Pulmonary eosinophilia occurs in a wide range of circumstances and many different classifications have been suggested[1-4]. Recent studies of eosinophil function have shed much light on the role of this leucocyte in disease and the pathogenesis of the pulmonary eosinophilias is therefore easier to understand.

Definitions
The classical definition of pulmonary eosinophilia is the combination of chest X-ray shadowing with a peripheral blood eosinophilia; both parts of this definition need defining. The normal blood eosinophil count increases during the night and falls in the early morning, is increased in the presence of atopy which affects up to a third of the population, and is influenced by a wide range of drugs and, in particular, is reduced by corticosteroids. A peripheral blood eosinophilia of > 400/mm³ is usually considered abnormal but a single lower count does not exclude an eosinophilic disorder. Most patients with pulmonary eosinophilia have repeatedly high counts ranging from 1,000–50,000/mm³ but there is considerable day-to-day variability.

There are two difficulties in using chest X-ray shadowing as a part of the definition. In the first place a considerable eosinophilic infiltrate can exist before it can be seen on a chest radiograph[5]. This is usually proved by lung biopsy but recently broncho-alveolar lavage has become popular and is the simplest way of confirming an eosinophilic infiltrate[6]. The second problem involves the histological nature of the radiographic shadowing. It is probably best to restrict the diagnosis of pulmonary eosinophilia (PE) to those conditions in which there is a predominance of eosinophils in the pulmonary infiltrate, thus excluding a wide range of miscellaneous lung disorders that happen to have an associated eosinophilia from time to time, for example, neoplasms, infections, etc. In clinical practice broncho-alveolar lavage or lung biopsy are seldom necessary as the clinical patterns are so characteristic.

A simple diagnostic and aetiological classification of the pulmonary eosinophilias is given in Table 1.

Eosinophil Properties and Functions[7-9]
The eosinophil has two main functions: cytotoxic and anti-inflammatory. Its contents, surface receptors and tissue distribution appear to be adapted to control these two functions, both of which are normally beneficial to the host. However, the cytotoxic proteins that are normally directed against parasites also have the capacity to damage host tissues and when this happens the eosinophil has a role in the pathogenesis of disease.

Eosinophil Contents
The eosinophil is a polymorphonuclear leucocyte containing about 200 granules/cell which stain with acid dyes (e.g. eosin). There are probably three sub-populations of these membrane-bound granules which contain a range of different proteins. The largest granules have a crystalline core about half of which is made up of major basic protein (MBP), molecular weight about 10,000 which contains numerous arginine residues and has an isoelectric point over 10. This, together with eosinophil cationic protein (ECP), is cytotoxic to a range of different tissues but particularly to intact helminths. Other contents of the granules include the anti-inflammatory enzymes histaminase, acid phosphatase, phospholipase D, arylsulphatase B, eosinophil peroxidase and some lysosomal hydrolases. These are all capable of degrading various inflammatory mediators and so modulating immune reactions, especially those involving mast cell degranulation.

Surface Receptors
Eosinophil cell surface receptors have been demonstrated for various complement components and especially C3b
as well as for IgG and IgE. These receptors influence the degranulation of the cell in association with various inflammatory events. In particular, when helminths are coated with specific antibodies the latter can then link with eosinophil surface receptors which promote local degranulation. There are also oestrogen and glucocorticoid receptors whose role is less certain.

**Tissue Distribution**

Eosinophils develop in the bone marrow, circulate briefly in the peripheral blood and then distribute to the tissues. For each blood eosinophil there are 100 in the bone marrow and a further 100 in the tissues. The normal tissues with a high population of eosinophils are those in contact with the outside environment, namely, skin, gut and lungs. The eosinophil is thus ideally placed to patrol the frontiers against parasites and also to damp down any uncontrolled immunological fires.

The attraction of eosinophils from the blood to tissues secondary to parasite entry or inflammatory reactions depends on a complex interplay of inflammatory and chemotactic factors. Diapedesis from the capillaries is aided by various mediators and vasoactive amines which open intercellular junctions. Thereafter the eosinophil is attracted by products of mast cells and basophils (eosinophil chemotactic factor A, histamine and various lipid derived factors) as well as by products of other cells (lymphokines, prostaglandins) and some serum factors (complement, IgE). Various parasite extracts are also chemo-attractants.

A number of factors influence the production and distribution of eosinophils. Lymphocyte-derived products stimulate the development of eosinophils and their release from the bone marrow while glucocorticoids inhibit eosinophil chemotaxis as well as enhancing margination and tissue destruction. The peripheral blood eosinophil count is increased by exercise and beta-adrenergic blockade and reduced by stress, menstruation and glucocorticoids. The influence of these on tissue infiltration and distribution is less well studied.

**Eosinophil Function in Disease**

There appear to be three main functions of eosinophils in disease (Fig. 1).

- **Helminthotoxic.** Eosinophils can kill trichinella, schistosomes and their eggs, fasciola, filaria and other parasites *in vitro*. The process is probably initiated by binding of IgG, C3b and IgE to the parasite, with consequent degranulation of eosinophils. The chief killer proteins are MBP and ECP.

- **Modulation of Immediate Hypersensitivity.** Many mast cell mediators are inactivated by eosinophil enzymes. The precise function of the eosinophil as an anti-inflammatory cell in immediate hypersensitivity and other forms of immunological reactions is, however, not yet clear.

- **Tissue Damage.** This may occur in any disease in which there is an eosinophilic infiltrate and is chiefly due to the cytotoxic proteins MBP and ECP. The balance between host benefit and damage is obviously a fine one which is likely to depend upon the number of eosinophils and how long they are present. Transient eosinophilic reactions around parasites are probably wholly beneficial, while chronic infiltrates secondary to drug, vasculitic disorders or the hyper-eosinophilic syndrome can cause permanent damage.

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Fig. 1. *Eosinophil chemotaxis and function.*
The Pulmonary Eosinophilias (PE)

**Fungal Allergy[10,11]**

Almost all fungal pulmonary eosinophilia is caused by *Aspergillus fumigatus*. A few cases are caused by candida, penicillium, stemphyllum, geotrichum, culvularia and dreherseria[12] and it is likely that other fungi will be implicated in the future but these causes are all very rare. Diagnosis can be suspected from the clinical pattern and confirmed by skin prick test and serum precipitating antibodies to the fungus. Aspergillus may also be found in the sputum but this is not essential for diagnosis.

Fungi and especially aspergillus favour places that are warm, wet and dark. The bronchial tree is thus well suited for colonisation. The probable sequence of events is immediate hypersensitivity with eosinophilia causing asthma and tissue inflammation which itself allows deeper penetration of fungal antigen. Eosinophils are attracted into the lung in relation to the affected airway, and fleeting segmental infiltrates are seen on the radiograph. The antigenic penetration results in precipitating antibody formation and immune complex deposition around the affected airways. The resulting inflammation may increase airflow obstruction, promote mucous plugging and eventually damage the airway. Since proximal airways are usually involved, the eventual result is proximal segmental bronchiectasis. Sometimes a more generalised pattern of airway damage results in fixed airflow obstruction together with a generalised thickening of the bronchial wall.

A number of different clinical patterns can therefore be seen.

**Simple asthma** without pulmonary infiltrates but with eosinophilia and evidence of aspergillus allergy. These patients respond well to standard asthma therapy.

**Fleeting segmental eosinophilic pneumonias.** The radiographic shadowing flits from one part of the lung to another, usually altering over a few days. There is fever, a high serum IgE and a moderately high eosinophil count (typically 1,000-3,000/mm³). Systemic corticosteroids clear the radiograph and the fever within a few days but chronic steroid treatment may be needed to prevent progressive pulmonary damage from repeated episodes.

**Mucoid impaction.** Low-grade fever, malaise and fixed breathlessness are more common than asthma or pneumatic illness in this form. The radiograph shows mucus impacted in a part of the bronchial tree with a typical gloved finger or rabbit's ear appearance. However, more severe mucus plugging can result in the collapse of a lobe, or even a whole lung. Corticosteroids may resolve the impaction but bronchoscopic clearance is often needed. Failure of resolution of mucus impaction causes some cases of bronchocentric granulomatosis.

**Chronic airway damage.** Airflow obstruction becomes progressively fixed as more damage occurs. The radiograph shows proximal segmental bronchiectasis or more generalised fibrotic shadowing, especially in the upper zones. Recurrent infections eventually dominate the clinical picture.

Figure 2 summarises eosinophilic function in this disease. The inflammatory reaction is based on fungal colonisation of the airways. The dominant clinical and radiographic features are therefore due to airway disease with asthma and segmental infiltrates or mucus impaction. Chronic tissue damage occurs in the airways either as proximal segmental bronchiectasis or fixed airway obstruction.

**Drugs and Toxins[13,14]**

Almost any drug in any pharmacological group can cause pulmonary eosinophilia. Although antibiotics such as nitrofurantoin[15] and sulphonamides are perhaps best known and reports of PE with non-steroidal anti-inflammatory drugs are common, this probably reflects how often the drugs are used rather than a special liability to the adverse effect. The Spanish toxic oil syndrome is perhaps the best example of a pulmonary eosinophilia due to an ingested toxin.

The pathogenesis of drug-induced PE has seldom been studied, so the mechanisms can only be guessed at. Almost always the drug reaches the lungs via the blood, so the reaction must be based in the pulmonary blood-vessels rather than the airways. A wide range of drugs (usually basic lipophilic amines) are known to accumulate in the pulmonary circulation[16] and this may be the initial event. Probably the drug or a metabolite attaches to the vascular endothelium or modifies it and an allergic reaction is then centred on that blood-vessel. There is commonly an associated rash, presumably due to an equivalent reaction in the capillaries of the skin. The pattern of the drug reaction in the lungs is highly variable, partly due to the size of the blood-vessel on which the reaction is based and partly to whether the reaction is focal or diffuse. For example, a reaction based on a few segmental pulmonary arteries resembles a pneumonia or pulmonary infarct while one based on many capillaries resembles a diffuse pneumonitis. If the
drug is continued and the inflammatory reaction becomes chronic, permanent damage occurs, with progressive interstitial fibrosis, especially at the lung bases.

There are three main clinical patterns.

**Pneumonic.** Fever, malaise, breathlessness and sometimes chest pain develop acutely within a few days of starting a drug. The white count is elevated, with an eosinophilia of 1,000–5,000/mm³, and the radiograph shows alveolar infiltrates sometimes in a single lobe but more usually with a patchy distribution. Transient pulmonary infiltrations without symptoms are sometimes seen and may well be a minor drug reaction analogous to a transient rash. The illness and radiographic changes improve rapidly on stopping the drug and recur if it is restarted.

**Pulmonary Vasculitis.** The clinical picture is similar to the pneumonic form although pleuritic pain and pleural effusions may suggest pulmonary infarction. These reactions are somewhat more severe and take longer to resolve than the simple pneumonic form. Corticosteroids are sometimes given to speed resolution.

**Fibrosing Alveolitis.** The best known example is nitrofurantoin lung. There may be low-grade fever and malaise with a slight eosinophilia but usually progressive breathlessness is the only symptom. The radiograph shows diffuse lower zone fibrosis. The amount of resolution which occurs after stopping the drug depends upon how long the reaction has lasted. Some degree of permanent damage is quite usual and corticosteroids may be given to ensure maximum resolution.

Figure 3 summarises these patterns. The inflammatory reaction is based on blood-vessels producing a pneumonic or vasculitic pattern; prolonged inflammation causes diffuse fibrosis.

**Parasitic Pulmonary Eosinophilia [2,17]**

Many different helminth infestations can cause PE. These include nematodes, such as ascaris, strongyloides, ankylostoma and filaria, and flat worms such as paragonimus and schistosoma.

The details of each life-cycle make exciting reading and are beyond the scope of this article. Nevertheless, they all have one event in common, namely the arrival of the parasite in the lungs, usually via the blood, and its passage into the alveoli and then to the airways. As the parasite migrates through the lungs, eosinophilic attack results in eosinophilic pulmonary infiltrates. The pulmonary vessels are often damaged while the parasite is moving into the lungs or when it is being killed, so haemoptysis is common. Furthermore, a number of dying parasites may set up a vigorous allergic reaction with consequent mediator release and asthma. Chronic damage is probably rare but diffuse fibrosis can follow microfilarial infection, pulmonary hypertension can follow obliteration of much of the pulmonary circulation by schistosomes, and paragonimiasis can cause lung cysts and local fibrosis. Clinical patterns are difficult to classify due to the large number of different parasites and the fact that multiple infestations are common.

**Fleeting Infiltrates.** Transient alveolar shadowing on the radiograph represents an eosinophilic reaction to the pulmonary migration of nematodes, and associated cough, transient haemoptysis, anaemia and weight loss are common. Spontaneous resolution of the infiltrate is usual. Peripheral eosinophil counts may be as high as 50,000/mm³ and the serum IgE is usually very high.

**Asthma.** This form of parasitic pulmonary eosinophilia is usually caused by microfilariasis due to *Wuchereria bancrofti* and has become known as tropical pulmonary eosinophilia. Donohugh’s [18] diagnostic criteria are (a) residence in the tropics; (b) asthma; (c) eosinophil count > 2,000/mm³; (d) positive filarial complement fixation test, and (e) response to diethylcarbamazine.

This approach remains useful for precise diagnosis since both asthma and filarial infestation are common and may co-exist by chance. The chest radiograph usually shows micronodular shadows although rare patterns include cavities, pleural effusions and large pneumonia shadows. Chronic disease causes basal pulmonary fibrosis or persisting asthma.

Figure 4 summarises the disorders. Pulmonary eosinophilia due to parasites is caused by their passage through the lungs with transient shadowing and haemoptysis. Tropical pulmonary eosinophilia is the particular association of asthma and micronodular shadowing caused by microfilariasis. Chronic damage leads to lung fibrosis (microfilaria) or pulmonary hypertension (schistosoma).

**Cryptogenic Vasculitis—Granuloma Spectrum**

The pulmonary eosinophilias of unknown cause present a spectrum of disorders that vary from the localised ‘cryptogenic pulmonary eosinophilia’ to a generalised disease with vasculitis and granulomata. In pathological terms three features are present in variable degrees: eosinophilic infiltrate, granuloma formation and vasculitis. Descriptions of these diseases have depended on the relative...
amounts of each pathological change, the type of blood-vessel involved and the organs which have been predominantly affected. As a result there are a number of quite confusing classifications. The largest single source of confusion stems from two early descriptions of pulmonary eosinophilia with systemic vasculitis. An American paper in 1951 by Churg and Strauss[19] reported ‘allergic granulomatosis, allergic angiitis and periarteritis nodosa’ and this became known as the Churg-Strauss syndrome, while a UK paper[20] in 1957 described polyarteritis nodosa as having two forms, one with and one without lung involvement and granulomatous. As a result, UK texts have continued to link pulmonary eosinophilia and polyarteritis nodosa, while American classifications include the Churg-Strauss syndrome and reserve the diagnosis of polyarteritis nodosa for a necrotising vasculitis of small and medium sized muscular arteries in which lung involvement and granulomata do not occur. The Americans have now won the classification dispute, as shown in Table 2. The way in which the pulmonary eosinophilias link up with the systemic vasculitides is shown in Fig 5.

Table 2. Classification of the vasculitides[21].

| Systemic necrotising vasculitis: | Polyarteritis nodosa |
|---------------------------------|----------------------|
|                                 | Allergic granulomatosis |
|                                 |Overlap syndrome |
| Hypersensitivity vasculitis:    | Serum sickness |
|                                 | Henoch-Schönlein purpura |
|                                 | Essential mixed cryoglobulin-aemia with vasculitis |
|                                 | Vasculitis with primary diseases, e.g. malignancy |
| Giant cell arteritis:           | Temporal |
| Granulomatosis:                 | Wegener’s |
|                                 | Lymphomatoid |

The pathogenesis of these conditions is unclear. A number of immunological mechanisms, including immune complex and cell-mediated inflammation, can be implicated. These all have the capacity to attract eosinophils and macrophages and so set up vascular damage with variable eosinophilic infiltrate and granuloma formation, but the antigen that starts the immune reaction is usually unknown. The association of allergic granulomatosis with asthma, and often with demonstrable extrinsic allergens, suggests that an external agent which becomes associated with blood-vessels or airways may sometimes be the target, but some unmasked or altered host antigen is an equal candidate. The association of polyarteritis nodosa with hepatitis antigen or drugs and the persistent vasculitis of the Spanish toxic oil syndrome provide good examples of external trigger agents, but these conditions are rare. The dominant site of the immune reaction is in the blood-vessels, although airways can also be involved, particularly when the histology is predominantly granulomatous.

There are two clinical patterns of this disorder.

Cryptogenic Pulmonary Eosinophilia[22]. Fever, weight loss and low-grade respiratory symptoms are associated with a very characteristic chest radiograph. There is widespread alveolar shadowing peripherally and in the upper zones. The blood eosinophil count is usually greater than 2,000/mm³ but is occasionally normal, when broncho-alveolar lavage or biopsy show a predominandy eosinophilic infiltrate. The response to steroids is rapid, with resolution of the fever and radiographic shadowing, and there is subsequent weight gain. Steroid dosage should be reduced slowly, as recurrences are quite common, but most patients are entirely well with no therapy in 1–2 years. Multi-system disease is not usually apparent clinically although a few patients progress into the second pattern. Asthma is present in a significant proportion of patients but is not universal. Lung biopsy shows an interstitial eosinophilic infiltrate with only occasional areas of vasculitis.

Allergic Angiitis and Granulomatosis[19,20,23]. Asthma is almost always present and may precede the multi-system disease by many years. Fever, weight loss, radiographic shadowing and multi-system disease are usually present at the onset but thereafter the clinical course is highly variable. The chest radiographic changes include transient pneumonic infiltrates, nodules which may be massive and show cavitation; pericardial or pleural effusions only rarely occur and diffuse interstitial changes have also been reported. There is a blood eosinophilia at some stage and the ESR is usually raised. Lung biopsy shows a vasculitis involving small arteries and veins and a perivascular eosinophilic infiltrate and extravascular granuloma. The lungs may not be the best place to look for allergic granulomas, liver, spleen or skin often being better.

Any other organ may be involved, but the skin, central nervous system and heart are particularly affected while renal disease is rare. There is usually a good response to steroids but when these fail azathioprine or cyclophosphamide are effective. The original appreciable mortality has been reduced by cytotoxic drug therapy. A few patients still die from cardiac failure or infectious complications.
and permanent neurological deficits are quite frequent in survivors.

Other patterns of disease have been reported under such titles as eosinophilic pneumonitis, eosinophilic non-necrotising angiitis, bronchocentric granulomatosis or necrotising alveolitis. Churg and Strauss[24] have recommended that all these should be considered part of the spectrum of a single disease rather than separate entities.

Hyper-eosinophilic Syndrome[25]

This rare condition is quite distinct from the cryptogenic pulmonary eosinophilias. The eosinophilic infiltrate occurs without any evidence of an inflammatory or allergic initiating event, there is no vasculitis and no granulomata are seen. It is therefore unclear why the eosinophils have infiltrated the tissues and whether they have any beneficial role. It is almost as if there is uncontrolled production of eosinophils which therefore accumulate. Although the clinical course may be prolonged before symptoms develop, tissue damage eventually occurs, notably in the heart and central nervous system. Few, if any, progress to a frank eosinophilia leukaemia. Men are affected nine times as often as women, usually in the 20–50 age range, and the disease has a worldwide distribution. It has two clinical patterns.

Pulmonary Eosinophilia. There are few symptoms, although there is occasionally an associated angio-oedema and a raised IgE. Allergy is not otherwise seen. The blood eosinophil count is as high as 50–100,000/mm³. The chest radiograph shows a non-specific diffuse infiltration. There is usually a response to corticosteroids with a reduction in the blood eosinophil count and the pulmonary infiltrate. The prognosis is good unless the heart becomes involved.

Predominant Cardiac or Central Nervous System Involvement. The eosinophils in the heart cause a restrictive and obliterative cardiomyopathy while diffuse brain infiltration causes intellectual impairment and more local deposits may cause focal abnormalities. There is often complicating thrombo-embolic disease of large and medium bloodvessels. Hydroxyurea and vincristine have been suggested as logical therapy to reduce the bone marrow production of eosinophils.

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**A Note on Dr Frank Buckland**

Fellows may have noticed a blue plaque let into the wall at the east end of the College garden, recording the fact that Dr Frank Buckland, Medical Naturalist, lived in a house on this site from 1863 to 1880.

Buckland, whose given names were Francis Trevelyan, was born in 1826, the son of William Buckland, a Canon of Christ Church, Oxford, who later became Dean of Westminster. William was also a distinguished geologist and naturalist, and in addition a considerable eccentric. He once expressed a wish to eat his way through the whole of the animal kingdom, but had some difficulty with the bluebottle and the mole.

Frank qualified in medicine from St George’s Hospital, but his only medical practice was a period as Assistant Surgeon to the 2nd Life Guards. The rest of his life was devoted to the study of natural history. His special interest was pisciculture, and in 1867 he was appointed Inspector of Salmon Fisheries. His numerous publications included *Curiosities of Natural History* and books on pisciculture and fishing.

In 1863 he came to live in Albany Street. My father, Arthur Clement Cooke, then aged 11, lived nearby. Like many small boys he was interested in natural history, and used to go fishing in the Regent’s Park canal. There he collected some specimens of the 10-spined stickleback, a rare species. My grandfather suggested to Arthur that he should show them to Frank Buckland down the road. This he did, and the schoolboy and the eminent naturalist became firm friends. Frank was not so eccentric as his father, but delighted in keeping numerous pets of most unusual species, which were allowed to roam freely in the house. It must have been a splendid place for a small boy to visit.

Needless to say my father retained a keen interest in natural history until his death at 93. When I was a boy we went to the London Zoo almost every Sunday morning. I too am fascinated by medicine and the other biological sciences, and my son is a professional zoologist, all of which I attribute in some degree to Frank Buckland.

As I walk past the plaque, I have a pleasant awareness of the continuity of history.

**ALEXANDER COOKE**

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