The sarcoid granuloma is a battleground between antigen and the cellular and humoral defences of the body. Macrophages are stimulated by the antigenic attack and eventually coalesce into giant cells and epithelioid cell granulomas (Fig. 1). T helper cells are mobilised to this point of activity and co-operate with macrophages, which leads to B cell overactivity. The T cells provide various lymphokines and the B cells produce immunoglobulins and various antibodies. The enzymes secreted by the granuloma include angiotensin-converting enzyme, lysozyme, glucuronidase, collagenase and elastase. With ageing, the granulomas are infiltrated by fibroblasts, and early fibrosis is recognised by increasing deposition of reticulin, which is gradually replaced by collagen which in turn is transformed into structureless eosinophilic hyaline material.

Activated macrophages within various sarcoid granulomas are now being finger-printed by a combination of immunofluorescent and histochemical techniques, and by monoclonal antibodies directed against antigen-presenting macrophage subsets. This dynamic approach should lead to a better understanding of both the basic molecular biology and the aetiology of sarcoidosis.

Macrophages with the phenotype HLA-DR+, RFD2+, acid phosphatase (ACP)±, adenosine triphosphatase (ATPase)+, make up 66 per cent of the cell population of the sarcoid granuloma, the remainder being T cells. The suppressor-cytotoxic T8 cells are limited to the periphery of the granuloma, whereas the T4 cells are found throughout the granuloma (Fig. 1). The T4:T8 ratio is of the order 5:1 to 3:1. The same configuration is observed in the Kveim granuloma.

We are now able to recognise three different types of macrophages in the sarcoid granuloma (Table 1). The periphery contains a large number of antigen-presenting interdigitating (ID) cells similar to those found in the lymph node paracortex and at the cortico-medullary junction of the thymus. The centre of the granuloma consists of epithelioid and giant cells, which are derived from macrophages. The third type, tissue histiocytes, are

---

**Fig. 1.** The sarcoid granuloma. M = macrophage. Ep = epithelioid cell. G = giant cell. T4 = thymus-mediated helper cell. T8 = suppressor-cytotoxic.
Table 1. Frequency and distribution of cell types in sarcoid and Kveim granulomas, and in negative tuberculin skin biopsies in sarcoidosis. Percentages represent proportion of total lymphoid cells of total non-lymphoid cells in granuloma. UCHT = University College Hospital. TO 15 = B cell monoclonal antibody. RFD = Royal Free. ACP = acid phosphatase. ATPase = adenine triphosphatase.

| Cell Type            | Phenotype        | Sarcoid/Kveim granuloma | Negative tuberculin |
|----------------------|------------------|-------------------------|---------------------|
| T                    | UCHT1 + HLA-DR - | 40%                     | 40%                 |
|                      | TO 15 -          |                         |                     |
| OKT4:T8 ratio        | OKT4:OKT8        | 5:1                     | 3:2                 |
|                      | HLA-DR + RFD 2 + |                         |                     |
|                      | RFD 1 - ACP +    | 66%                     | 60%                 |
|                      | ATPase +         |                         |                     |
| Macrophages          | As for macrophages | 50%                 | 27%                 |
| Activated macrophages |                 |                         |                     |
| epithelioid and      |                 |                         |                     |
| giant cells          |                 |                         |                     |
| Interdigitating      |                 |                         |                     |
| cells                |                 |                         |                     |
|                      | HLA-DR + RFD 2 + |                         |                     |
|                      | ACP + ATPase +   |                         |                     |
| Tissue               |                 |                         |                     |
| histiocytes          |                 |                         |                     |
|                      | HLA-DR - RFD 2 + |                         |                     |
|                      | ACP - ATPase +   |                         |                     |
|                      | RFD 1 -          |                         |                     |

occasionally seen, more diffusely distributed in the granuloma and not even restricted to the granuloma itself. There is evidence of synergism between the interdigitating cells and T8 cells in the periphery of the granuloma and the epithelioid cells with T4 cells in its centre[1]. This pattern is also seen in skin biopsies of patients with tuberculous leprosy, but not in those with lepromatous leprosy. It is suggested that the architectural segregation of T lymphocyte sub-populations in the tuberculous leprosy granuloma is immunologically efficient in reducing the bacillary load, whereas the haphazard arrangement in lepromatous leprosy favours bacillary proliferation[2]. This configuration may be important in the pathogenesis of sarcoidosis and other granulomatous diseases.

Lymphokines and Monokines

Lymphokines are the humoral products of antigen-stimulated sensitised T cells.

The activated macrophage, bearing cell-surface HLA-DR+ gene products, when stimulated by antigen produces interleukin 1, which in turn activates OKT4 helper-inducer cells. These activated T4 cells produce interleukin 2 which then causes a tenfold clonal replication of these T4 helper cells. Interleukin 2 is a 15,000-20,000 dalton glycoprotein; it is the T cell growth factor which signals clonal proliferation in the lungs. It does not stimulate blood T lymphocytes[3]. The action of interleukin 1 on the T lymphocyte may call into play a prostaglandin-induced feedback mechanism that is inhibited by prostaglandin inhibitors. Interleukin 2 production is inhibited by cyclosporin A.

Several other soluble and secretory products play an important role in inhibiting macrophage migration away from the sarcoid battleground.

Classification of Granulomatous Disorders

The sarcoid granuloma is a non-specific response to many different antigens or irritants, some of which are recognised and others still unknown. The inciting agents are persistent or poorly degradable. The best-recognised causes are infections, chemicals, an enzyme defect, neoplasia and those antigens causing extrinsic allergic alveolitis (Table 2).

The naked non-specific sarcoid granuloma needs to be clothed with clinical features in order to make it recognisable. This classification represents the differential diagnosis of these granulomatous processes. An effort is made to delineate and classify them because they are the source of considerable histological confusion. Moreover, the recognition of a causal agent may lead to a more rational form of treatment. Finally, improved knowledge of the mechanisms in one granulomatous disorder may lead to a better understanding of the pathogenesis of other granulomatous disorders.

Infectious Granulomas

Infectious granulomas are caused by fungi, protozoa, metazoa, spirochaetes, mycobacteria and bacteria. They are differentiated by culture and special stains so that the causal organism or antigen becomes recognisable.

Worldwide, the most important are mycobacteria, which cause human tuberculosis, opportunistic infections and leprosy. There are points of similarity and differences between sarcoidosis and tuberculosis (Table 3) and between sarcoidosis and leprosy (Table 4).

Chemical Granulomas

Sarcoid granulomas may be produced by beryllium, zirconium, silica and starch.

Beryllium Disease. This is an occupational hazard with important points of differentiation from sarcoidosis (Table 5).

Zirconium. This chemical caused sarcoid granulomas in the axillae of women sensitised by deodorants containing zirconium.

Silicosis. Inhalation of silica leads to dense nodular lesions of the lung and, rarely, diffuse pulmonary fibrosis. Hilar adenopathy is not a feature and extrathoracic lesions are rare. Silica and silicate granulomas are readily identified.
by finding crystalline birefrigent crystals in macrophages with foreign body rather than Langhans' giant cells.

**Pulmonary Talc Granulomatosis.** Pulmonary talc granulomatosis is due to inhalation or intravenous administration of talc or intravenous pentazocaine, which is 75 per cent talc. Six patients developed lung granulomas following prolonged intravenous pentazocaine, mimicking sarcoidosis with raised serum angiotensin converting enzyme (SACE), positive gallium scans and increased lymphocyte counts in fluid from bronchoalveolar lavage. The diagnosis was established by finding talc crystals in miliary pulmonary granulomas and in bronchoalveolar fluid[4]. Crystal size distinguishes inhaled (3.57 μm) from injected (14.7 μm) crystals[5].

**Immunological Aberrations**

There are several well-recognised disorders in which sarcoid granulomas are produced in one or several organs because of some immunological upset (Table 2). Sarcoidosis, Crohn’s enteritis and primary biliary cirrhosis have histological similarities but many clinical differences (Tables 6 and 7).

**Chronic Granulomatous Disease of Childhood (CGDC).** 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 CGDC 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 lyso-
zyme or lactoferrin, each perhaps contributing a different clinical profile.

The classical X-linked disorder occurs in boys aged about five years, who present with hepatosplenomegaly, generalised lymphadenopathy, weeping granulomatous skin lesions and diffuse miliary lung infiltration. The histology is of multi-system sarcoid granulomas. There may be more than one X-linked form and also more than one autosomal recessive variety. The group is heterogeneous because there are now reports of defective oxidative metabolism with phagocytic stimuli such as bacteria but not with non-phagocytic metabolic stimuli such as sodium fluoride or concanavalin A. There is certainly more than one mechanism for initiating oxidative metabolism.

Patients with CGDC only suffer from 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 (NBT) to form blue-black formazan granules in the cytoplasm. This fails to occur in the leucocytes of CGDC children or in the mothers of boys with the X-linked disorder.

**Neoplasia**

Sarcoid granulomas related to tumours may cause diagnostic difficulty, particularly in Hodgkin’s disease. Intra-thoracic 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 sarcoidosis they stand away from the cardiac border. Both diseases show depression of cellular immunity, but Hodgkin’s disease is not associated with significantly raised serum immunoglobulins, the Kveim test is negative and SACE levels are seldom elevated. The histological distinction of granulomas in Hodgkin’s disease is considerably helped by the frequent admixture of eosinophils and the close proximity of the tumour. Diagnostic difficulty may arise in the interpretation of small aspiration liver biopsy specimens, or in the occasional patient whose spleen has been replaced by sarcoid tissue which has obliterated tumour tissue.

Isolated sarcoid granulomas may be noted in lymph nodes draining carcinoma of the lung, stomach and uterus. Two patients with testicular carcinoma treated by radiotherapy or cytotoxic therapy developed bilateral hilar lymphadenopathy containing sarcoid granulomas [6].
Extrinsic Allergic Alveolitis (EAA)

An increasing number of inhaled antigens, usually organic, are being recognised as a cause of antigen-antibody-induced lung disease in which identical sarcoid granulomas may be present (Table 8). The essential basis for distinction from sarcoidosis is a history of exposure, environmental and often occupational; prominent alveolitis; the presence of circulating antibodies to the causative antigens and a negative Kveim-Siltzbach skin test. The prototype of this family of pulmonary granulomatoses or hypersensitivity pneumonitis is farmers' lung. Antibodies indicate exposure but not necessarily the disease itself. The granulomas of EAA are very similar to sarcoidosis but Schaumann bodies are rare. In the chronic stage of EAA the granulomas somewhat surprisingly disappear without leaving the small round hyalini-ised scars which are the hallmark of sarcoidosis.

Sarcoidosis

Aetiology

The cause of sarcoidosis remains unknown despite an extensive search to uncover an infective agent, an immunological upset, an allergic mechanism, or a specific diathesis.

Is it an Infection? It was traditional to regard sarcoidosis as an odd form of tuberculosis, and the two diseases have certainly been confused with each other throughout this century. There are crucial differences (see Table 3). Attempts have been made to detect granulomagenic components of various mycobacteria in sarcoid tissue. The presence of mycolic acid esters aroused interest, but they are also found in normal tissue. Muramyl dipeptide and bacterial lipopolysaccharides are granulomagenic at injection sites but they do not produce multi-system granulomas.

Many claims have been made for infection due to fungi, viruses and bacteria as a cause of sarcoidosis; the occasional presence of these infective agents seems coincidental rather than causal.
Table 7. Features distinguishing sarcoidosis from primary biliary cirrhosis.

| Features                                | Sarcoidosis | Primary biliary cirrhosis |
|-----------------------------------------|-------------|----------------------------|
| Sex F:M                                 | Equal       | 8:1                        |
| Decade of onset                         | 3, 4        | 5                          |
| Diagnosis over 40 years                 | Rare        | Frequent                   |
| Erythema nodosum                        | Yes         | No                         |
| Uveitis                                 | Yes         | No                         |
| Respiratory                             | Yes         | No                         |
| Pruritus                                | No          | Yes, eventually            |
| Jaundice                                | No          | Yes, late                 |
| Xanthomas                               | No          | Yes, late                |
| Clubbing                                | No          | Yes                        |
| Hepatomegaly                            | Infrequent  | Usually                    |
| Splenomegaly                            | Yes         | Yes                        |
| Skin pigmentation                       | No          | Yes                        |
| Steatorrhoea                            | No          | Yes with jaundice          |
| Bilateral hilar lymphadenopathy         | Yes         | No                         |
| Kveim-Siltzbach test                    | Positive in 80% | Always negative            |
| Depression of delayed-type hypersensitivity | Yes   | Yes                        |
| Circulating mitochondrial antibodies    | No          | Yes (in 99%)              |
| Calcium metabolism                      | Hypercalcaemia | Hypocalcaemia (steatorrhoea) |
| Raised alkaline phosphatase             | Yes, minority | Yes, in most              |
| Raised angiotensin-converting enzyme    | Yes, in 60% | Yes, in 16%               |
| Liver granulomas                        | Yes         | Yes                        |
| Corticosteroids                         | Helpful     | Contraindicated           |
| Vitamin D                               | Contraindicated | Helpful                 |
| Cholestyramine                          | Not necessary | Helpful                 |
| Prognosis                               | Very good   | Variable                   |

Table 8. Differences between sarcoidosis and extrinsic allergic alveolitis.

| Feature                                | Sarcoidosis | Extrinsic allergic alveolitis | Hypersensitivity pneumonitis |
|----------------------------------------|-------------|-------------------------------|-----------------------------|
| History                                | Very similar. Look for foreign body giant cell reaction | | |
| Birefringent bodies                    | No          | Yes                           |                             |
| Occupational history                   | No          | Yes                           | Sometimes                   |
| Multi-system                           | Always      | Absent                        |                             |
| Erythema nodosum                       | Common      | Absent                        |                             |
| Hilar adenopathy                       | Frequent    | Infrequent                    |                             |
| Wheezing                               | Rare        | Common                        |                             |
| Uveitis                                | Frequent    | Absent                        |                             |
| Depression of delayed type hypersensitivity | Yes   | Yes                           |                             |
| Raised or abnormal immunoglobulins    | Yes         | Yes                           |                             |
| Kveim-Siltzbach test                   | Positive    | Negative                      |                             |
| Serum angiotensin-converting enzyme    | Raised      | Normal                        |                             |
| Abnormal calcium metabolism            | Frequent    | Absent                        |                             |
| Response to steroids                   | Good        | Good                          | Good if removed from exposure to antigen |
| Prognosis                              | Good        |                               |                             |

Is it an Immunological Aberration? Sarcoidosis is a lymphoproliferative disorder with evidence of depression of delayed-type hypersensitivity, imbalance of OKT4:T8 subsets, hyperreactive B cells and frequent circulating immune complexes. Could this be a background factor which provides an infective agent or other antigenic insult with a salubrious soil?

Is it due to Hypersensitivity? Claims have been made for such diverse regional contributory factors as pine pollen, peanut dust, clay-eating and chewing pine pitch. Beryllium and zirconium are known to produce sarcoid granulomas in sensitised individuals.

Is there a Predisposition? Hormonal factors play some part, for erythema nodosum due to sarcoidosis commonly occurs in women of child-bearing age, during early pregnancy, and also in women taking the oral contraceptive pill.

Sarcoid arthritis and erythema nodosum are most likely to occur in women who are HLA-B8, A1, CW7, DR3. This predisposition is associated with a short course and good prognosis, whereas HLA-B13 is more likely to be associated with chronic disease (Table 9).

Epidemiology

Sarcoidosis has a worldwide distribution but is more frequently recognised in sophisticated communities. Whenever tuberculosis or leprosy is rampant, sarcoidosis
is in eclipse, but as they are brought under control so will sarcoidosis become more evident. It has a similar prevalence in the Western world and in Eastern Europe.

Sarcoidosis is ten times more frequent in the American black population than in the white. It is a very common disorder in the black population of the Caribbean, particularly when they migrate to London (from the British West Indies) or to Paris (from Martinique). Likewise it is common in Puerto Ricans living in New York. Whether it is due to genetic predisposition or environmental factors confronting susceptible individuals migrating from a rural to an urban community is unknown, and the breeding ground for sarcoidosis may be the native environment or the sophisticated new world or both.

Sarcoidosis is also becoming more evident in the black populations of Africa. In the next thirty years it is likely to become a common disorder of the African, either at home or, particularly, when he lives abroad.

It is also frequently seen in the white population of Europe. That it is well recognised in Japan is shown by the fact that the Japanese have a special commission on the look-out for it. It is extremely rare in the rest of Asia, possibly because it is obscured by the considerable presence of tuberculosis.

**Clinical Features**

We have analysed a series of 818 patients with clinical and histological evidence of sarcoidosis attending the Royal Northern Hospital, London. Five hundred (51 per cent) were female, nine-tenths were Caucasian and one-tenth from the Caribbean. Seven hundred (88 per cent) had radiographic evidence of intrathoracic sarcoidosis. Since sarcoidosis is a multi-system disorder, it was also evident in other systems, notably the skin (overall in 50 per cent of the series), eyes (27 per cent), reticulo-endothelial system (39 per cent) and upper respiratory tract (6 per cent).

We have compared this series from one London hospital with sarcoidosis seen in various centres throughout the world[7] (Table 10).

**Table 9. HLA types and their significance in sarcoidosis.**

| HLA Type     | Significance in sarcoidosis |
|--------------|----------------------------|
| B8/A1        | Sarcoïd arthritis          |
| B13          | Erythema nodosum           |
| CW7          | Sarcoidosis in English      |
| B8/CW7/DR3   | Good prognosis in sarcoidosis in English |
| DR3          | Short duration of disease  |
| B7           | Symptomatic tuberculin-negative Swedish |
| BW15         | Black Americans            |

**Table 10. Features of sarcoidosis in the Royal Northern Hospital series compared with a worldwide survey.**

| Sarcoidosis                          | Royal Northern Hospital No. = 818 | Worldwide No. = 3,676 |
|--------------------------------------|-----------------------------------|-----------------------|
|                                      | %                                | %                     |
| Female                               | 500                              | 2082                  | 57                    |
| Presentation <40 years               | 604                              | 2504                  | 68                    |
| Caucasian                            | 728                              |                       |                        |
| West Indian                          | 81                               |                       |                        |
| Intrathoracic                        | 700                              | 3224                  | 87                    |
| Ocular                               | 224                              |                       |                        |
| Erythema nodosum                     | 251                              | 640                   | 17                    |
| Lupus pernio                         | 35                               | 324                   | 9                     |
| Other skin lesions                   | 113                              | 134                   | 4                     |
| Ocular lesions                       | 224                              | 539                   | 15                    |
| Parotid enlargement                  | 52                               | 160                   | 4                     |
| Nervous system                       | 77                               | 109                   | 3                     |
| Bone                                 | 31                               |                       |                        |
| Lymph nodes and spleen               | 326                              | 1031                  | 28                    |
| Lymphadenopathy                      | 225                              |                       |                        |
| Splenomegaly                         | 101                              | 12                    |                        |
| Hepatomegaly                         | 82                               | 10                    |                        |
| Heart                                | 27                               | 3                     |                        |
| Lacrimal gland                       | 22                               | 3                     |                        |
| Kidney                               | 10                               | 1                     |                        |
| Upper respiratory tract              | 53                               | 6                     |                        |
| Systemic corticosteroid therapy      | 344                              | 1738                  | 47                    |
| Mortality due to sarcoidosis         | 25                               | 84                    | 2.2                   |
| Other causes                         | 23                               | 54                    | 1.4                   |
| Skin tests                           |                                   |                       |                        |
| Positive Kveim-Siltzbach             | 550/657                           | 1714/2189             | 78                    |
| Negative tuberculin test             | 488/702                           | 2093/3268             | 64                    |
| Hyperglobulinaemia                   | 161/326                           | 808/1832              | 44                    |
| Hypercalcaemia                       | 99/547                            | 200/1760              | 11                    |
Criteria of Activity

In the last 100 years there have been very few markers of activity of sarcoidosis. During the last ten years we have been inundated with too many, so it is becoming increasingly difficult to choose the most helpful. We have grouped them into the following categories (Table 11):

1. Clinical features which indicate activity, and bedside techniques which proclaim activity.
2. Biochemical markers.
3. Immunological markers.

Table 11. Markers of activity of sarcoidosis. LACE = lung angiotensin converting enzyme. KCO = carbon monoxide factor.

| Clinical | Biochemical | Immunological |
|----------|-------------|---------------|
| Erythema nodosum | Hypercalcaemia | B2 microglobulins |
| Uveitis | Hypercalciuria | TM helper cells in BAL |
| Maculopapular rash SACE | | Increased OKT4:OKT8 ratio (in BAL) |
| Dactylitis | LACE | |
| Polyarthralgia | Serum lysozyme | Decreased OKT4:OKT8 ratio (in blood) |
| Myopathy | Serum collagenase | Kappa and lammad light chains (by radio-immunoassay) |
| Neuropathy | Urinary hydroxyproline | Circulating immune complexes |
| Granulomatous scarring | Glucuronidase | |
| Splenomegaly | | |
| Lymphadenopathy | | |
| Salivary and lacrimal gland enlargement | | |
| Cardiac arrhythmia | | |
| Changing chest X-ray | | |
| Transfer factor | | |
| Exercise KCO | | |
| Fluorescein angiography | | |
| Tuberculin skin test | | |
| Kveim-Siltzbach skin test | | |
| Biopsies | | |
| Radioactive gallium scan | | |
| Thallium 201 myocardial scan | | |
| 24 hour ECG tape | | |
| Bronchoalveolar lavage | | |

In clinical practice, we would prefer to choose a measure that is specific and reliable, reproducible around the world, preferably cheap, and sufficiently easy to permit serial measurements to monitor progress. Each of the methods to be discussed has some defect which prevents it from being the perfect bedside tool.

Serum Angiotensin Converting Enzyme (SACE). SACE is elevated in about 60 per cent of patients with active sarcoidosis but it is also associated with a false positive rate of about 10 per cent; thus it is not a good diagnostic test. Its true value is in monitoring the progress of known sarcoidosis[8]. In this respect it is a more sensitive index of activity of epithelioid cell granulomas than the chest radiograph. Its introduction should halve the number of chest radiographs done, since many are unnecessary. It is an invaluable monitor in pregnancy.

The Japanese have just introduced a do-it-yourself bedside kit which should be as helpful as bedside blood glucose sticks for diabetes mellitus.

Radioactive Gallium-Scanning. The activated macrophages in granulomas avidly accumulate gallium and delineate the extent of granulomatous involvement in lungs and hilar lymph nodes. Gallium is taken up by liver, spleen and bone in the normal person, so it is not helpful in detecting granulomas in the abdominal viscera or the central nervous system. Lung uptake is crudely measured by comparison with the density of liver uptake. Radioactive gallium is also taken up by the protein of inflammatory exudates so it is not specific for sarcoidosis. Positive scans are found in asbestosis, silicosis, fibrosing alveolitis, cancer, bleomycin lung and lymphomas. Its value, like SACE, is as a monitor of progress. Its other defect is its cost, which would be prohibitive in many centres.

Bronchoalveolar Lavage (BAL). Bronchopulmonary lavage with about 100–300 ml of fluid provides specimens which can be measured for alveolar macrophages, lymphocytes, T and B cells, angiotensin-converting enzyme, lysozyme, protein, complement and immunoglobulins. The more active the pulmonary disorder, the richer the yield, and the more interesting the differential diagnosis. Findings differ in various interstitial lung disorders[9].

Lung Function Tests. Sarcoidosis is a restrictive lung disease with abnormal gas exchange; its pathophysiology is similar to that of other interstitial lung diseases, with decreased lung compliance, volumes and capacities as the main features. There is diminished carbon monoxide diffusing capacity and an increased alveolar-arterial oxygen gradient. The latter may cause hypoxaemia at rest and this worsens with exercise. These tests are helpful in defining the functional impairment and in monitoring progress. However, quite often they do not correlate with the symptoms or signs or with the stage of chest X-ray abnormality, or with the immunological upset.

Treatment

Steroids

Corticosteroid therapy constitutes a mainstay of treatment around the world. It is particularly indicated for ocular involvement; an abnormal chest radiograph associated with a significant elevation of SACE, a positive gallium scan, or abnormal bronchoalveolar fluid; troublesome breathlessness; persistent hypercalciuria; disfigur-
ing skin lesions; or involvement of myocardium, nervous system or lacrimal and salivary glands. It may be needed on a long-term basis for troublesome involvement of the upper respiratory tract, or for pain, swelling and deformity associated with bone cysts.

**Alternative Regimens**

Steroid therapy may be contra-indicated or need reinforcement. Alternative drugs include indomethacin and oxyphenbutazone for acute exudative disease, methotrexate and chloroquine for chronic fibrotic persistent sarcoidosis.

Cyclosporin A is a fungal metabolite with interesting immunosuppressant properties. It acts selectively on T helper cells, interfering with interleukin 2 production and thereby preventing organ rejection. It exerts profound effects on experimental epithelioid cell granulomas produced in rats by injections of various mycobacteria and then treated with oral cyclosporin in a dose of 20 mg/kg. It prevents the formation of epithelioid cell granulomas or the development of caseous necrosis[10]. Its value in sarcoidosis has not yet been assessed.

**Acknowledgements**

This work has been sustained by the E. B. Hutchinson Trust, Roger Gibbs Research Foundation and the Friends of the Royal Northern Hospital.

**References**

1. Mishra, B. B., Poulter, L. W., Janossy, G. and James, D. G. (1983) Clinical and Experimental Immunology, in press.
2. Modlin, R. L., Hofman, F. M., Meyer, P. R. et al. (1983) ibid., 51, 430.
3. Pinkerton, P., Bitterman, P. B. and Crystal, R. G. (1983) New England Journal of Medicine, 308, 793.
4. Farber, H. W., Fairman, R. P. and Glaiser, F. L. (1982) American Review of Respiratory Disease, 125, 258.
5. Abraham, J. L. and Brambilla, C. (1979) ibid., 119, 196.
6. Trump, D. L., Ettenger, D. S., Feldman, M. J. and Dragon, L. H. (1981) Archives of Internal Medicine, 141, 37.
7. James, D. G., Neville, E., Siltzbach, L. E. et al. (1976) Annals of the New York Academy of Sciences, 278, 321.
8. Studny, P., Bird, R., James, D. G. and Sherlock, S. (1978) Lancet, 2, 1331.
9. Crystal, R. G., Roberts, M. C., Hunninghake, G. W. et al. (1981) Annals of Internal Medicine, 94, 73.
10. Muller-Hermelink, H. K., Kaiserling, E. and Sonntag, H. G. (1982) Pathology Research Practice, 175, 80.

---

**Langerhans and Langhans**

The similarity in the names of Langerhans and Langhans has led to some confusion in the spelling of the eponymous labels attached to the discoveries of these two famous German morbid anatomists.

Paul Langerhans (1847-1888), born in Berlin, was a student of Rudolf Virchow and qualified MD Berlin in 1869. In 1871 he was appointed morbid anatomist at Freiburg where he remained until, for health reasons, he retired early to Madeira and died there. In 1869, he described in rabbits 'clumps of epithelial-like protoplasmic cells lying in the inter-alveolar tissue of the pancreas', for which he was not able to suggest a function. His findings attracted little attention at the time and it was not until 1893 that Gustave Edouard Laguesse of Lille labelled them the islets of Langerhans'. Langerhans found similar tissue in the gut wall of lower chordates and these came to be called the follicles of Langerhans'. In 1873, Langerhans also described the special cells in the stratum Malpighi of the epidermis, known since then as 'Langerhans' cells'.

Theodor Langhans (1839-1915), born in Usingen, qualified MD Würzburg in 1864; after being assistant to von Recklinghausen, he was in 1872 appointed morbid anatomist at Berne, where he remained for the rest of his life. In 1867 he described large multinucleated cells (so-called 'foreign-body type') in the tuberculous granuloma. These are usually referred to as 'Langhans' cells', although it is now recognised that they may be found in other granulomata, for instance sarcoid. In 1872 he was the first to describe the presence in Hodgkin's disease of giant cells, to which, thirty years later, attention was drawn in Vienna by Carl Sternberg (1898) and at Johns Hopkins by Dorothy Reed (1902). Finally, in 1870, Langhans described the layer of cells covering the chorionic villi beneath the syncytial layer—the cytotrophoblast—also known as the 'Langhans' layer', the individual cells being called 'Langhans' cells'.

**Alex Sakula**