

The Hypereosinophilic Syndrome: Clinical Features, Laboratory Findings and Treatment

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INTRODUCTION, HISTORICAL AND SCIENTIFIC BACKGROUND

Blood eosinophil counts of over $1.5 \times 10^9/l$ (hypereosinophilia), can be found in a wide range of diseases including parasitic diseases, drug reactions and malignant diseases (6, 103) (Table 1). However, in many patients with a persistent hypereosinophilia the disease is of unknown cause, and gives rise to one or more of a range of clinical complications, including lesions in the heart, skin, central nervous system and lungs. This cryptogenic hypereosinophilic disorder, or group of disorders, is now called "the hypereosinophilic syndrome" (20). Although this term was only introduced in 1968 (50), clinical descriptions of this syndrome have been published for over 70 years (43, 98, 109). At that time there was no consensus of opinion about the nature of this disorder. Some were considered to have eosinophilic leukaemia but others appeared to have eosinophilic leukaemoid reactions. In order to clarify this issue, Bousser (11) analysed the clinical features of a large number of patients diagnosed as having eosinophilic leukaemia or eosinophilic leukaemoid reactions in a selected group of major haematological centres in different parts of the world. He concluded that they were different disorders, with separate clinical features and responses to treatment.

Table 1	
Causes of hypereosinophilia: (blood eosinophil counts greater than $1.5 \times 10^9/l$)	
<i>Diseases which may be complicated by hypereosinophilia</i>	
Parasitic diseases, especially tropical (filarial) eosinophilia, visceral larva migrans, trichinosis, ascariasis.	
Infectious diseases, especially those occurring in immunodeficient children.	
Hypersensitivity diseases, especially drug reactions.	
Atopic and allergic diseases, especially intrinsic asthma.	
Vasculitic/granulomatous diseases, especially those involving the lungs, Wegener's granulomatosis, Churg and Strauss syndrome and cryptogenic pulmonary eosinophilic syndromes.	
Skin diseases, especially pemphigoid and Well's disease (119).	
Tumours (17, 56, 99) especially carcinoma of the lung and gut, T cell leukaemias and angioimmunoblastic lymphadenopathy.	
Connective tissue diseases, especially eosinophilic fasciitis.	
<i>Eosinophilic malignancies</i>	
Chronic and acute eosinophilic leukaemia.	
<i>Hypereosinophilia of unknown cause</i>	
The hypereosinophilic syndrome.	

Patients with eosinophilic leukaemoid reactions did not die from complications which were often seen in patients with leukaemia. Instead

they developed heart failure with lung or central nervous system involvement. He confirmed that patients with eosinophilic leukaemoid reactions had a distinct disorder, and recommended treatment with steroids and anticoagulants. He also emphasised the importance of searching for treatable underlying causes for the hypereosinophilia, even though none could be found in the majority of these patients. But, as there was no distinct name for this syndrome, many haematologists continued to diagnose "eosinophilic leukaemia" in all of these patients, distinguishing between acute blast cell types and those where the majority of cells were of a mature type (7, 8, 118).

At the same time it was recognised that patients with eosinophilic leukaemoid reactions could develop heavy deposits of collagen in the heart and this led to the introduction of alternative diagnoses such as "endocarditis parietalis fibroplastica" (66) and "eosinophilic collagen disease" (34, 76).

In 1968 Hardy & Anderson (50) made a major contribution in this field by drawing attention to the fact that a persistent hypereosinophilia of any type could be associated with a range of similar complications. Consequently they suggested grouping these together as "the hypereosinophilic syndromes" to draw attention to their similarities. Chusid et al. (20) confirmed this but restricted the diagnosis of the hypereosinophilic syndrome to patients in whom no underlying cause for the hypereosinophilia could be demonstrated. Over 150 patients with the hypereosinophilic syndrome have now been described.

The disease has a wide range of severity, with at least three different forms of the disorder. Some patients only have hypereosinophilia with lung involvement and angioedema. Their serum IgE levels may be very high and they often respond to treatment with steroids alone (15, 81). Other patients present with (or develop) severe cardiac and central nervous system involvement. This disease is usually treated with steroids and cytotoxic drugs, and usually has a bad prognosis (95, 106).

Although most patients with the hypereosinophilic syndrome do not have unequivocal

features of a leukaemic disorder, detailed haematological studies have defined a third and smaller number of patients who have eosinophil cytogenic abnormalities and other features of a leukaemic disease (110). Occasionally the second form of the disease terminates as a blast cell leukaemia (55).

The incidence of the hypereosinophilic syndrome is not known. However most district hospitals with about 200,000 patients can expect to see one to two new patients with an explained persistent hypereosinophilia each year. Most reported patients with this syndrome have been Caucasians (20, 100, 106), but it has occurred in black Americans (20) and black West Indians (Spry 1982, unpublished), American Indians (36), Nigerians (12), Pakistanis (58) and Arabs (33, 106).

There is a remarkable male predominance of the syndrome: nine males for every female (20). The reason for this is unknown. There appears to be no difference in the clinical features or severity of the disease in each sex.

The hypereosinophilic syndrome mainly affects patients between 20 and 50 years of age, mean 32–34 years (20, 106). There are a number of reports of very young children with this syndrome including one aged 5 months (91), one aged 3 (115) and one aged 5 (88) and some older children (34, 46). The principal disease to exclude in children with a persistent hypereosinophilia aged 2–6 years old is *Toxocara canis* infections. This was first recognised as a cause of hypereosinophilia (visceral larva migrans) in 1952. Earlier reports of hypereosinophilia in this age group are difficult to interpret.

Although most patients with the hypereosinophilic syndrome have an illness which has many similarities with a chronic parasitic or allergic disorder, no cause can be found. However, it is not uncommon for these patients to describe an earlier illness in which there was a marked but transient eosinophilia. This suggests that the defects in the regulation of eosinopoiesis, in patients with the hypereosinophilic syndrome, occurred as a result of their earlier illness (106). However, this cannot be determined until more is known about the factors

which regulate eosinopoiesis in health and disease.

CLINICAL FEATURES

Some patients with the hypereosinophilic syndrome are first detected when a routine blood count is done for an unrelated reason. Approximately one third of patients are detected in this way. Another third present with complications of the disease and usually go on to develop further problems. The remainder present with advanced or late stage lesions which usually have the worst prognosis (106). A wide range of tissues and organs can be affected in patients with the hypereosinophilic syndrome (Table 2). The most serious are cardiac involvement (eosinophilic endomyocardial disease), (26, 66, 79) and central nervous system disease (41).

Eosinophilic endomyocardial disease

Cardiac disease in patients with hypereosinophilia has been known for over 60 years (1, 98). Full descriptions of two patients were given in 1936 by Löffler (66) and subsequently over 100

patients have been described (20, 26, 77, 79, 121). Löffler's endomyocardial fibrosis was initially classified as a distinct and well-defined cardiac disease, but it is now clear that it always occurs as a part of a multisystem disorder (24). The incidence of cardiac involvement in patients with the hypereosinophilic syndrome is over 60% (79), reaching as high as 80% when attempts are made to diagnose early cardiac disease (106). It has been difficult to give a precise incidence, as cardiac involvement in the early necrotic stage (13) is difficult to diagnose clinically. Occasionally it gives rise to pulmonary oedema, arrhythmias and/or cardiac enlargement. It is best diagnosed by endomyocardial biopsy. The thrombotic stage of the disease, which develops several months later, can be detected by 2-D and M mode echocardiography (23). Angiocardiography is a valuable procedure in patients with late stage fibrotic disease which is characterised by left and/or right heart failure, with mitral and/or tricuspid regurgitation and features of a restrictive cardiomyopathy (26). Significant arrhythmias are found in late stage disease with chronic heart failure.

Cardiac involvement is nearly always biventricular, but spares the outflow tract where there is often a rolled edge separating normal and involved endocardial tissues (13). Patients with obliterative pericardial and hypereosinophilia (43) are more likely to have the Churg and Strauss syndrome (49, 51), than the hypereosinophilic syndrome.

There have been some notable recent advances in the medical and surgical treatment of eosinophilic endomyocardial disease. Prednisolone 20–60 mg/day appears to be effective in treating acute episodes of heart failure which can develop in the early stage of the disease, and may inhibit progression of the endomyocardial disease (26, 79). Late stage endomyocardial fibrosis with mitral and tricuspid regurgitation can be helped by valve replacement with or without endocardectomy (25).

Central nervous system disease

Central nervous system involvement is the second most clinically important complication

Table 2

Clinical abnormalities which may be found in patients with the hypereosinophilic syndrome, in order of frequency (106)

Eosinophilic endomyocardial disease
Skin involvement
Anorexia and weight loss
Thromboembolic disease
Lymph node and/or spleen enlargement
Ophthalmological complications
Fever, excessive sweating
Gastrointestinal involvement,
including diarrhoea
Central nervous system disease
Pulmonary involvement
Psychiatric disturbance
Myalgia
Arrhythmias
Renal impairment
Splenic infarction
Diarrhoea alone
Arthralgia
Pericarditis

of the hypereosinophilic syndrome as it is associated with chronic disability and a poor prognosis. Lesions may be diffuse, causing loss of intellect and poor coordination, or giving rise to hemiplegias or cranial nerve lesions (74). Some patients show features of diffuse parietal lobe defects with disorders of ocular fixation, which is defined as Balint's syndrome (41). Postmortem studies have shown thrombi and haemorrhages from small and large cerebral blood vessels with minimal eosinophil infiltration (Spry 1982, unpublished). This differs from patients with eosinophilic leukaemia who may develop eosinophilic central nervous system leukaemia or cranial myeloblastomas (31). The recent demonstration of vascular occlusions in retinal and choroidal vessels (18) and emboli in other organs (106) has suggested that many of these central nervous system lesions are due to emboli originating in the left side of the heart. However, local vascular occlusions may also occur as endothelial cell damage and thickening has been seen in cerebral and other blood vessels (41).

Human eosinophil granules contain a potent neurotoxin (30) which produces Purkinje cell injury and demyelination in experimental animals. The relevance of this to human central nervous system involvement in the hypereosinophilic syndrome is not clear, as these types of lesion are not seen in the hypereosinophilic syndrome or diseases where many eosinophils are found in the cerebrospinal fluid.

Some patients with the hypereosinophilic syndrome develop a peripheral neuropathy including mononeuritis multiplex (33). Paralysis of the abducent nerve has also been described (28).

Thromboembolic disease

Patients with hypereosinophilia appear to have an increased risk of developing thromboembolic disease in medium to large sized blood vessels. Endocardial thrombi are commonly found in the left (or right) ventricles. In 1946, a review of 110 patients with unexplained eosinophilia showed that 16 had ventricular thrombi (62). These give rise to peripheral emboli in large or small arteries. In some patients with hyper-

eosinophilia widespread thromboemboli dominate the clinical picture (57). Cerebral thromboembolic disease (41) and retinal vascular occlusions (10, 18) and emboli which occlude aortic vessels (20, 106) are now well described. Some patients also have a multiple thrombotic episodes (70) and there is a high incidence of splinter haemorrhages in the nail beds (13). Small blood vessel disease also occurs with thickening of intimal tissues which may be the site for thrombus formation (19). Arterial calcification has also been described (75).

As thromboemboli are a major cause of death in patients with the hypereosinophilic syndrome, treatment with anticoagulant and antiplatelet drugs has been attempted, but this has not prevented some patients from developing further thromboembolic complications (106). Heparin can reverse the effects of eosinophil cationic proteins, which have been shown to effect factor XI-dependent reactions and other components of the coagulation system (78). However, large amounts of heparin need to be used to inhibit eosinophil cationic proteins *in vitro* (111) and comparable levels are unlikely to be reached *in vivo*. No apparent clinical benefits have yet been reported with short or long term treatment with heparin.

Pulmonary involvement

A common clinical problem in patients with the hypereosinophilic syndrome is an episodic and transient severe cough which is often nocturnal. It is associated with sweating and sparse but viscous sputum. As the patients can be very breathless, a diagnosis of asthma is often considered, but lung function tests usually fail to show any signs of reversible airway obstruction (106). It is possible that these episodes are the result of large numbers of blood eosinophils marginating in the lung vasculature. These may interfere with gas exchange and promote mucus secretion (5).

Surprisingly, there are very few well described patients who have both bronchial asthma and the hypereosinophilic syndrome (106, 122). The reasons for this are not known but it is possible that some component of the

allergic reactions in asthma inhibits the development of the hypereosinophilic syndrome.

Focal or diffuse pulmonary infiltrates can occur in patients with the hypereosinophilic syndrome, but the presence of these lesions in patients with hypereosinophilia usually suggests that they have one of the many other causes of pulmonary eosinophilia (105). Empirical treatment with antibiotics and steroids is usually effective. These patients do not appear to have an increased susceptibility to infections, even when they are taking large doses of steroids. This may be due to a protective effect of large numbers of eosinophils in the blood and tissues.

Gastrointestinal involvement

Symptoms of abdominal pain and discomfort are common in the hypereosinophilic syndrome, but only a few patients develop diarrhoea or malabsorption. Eosinophils are often noted infiltrating the gut wall and mesenteric lymph nodes (40), and occasionally a mass of inflammatory tissue can develop in the small intestine (67). These features make it difficult to distinguish the disease from eosinophilic gastroenteritis (61), and by analogy it has been suggested that some features of the hypereosinophilic syndrome are due to the absorption of dietary antigens from the gut (96). In most patients gastrointestinal involvement is not associated with aggressive disease (94). Liver disease may also occur (elevated liver function tests and an abnormal liver biopsy), but these findings should alert one to the possible presence of a drug hypersensitivity reaction (104). Colonic disease has also been noted, and in one patient it responded to treatment with sulphasalazine (106).

Muscle pain and weakness

Many patients with the hypereosinophilic syndrome present with aches and pains, and in some this produces a skeletal myopathy with elevated serum levels of muscle enzymes and an abnormal muscle biopsy containing hypereosinophil infiltrates around blood vessels (21, 34).

Related disorders termed "eosinophilic myositis" (4), "eosinophilic perimyositis" (65) and "relapsing eosinophilic perimyositis" (97, 108) have also been described.

Joint disease

Joint pain, stiffness and even large joint effusions can occur in patients with the hypereosinophilic syndrome, but these are usually transient. Rarely, the skin may become erythematous and oedematous and contain increased amounts of collagen (86), as occurs in eosinophilic fasciitis (69). Hypereosinophilia can also occur during aspirin treatment of patients with seronegative rheumatoid arthritis (14) or juvenile rheumatoid arthritis (90), but these are probably the result of a hypersensitivity reaction to the drug. It is also occasionally seen during sodium aurothiomalate treatment of patients with rheumatoid arthritis (104).

Skin involvement

Diffuse, non-specific skin lesions with itching are common in the hypereosinophilic syndrome. Patients may also develop urticaria or localised macules, papules or nodules on the trunk, legs or arms which may ulcerate (63). Histology shows infiltration of eosinophils around blood vessels in the dermis with endothelial thickening (116). Most of these patients respond to treatment with prednisolone. One patient improved with dapsone (73).

Other related diseases are Kimura's disease (114), Well's disease (119) and subcutaneous angiolymphoid hyperplasia with eosinophilia (120). These patients often have hypereosinophilia, but the histological appearances of the skin or draining lymph nodes are distinctive.

Renal involvement

About one in five patients with the hypereosinophilic syndrome has (or develops) proteinuria and hypertension. It does not appear to progress to end stage renal disease, and it is probably due both to thromboembolic disease and vascular injury within the kidneys. Renal

biopsy shows interstitial fibrosis, tubular atrophy and glomerular lesions of the membranous type (100).

LABORATORY FINDINGS

The remarkably high blood eosinophil counts seen in patients with hypereosinophilic syndromes are the most significant laboratory findings. In one series, patients presented with mean blood eosinophil counts of $20.1 \times 10^9/l$ (range $3.3\text{--}132 \times 10^9/l$) (106) and this reached $174 \times 10^9/l$ in one patient. An important feature of the disease is the persistence of the eosinophilia despite changes in the clinical state or treatment with steroids and other drugs, although occasionally the eosinophil count may fall within the normal level for a few weeks or months before returning to the previously high levels (106).

There is some evidence to suggest that blood eosinophils in patients with hypereosinophilia (including those with the hypereosinophilic syndrome) are more mature than normal or are in an activated state. For example their nuclei are often hypersegmented (101). Another feature is their increased capacity to bind to complexed IgG, which provides an important stimulus for eosinophil degranulation (112). Normal eosinophils begin to develop the capacity to bind complexed IgG at the promyelocyte stage (53) but only develop a marked capacity to bind IgG after they have been stimulated (113). DR antigens, which are present on eosinophil progenitor cells (59), are not expressed on blood eosinophils in health or disease (64). Human blood eosinophils can also bind complexed IgE (16), but it is not known whether IgE binding is altered in patients with the hypereosinophilic syndrome. In these patients blood eosinophils have an increased capacity to kill endocytosed bacteria (70) and to lyse rabbit antibody coated chicken erythrocytes (35), antibody coated Chang or Girardi cells (80). This may be related to their altered metabolic state which includes an increased capacity to oxidize $1\text{--}^{14}C$ glucose (70) and generate superoxide radicals (87).

The finding that many blood eosinophils are

degranulated in the hypereosinophilic syndrome, has been of considerable interest. These eosinophils, with cytoplasmic vacuoles or areas with reduced numbers of granules were clearly described by Shapiro in 1919 (98), and McDonald & Shaw in 1922 (68) also showed that patients' eosinophils formed (Charcot Leyden) crystals after treatment with acids. A later study, involving phase contrast microscopy and histochemistry, confirmed and extended these findings (2).

Electronmicroscopy of these cells has shown altered granule structures with a reversal of the staining characteristics of crystalloid and granule matrix (107, 123). Recently, it has been found that degranulated eosinophils from patients with the hypereosinophilic syndrome have a decreased content of eosinophil cationic protein (Winquist & Olsen, personal communication 1981) and eosinophil peroxidase, but a normal content of arylsulphatase, which is a constituent of the separate small granules (Fattah & Spry 1982, unpublished). Raised levels of eosinophil cationic protein (106) eosinophil myeloperoxidase (Fattah & Spry 1982, unpublished) eosinophil major basic protein (117) and Charcot Leyden crystal protein (3) have been found in the sera of patients with the hypereosinophilic syndrome. These findings support the suggestions (60, 77, 102, 107) that some of the clinical complications of the hypereosinophilic syndrome are caused by a toxic effect of one or more of these proteins on tissues and cells, especially cardiac cells (12, 111). The nature and properties of these proteins have been discussed recently (78).

Bone marrow studies

Bone marrow biopsies show that 20–80% of the nucleated cells are eosinophils in all stages of maturation. Although they are morphologically normal by light and electron microscopy (2), there can be an increase in the number of myeloblasts with other abnormalities including myeloid dyspoiesis, basophilia, reduced numbers of megakaryocytes and increased reticulin or fibrous tissue (38). Occasionally the clinical picture of myelofibrosis can develop (47, 85).

A range of cytogenetic abnormalities have been found in bone marrow cells from a small proportion of patients with the hypereosinophilic syndrome (55). These include hyperdiploid nuclei and aneuploidy (9). There are single examples of isochromosome 17 (72), a short Y chromosome (37) and XXX (Spry 1982, unpublished). The translocation of chromosome 22 deleted material to chromosome 9, which is a common feature of chronic granulocytic leukaemia (93), is not a feature of the hypereosinophilic syndrome, which suggests that the diseases are not related (44). Rare examples of eosinophil chronic myeloid leukaemia have been documented clinically, and in one case this was confirmed by showing increasing numbers of eosinophilic colonies (CFU-Eo) in agar cultures of bone marrow (45). Eosinophil progenitor cells in patients with the hypereosinophilic syndrome have only a slightly increased capacity to form CFU-Eo, with some increased sensitivity to lymphocyte derived colony stimulating factors (52). The Phi chromosome has been found in some patients with hypereosinophilia (48, 110). Other markers of chronic myeloid leukaemia have been found in some patients with the hypereosinophilic syndrome who do not appear to have eosinophilic chronic myeloid leukaemia. These include a low granulocyte alkaline phosphatase score (38) and greatly elevated serum B12 levels (27, 39).

A mild or moderate anaemia is often present when patients have high blood eosinophil counts, and this often improves when steroids and cytotoxic drugs are given. About one third of patients have thrombocytopenia, but this seldom causes bleeding, and it responds well to treatment with vincristine (see later). Blood neutrophil counts are normally maintained within normal limits, but during episodes of increased disease activity they can increase in parallel with blood eosinophil counts. Some patients show toxic granules in bone marrow and peripheral blood neutrophils, the nature of which remains unknown.

Immunological abnormalities

A search for possible immunological abnormali-

ties in a number of patients with the hypereosinophilic syndrome has failed to demonstrate any consistent defect (83). However, many patients have been found with raised serum IgM (106) and IgE (20, 83, 106). Some patients have extremely high serum IgE levels (84). These increases are polyclonal, which suggests that immunoglobulin production is stimulated non-specifically in this syndrome.

TREATMENT

Medical treatment of the hypereosinophilic syndrome follows several principles. The first is based on the recognition that few patients have a malignant disease. The second is that the outlook depends mainly on the presence and severity of the complications of the disease, rather than the over-production of eosinophils themselves. Principal amongst these are cardiovascular complications, thromboembolic disease and central nervous system involvement. Earlier reports stressed the severity of the disease and survival for more than 1 or 2 years was unusual, although occasional patients survived for over 10 years (89). The prognosis of patients who had more moderately raised blood eosinophil counts of unknown cause was however excellent (54). Before 1975, a retrospective study concluded that the average survival of patients with the hypereosinophilic syndrome was about 6 months (20). The introduction of steroids and selective use of cytotoxic drugs appears to have improved the prognosis considerably (95).

The earliest form of treatment was splenectomy which was introduced 60 years ago (68). This causes a rise in blood eosinophil counts, but relieves abdominal pain from splenic infarction, and is essential when splenic rupture occurs spontaneously (106). The long term effects of splenectomy in the hypereosinophilic syndrome are not known, but it has been found that the spleen is a major site for the localisation of injected radiolabelled eosinophils in these patients (22, 106).

Steroids and cytotoxic drugs

Medical treatment of the hypereosinophilic syndrome began in 1950 when ACTH was first used (29) but it had little apparent benefit (92). Recently the value of prednisolone was clearly shown in a study of 16 patients with progressive disease. Six responded to treatment with prednisolone alone, and eight improved on prednisolone with hydroxyurea (81). Patients with pulmonary eosinophilia, purpura, congestive cardiac failure and raised serum IgE levels appear to respond particularly well to prednisolone (15). A method for defining which patients require prednisolone has been put forward, based on haematological findings (38) and clinical features (94).

Some patients with mild disease require only short courses of treatment for episodes of increased disease activity (106). The mechanism by which steroids affect tissue injury in hyper-eosinophilic syndrome is not known. Although there is an initial fall of blood eosinophil counts, they return to pre-treatment levels. The main effect of steroids may be to inhibit the mechanisms which cause eosinophil activation and/or degranulation in tissues, and this may take several weeks.

Hydroxyurea, which has been used extensively in patients with chronic granulocytic leukaemia, has also benefited some patients with the hyper-eosinophilic syndrome (81, 82). It is used to reduce eosinophil production and lower blood eosinophil counts, which leads to reduced tissue injury (95). A second important function of hydroxyurea is to allow prednisolone dosages to be reduced in patients requiring maintenance treatment.

Vincristine has a number of advantages when compared with hydroxyurea and has been used recently in a number of patients with aggressive disease (106). It produces a fall in eosinophil counts within 3 days and this is often associated with an increase in platelet counts to normal levels. Maintenance doses can be given for many months and dosages can be reduced when paraesthesia or other signs of a peripheral neuropathy occur. It can be given in outpatients at weekly or fortnightly intervals. Patients notice

an increase in well-being which often fails to occur in patients given hydroxyurea.

A small number of patients have been treated with a variety of other cytotoxic drugs, including 6 mercaptopurine and cyclophosphamide, but their role in treatment remains to be defined.

Anticoagulation

As encocardial thrombi are an important feature of hyper-eosinophilic diseases, anticoagulants have been recommended to prevent embolic complications for many years (11, 42). Recent reports of a high incidence of thrombo-embolic disease in patients with the hyper-eosinophilic syndrome also support this view (106). However, anticoagulation has not always prevented the occurrence of small and large vessel thrombotic occlusions, raising the possibility that they developed as a result of vascular or platelet injury.

Leucapheresis and plasma exchange

The removal of large numbers of circulating eosinophils from a patient with hyper-eosinophilia possibly due to sulfasalazole hypersensitivity, was reported in 1974 (32). This appeared to improve the patient, but only moderate benefit developed in a further patient treated with 12 leucaphereses (10). Recently four patients with the hyper-eosinophilic syndrome have been treated by leucapheresis which produced a small fall in blood eosinophil counts but no clinical benefit. On the other hand when these four patients had 4 litre plasma exchanges under identical conditions, blood eosinophil counts fell to half the initial level within a few hours of the exchanges (106). This suggested that some circulatory factor was involved in the retention of eosinophils within the circulation. However, as neither leucapheresis nor plasma exchange appeared to give rise to any clinical benefit, it is not recommended as a general treatment for hyper-eosinophilia, unless the patients also have increased whole blood viscosity and widespread vessel occlusions.

CONCLUSIONS

This review has shown that the hyper eosinophilic syndrome is a striking but complicated clinical problem involving many medical specialities. The syndrome is easily recognised on the basis of persistently raised blood eosinophil counts, with a range of complications, including cardiovascular and central nervous system disease. Patients with these features have the highest mortality, but medical and surgical treatment offers some alleviation and improvement in prognosis.

The underlying defect involved in the generation of excessive numbers of blood eosinophils has still to be determined. It is not clear whether this disease is a disorder of eosinophil precursor cells, or whether there is an as yet undefined disease stimulating excessive eosinophil production. It is important to find out whether there is an intrinsic defect in eosinophil production as bone marrow transplantation could be curative in these patients. When more is known about the cause(s) of this syndrome it may be possible to separate different classes of patients, who are at present collected together in this wide diagnostic group. Until then it is best to consider them together, as they have a similar range of clinical problems.

Initial investigations of these patients usually require admission to a well-equipped hospital, where early lesions in the heart and other sites can be detected and treatment begun. These may include invasive studies to detect early cardiac involvement. The follow-up, and long term management is probably best done in centres which have some experience of this disease, so that new episodes of disease activity can be detected early and treated accordingly.

The study of these patients has given a great impetus to work on the nature and properties of eosinophils and their possible rôles in disease. It is hoped that this in turn may give an important insight into the way in which hyper-eosinophilia leads to tissue injury, and methods to prevent and treat this syndrome.

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