexes. Markers of activity include raised levels of serum angiotensin converting enzyme and monocyte chemoattractant protein-1; abnormal calcium metabolism; a positive Kveim-Siltzbach skin test; intrathoracic uptake of radioactive gallium; and abnormal fluorescein angiography.

The course and prognosis correlate with the mode of onset. An acute onset usually heralds a self limited course of spontaneous resolution whereas an insidious onset may be followed by relentless progressive fibrosis. Corticosteroids relieve symptoms, suppress the formation of
granulomas (including Kveim-Siltzbach granulomas), and normalise both levels of serum angiotensin converting enzyme and the uptake of gallium. A synthesis of clinical features, radiology, histology, biochemical changes, and immunological abnormalities helps to distinguish it from non-specific local sarcoid tissue reactions.

Tumour necrosis factor alpha (TNF-α) is a proinflammatory cytokine widely recognised and implicated in inflammatory disorders including sarcoidosis. It is inhibited by tumour necrosis factor receptor (TNF-R) which is recognised in two forms p55 (CD120a) and p75 (CD120b) receptors. This TNF-TNF-R balance in favour of inhibition may represent a homoeostatic mechanism which protects the patient from excessive TNF production in sarcoidosis. TNF-R p55 is increased in stage I more than stage II/III sarcoidosis, suggesting that homoeostasis is responsible for a more benign outcome at this early stage of sarcoidosis.11

**Crohn’s disease**

The commonest cause of granulomatous inflammation in the gastrointestinal tract is Crohn’s disease. This reaction seems to centre on the blood vessels of the intestinal wall causing multifocal gastrointestinal infarction. There may be associated lung changes, including pulmonary vasculitis, granulomatous interstitial lymphocytic infiltration, alveolitis, and interstitial fibrosis. Alveolar macrophages may show an increased spontaneous superoxide anion production. An increase in CD4 cells is found in bronchoalveolar fluid and even in sputum. Serum antibody increases include antireticulin antibody, antisaccharomyces cerevisiae antibody (ASCA), and p-antineutrophil cytoplasmic antibody (ANCA). There is concordance between ASCA and p-ANCA. ASCA occurs in up to 60% of patients, particularly with familial Crohn’s disease; and ASCA is evident in 20% of first degree relatives.5 12 13

**Primary biliary cirrhosis (PBC)**

PBC is a chronic non-suppurative destructive cholangitis14 in which epithelioid granulomas are in close association with bile ducts. It predominates in women of the reproductive years and it is distinguished by the presence of serum mitochondrial antibodies. It is classified as an autoimmune disorder and overlaps with other autoimmune disorders including Sjogren’s syndrome, rheumatoid arthritis, the calcinosis Raynaud oesophagus scleroderma telangiectasia (CREST) syndrome, scleroderma, and systemic lupus erythematosus. Cholangiocytic apoptosis is responsible for bile duct destruction due to aberrant expression of the major autoantigen, the E2 subunit of the pyruvate dehydrogenase complex. There is some evidence that PBC with high titres of antinuclear antibodies progress slower and result in a better prognosis than those with low titre or negative antinuclear antibodies. PBC histology may be granulomatous or alternatively eosinophilic. Could this be due to the predominant influence of either the Th1
cytokine cascade producing granulomas or the Th2 cascade causing an eosinophilic response?

The aetiology of PBC remains unknown. There are similarities between Escherichia coli and mitochondrial components; cross-reactivity between bile duct mitochondria and bacteria is a possibility. An increased incidence of Gram negative urinary tract infections is recognised in PBC. It has been likened to the chronic graft-versus-host reaction with similar structural change in the bile ducts, lacrimal and pancreatic ducts, which have a high concentration of HLA class II antigens on the epithelial surface.

A differential diagnosis of some hepatic granulomatous disorders is appended (table 6).

**Langerhans’ cell granulomatosis**

The term Langerhans’ cell granulomatosis refers to proliferative disorders of histiocytes, previously referred to as histiocytosis X. It encompasses a group of disorders of unknown aetiology characterised by granulomatous infiltration of the lungs, bone, skin, lymph nodes, and brain. The clinical conditions have been known by several names, based on the type of presentation, sites of involvement, rate of progression, and degree of associated immune dysfunction. They include eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian disease. They are different expressions of the same basic disorder, in which the proliferation of Langerhans’ cells results from disturbances in immunoregulation.

Langerhans’ histiocytes are bone marrow derived monocyte macrophage cells; they include Langerhans’ epidermal cells, Kupffer’s cells in the liver, osteoclasts, and alveolar macrophages. They are human leucocyte antigen DR positive functioning macrophages that present antigen to T cells and play a part in cell mediated immunity. Unlike histiocytes, Langerhans’ cells can be stained immunohistochemically for S-100 protein and OKT-6.

Lung biopsy reveals a mixed cellular exudate, foam cells, eosinophils, and characteristic X bodies (Birbeck granules) in macrophages. Langerhans’ or X bodies are an ultrastructural feature in 90% of patients. They are identical to the granules in Langerhans’ epidermal cells and consist of intracytoplasmic rod, plate, or cup-like pentalaminar structures. The presence of these tennis racket shaped ultrastructural Birbeck granules is diagnostic of the disorder. They have surface adenosine triphosphate activity identifiable by gold fluorescence. These diagnostic cells are readily found by bronchoalveolar lavage, and this technique may make lung biopsy unnecessary. It may also be a likely means of detecting a possible causal agent in the future.

**Orofacial granulomatosis (Melkersson-Rosenthal syndrome)**

This is a rare granulomatous disorder of the mouth and adjacent tissues, involving the oral mucosa, gums, lips, tongue, pharynx, eyelids, and skin of the face.

Melkersson described an association between facial oedema and facial paralysis. Rosenthal added the features of lingua plicata or scrotal tongue. Other clinical features include granulomatous cheilitis, oedema of the gums and scalp, salivary gland dysfunction, granulomatous blepharitis, trigeminal neuralgia, Raynaud’s phenomenon, and even chronic hypertrophic granulomatous vulvitis. Patients with this disorder do not have chest radiography changes, nor uveitis; and the Kveim-Siltzbach skin test is negative. This rare disorder may be immunologically mediated for the T cell receptor B (TCRβ) repertoire is restricted. This is evident in oral mucosal lymphocytes, and it is associated with a local T cell clonal expansion. These features suggest a delayed type reaction in response to an unknown antigen. Local cytokine release may be responsible for the granulomatous reaction.

**Blau’s syndrome**

Edward Blau is a Wisconsin paediatrician who described a multisystem granulomatous disease of the skin, eyes and joints, resembling childhood sarcoidosis. The histology may be indistinguishable so paediatricians should be aware of significant differences between the two disorders. The most frequent manifestation is swelling of the wrists, fingers, ankles, and elbows in the first decade of life. Because of the granulomatous histology of synovial tissue, it may be misdiagnosed as tuberculosis of bone. There may be progression of flexion contractions of joints (campodactyly) due to post-inflammatory fibrotic scarring at insertion points of finger and toe flexor tendons. There is a granulomatous red papular eruption of the skin with a butterfly distribution on the face. It coincides with exacerbations of the granulomatous iritis.

Blau’s syndrome is a multisystem disorder in which there is no lung involvement; this may be an important difference from other granulomatous disorders.

The granulomas of Blau’s syndrome are indistinguishable from those of sarcoidosis by light microscopy or by immunocytochemistry.
However asteroid, Schaumann and conchoid bodies, organisms, calcification and crystalline inclusions, necrosis and fibrin deposition are absent.

**Granulomatous hypogammaglobulinaemia**

On rare occasions, one wonders whether the patient has hypogammaglobulinaemia or sarcoidosis or both. Confusion arises since both conditions may present with multisystem granulomas, hypersplenism, and poor cellular immunity. The hypogammaglobulinaemia may be selective IgA deficiency or a more widespread deficiency of IgA, IgG, and IgM. There is bedside clinical evidence of loss of both B and T lymphocyte function, which is also evident in vitro lymphoproliferative assays.

(4) **LEUCOCYTE OXIDASE DEFECTS**

Killing of bacteria depends on a burst of respiratory enzyme activity which leads to the production of hydrogen peroxide and superoxide in phagocytes. Neutrophils in chronic granulomatous disease of childhood (CGD) are unable to kill some ingested bacteria because they are deficient in enzymes needed for this superoxide respiratory burst. These defective enzymes may be nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, myeloperoxidase, cytochrome B, pyruvate kinase, glucose-6-phosphate dehydrogenase, or the lack of lysosome or lactoferrin, each perhaps contributing a different clinical profile. The classical X linked disorder occurs in boys aged about 5 years, presenting with hepatosplenomegaly, generalised lymphadenopathy, weeping granulomatous skin lesions, and diffuse miliary lung infiltration. The history is of multisystem sarcoid granulomas. There is more than one X linked form and also more than one autosomal recessive variety, for there is more than one mechanism for initiating oxidative metabolism. Patients with CGD suffer from infections with catalase-producing staphylococci and enterobacteria. Organisms that lack catalase supply the neutrophil with the hydrogen peroxide for their own destruction. Thus catalase negative organisms, such as pneumococci or streptococci, present no problem to these patients. Neutrophil leucocytes of normal patients with bacterial infections reduce nitroblue tetrazolium from colourless to form blue-black formazan granules in the cytoplasm. This fails to occur in the leucocytes of CGD children or in the mothers of the X linked variety. The X linked variety is due to mutations in the gene for the gp 120-phox subunit of the phagocyte cytochrome b, an essential component of superoxide-generating NADPH oxidase. Most patients have undetectable levels of cytochrome b and no phagocyte NADPH oxidase activity. This gives rise to life threatening bacterial and fungal infections in infancy. Some patients have a milder course because they retain some cytochrome NADPH oxidase activity.

IFN-γ has proved helpful in enhancing host defences and thereby reducing the incidence of life threatening infections, particularly those infections characterised by persistence in macrophages (toxoplasmosis, leishmaniasis, and mycobacteriosis). Thrasher et al used an adenovirus vector expressing p47-phox to transduce patients' defective monocytes. Nitroblue tetrazolium staining indicated that NADPH oxidase activity was restored to those cells. This technique offers a rapid means for molecular diagnosis and points to a therapeutic future of gene transduction.

**Chronic granulomatous disease in adults (CGD)**

Chronic granulomatous disease is being recognised more commonly in adults. Although it is still rare it should be excluded in adults with unexplained granulomas or infections. Antibiotic prophylaxis and the use of IFN-γ has allowed children, mostly with reduced gp91-phox (X91-CGD), to present for the first time in young adult life. The NBT is insufficient as a screening test for it may give values close to normal in adults. It should be complemented by chemoluminescence or cytochrome b reduction. This is important because of the benefits of earlier diagnosis and treatment, infection prophylaxis, and genetic counselling.

(5) **HYPERSENSITIVITY PNEUMONITIS (EXTRINSIC ALLERGIC ALVEOLITIS)**

Repeated inhalation of various antigens may provoke a granulomatous inflammatory response in the bronchoalveolar spaces and interstitium giving rise to a family of pulmonary disorders termed hypersensitivity pneumonitis or extrinsic allergic alveolitis. The best recognised members of the family are farmers' lung, pigeon breeders' lung, and humidifier fever. The clinical picture may be acute and explosive, subacute and insidious, or chronic and protracted; cough and dyspnoea on exertion, fatigue, and weight loss are common. The end stage is characterised by irreversible restrictive lung function and cardiac failure. Pathogenesis involves a complex interplay of circulating immune complexes, immediate hypersensitivity, and exuberant cell mediated immunity. The diagnosis is established by a history of occupational exposure; suggestive clinical and radiological changes; and demonstration of precipitating serum antibodies. Mid to late inspiratory crackles are notable features. An increase in CD8+ T cells in bronchoalveolar fluid is also noteworthy.

(6) **CHEMICALS**

There are four granuloma forming chemicals: beryllium, zirconium, silica, and talc. Beryllium disease mainly affects the lungs following inhalation of soluble, finely particulate beryllium and its salts. Direct implantation may also give rise to skin ulcers and nodules. Pulmonary disease may be acute or chronic (CBD); the former is a chemical pneumonitis after massive exposure to fumes whereas CBD is a chronic granulomatous disorder. It is due to occupational exposure in a variety of industrial processes, alloy workers, ceramic workers, and in space and atomic engineers. The respiratory symptoms are in keeping with diffuse and nodular fibrosis of the lungs, with pleural thickening and late cystic changes. The granu-
loma contains a variety of inclusion bodies, Schaumann and asteroid; they are end products of the actively secreting epithelioid cells. Diagnostic criteria include history of exposure; consistent clinicroadiological features, granulomatous histology, and tissue analysis for beryllium.

Zirconium
This chemical was recognised as a cause of deodorant axillary granulomas in sensitised individuals. A 1:10 000 solution of zirconium chloride or nitrate inoculated intradermally produced a palpable nodule, which, on biopsy, revealed sarcoid tissue. This was specific for zirconium hypersensitivity. This skin test is very similar to the Kveim-Siltzbach skin test for sarcoidosis. Zirconium is no longer in deodorants so these axillary granulomas are no longer seen. However it is of some academic interest that there are four granulomatous disorders in which skin tests behave in this peculiar fashion, mimicking the Kveim-Siltzbach test. The other two were the beryllium patch test and the Mitsuda skin test in lepromatous leprosy.

Silicosis
Inhalation of pure silica may be followed by dense nodular and rarely diffuse pulmonary fibrosis. The silica granuloma is readily identified by the presence of crystalline birefringent crystals in macrophages with foreign body rather than Langhans-type giant cells.

Pulmonary talc granulomatosis
This is due to the inhalation of talc in the form of talcum powder or by prolonged repeated intravenous administration of pentazocine (75% talc).

(7) NEOPLASIA
There is often a granulomatous component in malignant disease. Sarcoïd granulomas may be found in various tumours and in their draining lymph nodes, particularly those draining carcinoma of the lung, stomach, and uterus. They may also be found in tumours that have been treated by radiotherapy or chemotherapy, since treatment may produce a granulomagenic substance which spreads to draining lymph nodes.

There is diagnostic confusion between sarcoïdosis and Hodgkin’s disease, in which multisystem granulomas are also observed. The difficulty usually arises in the interpretation of small specimens of aspiration liver biopsies, or the occasional patient in whom the spleen is replaced by sarcoïd tissue obliterating tumour tissue. Intrathoracic Hodgkin’s disease most frequently affects the upper mediastinum rather than hilar lymph nodes, and it is predominantly unilateral. The hilar nodes tend to fuse with the right cardiac border whereas in sarcoïdosis they stand away from the cardiac border. Both disorders show depression of cell mediated immunity. In Hodgkin’s disease, the Kveim-Siltzbach test is negative and serum angiotensin converting enzyme levels are raised in only about 10% of patients, compared with 60% in sarcoïdosis.

(8) MISCELLANEOUS
Granulomatous angiitis
Granulomatous angiitis is a multifocal chronic inflammatory disorder in which magnetic resonance imaging may show multiple discrete granulomas. The initial diagnosis may suggest an infection, such as tuberculosis or toxoplasmosis, or alternatively intravascular lymphomatosis.

Granuloma annulare
These skin lesions may be single, multiple, or disseminated with flat centre and a well delineated edge. The histology is of a necrobiotic area with palisading granulomas in giant cells. A similar histological reaction may be seen in rheumatoid disease and with a ruptured sebaceous cyst.

Actinic granuloma
This disfiguring condition is a granulomatous reaction to excessive sun exposure. There is debate whether it is a distinct clinicopathological entity or a variant of granuloma annulare or multiforme and necrobiotics lipoidica. Treatment with isoretinoin has prevented development of new granulomas and produced almost complete resolution of established lesions.

Granulomatous rosacea
Rosacea has been described as the curse of the Celts.1 It is commoner in women, aged 30 to 50 years. There is a background diathesis of flushing and blushing, upon which develops erythema, papules, pustules, telangiectasia, furuncles on the face, neck and v-shaped area of the chest. Granulomatous or lupoid rosacea nodules may also involve the lower eyelids. Histology reveals perifollicular and perivascular granulomas; it needs to be distinguished from micronodular sarcoidosis, particularly since both conditions may be associated with iritis and conjunctivitis. Minidose isoretinoin, 2.5 mg to 5 mg daily, oral tetracycline, or metronidazole may be helpful for lupoid rosacea.

Other
Do not be surprised if the histological report of a removed sebaceous cyst indicates a granuloma. The same granulomatous reaction occurs in chalazion, dermoid, panniculitis, sebaceous cyst. The same granulomatous reaction may be seen in an infection, such as tuberculosis or toxoplasmosis. Granulomatous angiitis is a multifocal chronic inflammatory disorder in which magnetic resonance imaging may show multiple discrete granulomas. The initial diagnosis may suggest an infection, such as tuberculosis or toxoplasmosis, or alternatively intravascular lymphomatosis.

References
8 Spapen HDM, Segers O, DeWit N. Electron microscopic
detection of Whipple’s bacillus in sarcoidlike periodic acid-
9 Kikuchi M. Lymphadenitis showing focal reticulum cell
hyperplasia with nuclear debris and phagocytosis. Nippon
10 Kuo TT. Kikuchi’s disease (histiocytic necrotising lymphad-
enitis). A clinicopathological study of 79 cases with an
analysis of histologic subtypes, immunohistology, and DNA
11 Armstrong L, Foley NM, Millar AB. Inter-relationship
between tumour necrosis factor-alpha (TNF-
á
) and soluble
12 Vermeire S, Peeters M, Joossens S, et al. The value of
anti-saccharomyces cerevisiae antibodies (ASCA) as clinical
marker in Crohn’s disease (CD). Gastroenterology 1999;116:
abstr 3647.
13 James DG, Jones Williams W. Sarcoidosis and other
14 Sherlock S, Dooley J. Diseases of the liver and biliary system.
15 Hance AJ, Candranel J, Soler P, et al. Pulmonary and extra-
pulmonary Langerhans’ cell granulomatosis (histiocytosis
16 Melkersson E. U fall au recidiverande facialispare. Hjälp
1928;90:737–41.
17 Rosenthal C. Facialislahmung und lingua plicata. Z Neurol
18 Wiesenfeld D, Ferguson MM, Mitchell DN, et al. Oro-facial
granulomatoses. A clinical and pathological analysis. Q J
19 Larsson E, Westmark P. Chronic hypertrophic vulvitis—a
condition with similarities to cheilitis granulomatosa.
(Melkersson-Rosenthal syndrome). Acta Derm Venereol
(Stockh) 1978;58:92–3.
20 Lim SH, Stephens P, Caso QK, et al. Molecular analysis of T
cell receptor variability in a patient with orofacial granulo-
21 Blau EB. Familial granulomatous arthritis, iritis and rash. J
22 Curnette JT. Chronic granulomatous disease: the solving of
a clinical riddle at the molecular level. Clin Immunol
primary chronic granulomatous disease monocytes. Lancet
24 Schapiro BL, Newburger PE, Klemperer MS, et al. Chronic
granulomatous disease presenting in a 69 year old man. N