Behçet's syndrome

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ABSTRACT - We report our clinical experience of 230 patients referred to the Hammersmith hospital with a working diagnosis of Behçet's syndrome. The pathogenesis, diagnosis and management of the syndrome are discussed.

Sixty years after Behçet's first report there is no universally accepted diagnostic test for the syndrome and the diagnosis remains entirely clinical. In 1990, an international study group (ISG) proposed new diagnostic criteria, based on the analysis of 914 patients taken from seven countries (Table 1). In the absence of an alternative explanation, the diagnosis of Behçet's syndrome can be confidently made when recurrent oral ulceration is associated with at least two other major manifestations, which include ocular involvement, skin lesions, genital ulceration and pathergy. The ISG criteria are primarily intended to allow classification of patients for research, thereby enabling valid comparisons to be made between centres and between clinical studies. It is important to realise that a patient may still have Behçet's syndrome even if these criteria are not fully met.

Hammersmith hospital series

Over the last five years we have been referred 230 patients with a possible diagnosis of Behçet's syndrome. Of these, 111 (48.3%) were referred by their general practitioner, 50 (21.7%) by ophthalmologists and 39 (16.9%) by consultant physicians, while 28 (12.2%) were internal referrals and two (0.9%) patients referred themselves. On the grounds of fully satisfying the ISG criteria, we classified 119 (51.7%, range 18–79.1 years, median age 39.6 years) as 'definite'. A further 68 (29.6%, range 17–78.1 years, median age 39.8 years) were classified as 'probable', based upon the presence of two of the manifestations listed under the ISG criteria and a consistent overall clinical picture. The remainder (18.7%) were patients with a variety of other diagnoses, which included idiopathic ocular inflammation, inflammatory bowel disease with extra-gastrointestinal features, psoriatic arthropathy, Reiter's syndrome, and cerebral glioma with oral ulceration (one patient).

The prevalence of Behçet's syndrome in the UK is very low, with probably no more than 2,000 affected individuals.

There is a higher prevalence of this condition in a geographical region stretching from countries bordering on the Mediterranean through the Middle East to South-East Asia and Japan. This distribution has raised the possibility that the genetic susceptibility to Behçet's syndrome may have spread by migration along the Old Silk Route. Whilst 6% of our patients originated from these countries, 80% of those classified as having 'definite' or 'probable' Behçet's syndrome were native Caucasians.

Clinical features

The clinical features of the patients designated as having 'definite' (119) and 'probable' (68) Behçet's syndrome are shown in Fig 1. Importantly, patients with ocular involvement require only two further ISG criteria to be classified as 'definite', whilst patients with neurological disease or vascular lesions require three. The effect of this is that patients with involvement of the nervous or vascular systems often fall into the 'probable' group.

Oral ulceration

Oral ulceration occurring at least three times in a 12-month period is the only criterion that the ISG regards as essential. The ulcers, which are usually painful, may occur in any part

Table 1. International Study Group criteria for Behçet's syndrome.*

| Clinical presentation | Criteria |
|-----------------------|----------|
| Recurrent oral ulceration | Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient which recurred at least 3 times in one 12-month period |

Plus 2 of:

| Recurrent genital ulceration | Aphthous ulceration or scarring, observed by physician |
| Eye lesions | Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination OR retinal vasculitis observed by ophthalmologist |
| Skin lesions | Erythema nodosum observed by physician or patient, pseudofolliculitis or papulo-pustular lesions OR acneiform nodules observed by physician in post-adolescent patients not on corticosteroid treatment |

Positive pathergy test | Read by physician at 24–48 hours |

*The criteria are applicable only in the absence of other clinical explanations.2
of the mouth. They most commonly involve the non-keratinised epithelium of the labial and buccal mucosa or the lateral and inferior surfaces of the tongue, but may also involve the hard palate and pharynx. Approximately 80% are relatively minor (minor aphthous ulceration) and resolve after 10–14 days, but approximately 10% of patients develop ulcers that are larger, last longer and may scar (major aphthous ulceration). A similar percentage develop clusters of herpetiform-like lesions. Although it is difficult to be confident of the diagnosis of Behçet’s syndrome in the absence of recurrent oral ulceration, it should be noted that occasionally patients present with significant ocular or internal organ involvement prior to the development of mucocutaneous lesions (termed ‘pre-apthous’ phase). It must be stressed that up to 20% of the healthy population experience periodic oral ulceration, indistinguishable from the minor aphthous ulceration of Behçet’s syndrome. Oral ulcers may therefore be coincidental with another condition.

**Urogenital lesions**

Genital ulceration in both men and women with Behçet’s syndrome is painful and may be triggered by or interfere with sexual intercourse. In women, genital ulcers affect the vulva and vagina and sometimes the cervix. Occasionally, an ulcer may persist and need differentiating from a carcinoma. In men, genital ulcers usually occur on the scrotum and may scar, and less frequently affect the shaft and glans of the penis (in which case they should be distinguished from the balanitis of Reiter’s syndrome). Urethritis is not a usual feature of Behçet’s syndrome and should also raise the possibility of Reiter’s syndrome. Occasionally, a ‘kissing’ ulcer develops due to transfer of a genital ulcer to the contralateral inner thigh. We have seen eight male patients who experienced testicular pain and swelling at an early stage of the illness, presumably due to epididymitis.

Renal disease is uncommon, although immunoglobulin (Ig) A nephropathy has been described.

**Cutaneous lesions**

Pustules and acneiform lesions are the most common skin lesions, but in patients receiving corticosteroids may be an effect of treatment rather than a direct feature of the condition. Erythema nodosum may be indistinguishable from that due to other pathologies, but is sometimes characterised by central ulceration (Fig 2). Other cutaneous lesions that may occur include transient erythematous patches, small ulcers and pyoderma gangrenosum. Cutaneous ulcers may scar; the finding of such scars during the clinical examination adds weight to the diagnosis.

**Ocular involvement**

Ocular disease appears to be more frequent in men. Patients with ocular involvement tend to present with reduction of vision and/or floaters. The anterior uveitis of Behçet’s syndrome is rapid in onset and often described as ‘explosive’. It may lead to hypopyon formation due to accumulation of neutrophils in the anterior chamber. It is important to note that anterior segment inflammation in Behçet’s syndrome is usually associated with posterior uveitis and/or retinal vasculitis. Intra-ocular inflammation usually resolves spontaneously after 1–2 weeks but tends to recur. Long-term complications of recurrent panuveitis include anterior and posterior synechiae, cataract formation and secondary glaucoma, and retinal neovascularisation with sequelae such as vitreous haemorrhage and retinal detachment. Intra-ocular inflammation in Behçet’s syndrome is therefore sight-threatening and, when severe and untreated, may result in blindness in 3–4 years. Uncommon ocular manifestations include conjunctival and corneal ulceration, episcleritis and optic neuritis, leading to
optic atrophy. Sjögren’s syndrome is not thought to be a feature of Behçet’s syndrome. It is our usual practice to refer patients for ophthalmological assessment, but this is usually negative in the absence of ocular symptoms.

Musculoskeletal involvement

Arthralgias are common, and true arthritis with synovial swelling and/or joint effusions occurs in approximately 40% of patients. The most typical picture is a self-limiting non-erosive monoarthritis or symmetrical oligoarthritis involving predominantly the knees, ankles, wrists and elbows. Involvement of the spine and sacro-iliac joints is uncommon and long-term destructive changes are exceptional. Rare manifestations include transient localised myositis, localised osteolysis and polychondritis (the mucosal and genital inflammation with chondritis (MAGIC) syndrome).

Neurological involvement

Headaches are common and often migrainous in nature, but in the absence of other neurological abnormalities do not usually signify serious intracranial pathology. Uncommonly, headaches may be due to aseptic meningencephalitis or raised intracranial pressure caused by sagittal sinus thrombosis. Neurological manifestations are commonly transient and include cranial nerve palsies, mono- and hemiparesis, brain stem and cerebellar syndromes, and non-specific sensory symptoms. Disturbance of hearing and/or balance is common and often missed unless explored with a careful history and audio-vestibular testing. Peripheral neuropathy is very unusual but is an important side effect of thalidomide which can be used to treat severe mucocutaneous manifestations (see below).

Cerebrospinal fluid findings in acute neuro-Behçet’s syndrome are non-specific with pleocytosis, raised protein and sometimes low glucose. Clinically evident, objective neurological involvement has occurred in only 21% of our patients, similar to another published series. Conversely, with the advent of magnetic resonance imaging it has become clear that subclinical neurological involvement is more common, particularly when fluid-attenuated inversion recovery (FLAIR) sequences are performed. However, the long-term neuropsychiatric outcome in patients with subclinical disease needs to be established before we can judge whether active management is appropriate.

Vascular lesions

Vascular lesions have been documented in 17% of our patients, consistent with another published report. Vascular involvement is more common in men, it tends to occur early in the disease evolution and is associated with a positive pathergy test, erythema nodosum and ocular disease. The venous system is more commonly involved than the arterial tree. Superficial thrombophlebitis occurs frequently and can present as colourless, subcutaneous nodules or with cutaneous erythema overlying tender and often thrombosed superficial veins. Post-inflammatory pigmentation may occur along the course of an affected vein. The risk of major venous occlusion in the lower extremities is thought to be higher in patients with superficial thrombophlebitis than in those without. Importantly, Behçet’s syndrome can cause thrombotic occlusion of the venous system of the upper limbs, the inferior and superior vena cava, the dural sinuses and the hepatic (Budd-Chiari
syndrome) and renal veins. Pulmonary thromboembolism is unusual, possibly because the thrombus tends to become tethered to the inflamed vessel wall (Fig 3).

Arterial occlusions are rare and usually occur late in the disease but, in common with venous lesions, may affect any part of the arterial supply. The lower extremities are most frequently affected and patients typically present with claudication. Arterial aneurysms usually affect the large arteries and may coexist with occlusive arterial lesions. Spontaneous aneurysm formation carries a poor prognosis, usually because of rupture. When considering invasive imaging, it is important to remember that aneurysm formation can also develop at the site of arterial puncture as a manifestation of the pathergy phenomenon (discussed below). Because of this, digital subtraction angiography with intravenous injection of contrast is the preferred imaging modality.

Pulmonary artery aneurysms are well recognised; they often present with haemoptysis, and there is a strong association between them and the presence of deep vein thrombosis. Furthermore, on ventilation perfusion scans, pulmonary artery aneurysms can give a similar appearance to that of pulmonary thromboemboli. This is stressed because misdiagnosis of pulmonary thromboembolism in patients with pulmonary artery aneurysms presenting with haemoptysis may lead to inappropriate and potentially fatal anticoagulation. In these circumstances, spiral computed tomography imaging of the thorax is an accurate, non-invasive means of providing a definitive diagnosis.

**Gastrointestinal features**

Isolated mucosal ulcers can occur at any point along the gastrointestinal tract and perianal ulcers are common. A typical location for gastrointestinal ulcers is the ileo-caecal region (Fig 4). In practice, it is often difficult, either clinically or histologically, to distinguish Behçet's syndrome from inflammatory bowel disease associated with extra-enteric manifestations, because oral ulceration, erythema nodosum, vasculitis and thrombosis can occur in both conditions.

**Non-specific manifestations**

Fatigue, malaise and myalgia are extremely common, and patients often report transient fevers. Apart from the oral ulceration, pain and fatigue are commonly the symptoms that patients find most difficult to cope with. These non-specific symptoms are an important part of the syndrome and may be sufficiently severe as to limit the capacity to work.

**Pathergy**

Pathergy describes the excessive subacute inflammatory reaction to non-specific injury that appears to be central to the pathogenesis of Behçet's syndrome. When giving their medical history, many patients comment that their skin...
readily becomes inflamed in response to scratches or pricks, that their oral ulcers are induced or exacerbated by dental procedures or that they develop papules or pustules at venepuncture sites (Fig 5). Furthermore, surgery may be complicated by abnormal inflammation, often mistaken for infection, and which can result in the dehiscence of skin wounds and the breakdown of anastomoses. Inflammation in surgical wounds may become prolonged and vary with the activity of the illness (Fig 6). Other skin tests are difficult to interpret because of pathergy (eg the Mantoux test for tuberculosis).

Pathergy can be formally demonstrated clinically by the appearance of a papule or pustule 24-48 hours after insertion of a needle into the forearm skin – although whether or not pathergy occurs with formal testing depends to some extent on the size of the needle and the number of sites tested. Pathergy has been observed in up to 80% of Turkish inpatients with Behçet's syndrome, but is less common among Turkish patients in the community. The latter mainly had milder disease than their hospital counterparts, suggesting that disease activity contributes to the occurrence of pathergy. Pathergy is infrequent in Britain and has been seen in less than 10% of our 'definite' and 'probable' patient groups.

**Urate crystal test**

The urate crystal test is more sensitive than the formal pathergy reaction in demonstrating abnormal inflammation in Behçet's syndrome, probably because a visible inflammatory response occurs naturally. The usual response to an intradermal injection of urate crystals is an erythematous reaction, maximal at 24 hours and mostly resolved by 48 hours. In Behçet's syndrome, the erythema is qualitatively normal (ie not a papule or pustule like the pathergy reaction), but may be exaggerated, either in extent at 24 hours or, more tellingly, in its duration (Fig 7). Using a dose of 2.5 mg urate crystals in Turkish patients, prolongation of the erythematous response had a sensitivity of 61% and a specificity of 100% for Behçet's syndrome when

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**Fig 6. Persistent, variable inflammation at the site of a cholecystectomy scar in a patient with Behçet's syndrome.** Fluctuating erythema of the wound and suture marks have acted as a marker of disease activity in this patient.

**Fig 7. Positive urate crystal test.** There is persistent erythema at 48 hours in a patient with Behçet's syndrome following the intradermal injection of 2.5 mg monosodium urate crystals.

**Fig 8. Urate crystal test in healthy controls (13) and patients with definite Behçet's syndrome (17).** In healthy controls, the erythematous response is maximal at 24 hours and has substantially declined by 48 hours. In contrast, the majority of patients with definite Behçet's syndrome show a prolonged response. Mean values are depicted by the black circles and dashed line ($p = 0.002$ for comparison of 48:24-hour erythema ratios between healthy control and Behçet's syndrome groups, Mann-Whitney test).
compared to other rheumatic diseases. We have performed the urate crystal test on healthy controls, and on patients with 'probable' and 'definite' Behçet's syndrome and have found that many of the latter show a prolonged response (Fig 8). Ideally, the test should be performed before treatment, as a normal response is difficult to interpret once patients are taking anti-inflammatory agents.

Analysis of leukocyte trafficking and endothelial activation following intracutaneous injection of monosodium urate crystals in pigs has provided some insight into the possible reasons for the prolongation of the inflammatory response to urate crystals. Leukocytes start to enter the skin about two hours following injection of urate crystals; there is peak entry at 5–6 hours, after which trafficking drops dramatically. By the time erythema is maximal at 24 hours there is normally almost no white cell trafficking into the skin and the erythema must be entirely a reflection of post-migratory leukocyte activation. This therefore raises the question whether the prolonged response in Behçet's syndrome is due to a failure to downregulate leukocyte trafficking into the skin after the first 5–6 hours or to prolonged survival and activation of leukocytes following recruitment.

**Laboratory investigations**

Routine laboratory investigations need to be performed to exclude other pathologies, but the findings are often normal. Patients do not usually become anaemic, but may have a slightly raised neutrophil and/or platelet count. The acute phase response may be quite marked in a patient with an obvious flare of disease activity, but more often the erythrocyte sedimentation rate and C-reactive protein concentration are, at most, only modestly raised, and lower than would be typical for patients with other inflammatory rheumatic diseases. This absence of a marked acute phase response often leads physicians to underestimate the systemic nature of the syndrome. Ig levels are usually normal, although occasionally IgA is raised. Complement components are normal, and autoantibodies that characterise other inflammatory rheumatic diseases and vasculitic syndromes (eg rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies) are usually negative.

Antiphospholipid antibodies can be detected at low titre in about 25% of patients; they are not associated with antibodies to β2-glycoprotein 1, and are thought not to correlate with the presence of thrombosis. Likewise, increases in circulating factor VIII, fibrinogen and plasminogen activator inhibitor-1, and reduced fibrinolytic activity are well documented but currently do not help management. There are a few reports of thrombophilic tendencies underlying thrombosis in Behçet's syndrome (eg factor V gene mutations and acquired protein S deficiency). However, none of the 23 patients in our series with thrombosis had an abnormality on routine screening for the factor V Leiden mutation and antithrombin III, or protein C and protein S deficiencies.

**Pathology**

The characteristic feature of inflammatory lesions in Behçet's syndrome is an aseptic infiltration of tissues with neutrophils, together with infiltration of mononuclear cells. Intraluminal aggregates of leukocytes are often seen within blood vessels, suggestive of intravascular leukocyte activation and/or enhanced leukocyte traffic into the tissues. Opinions differ on the frequency with which frank vascular injury is seen. In our experience, frank endothelial cell injury, microvascular thrombosis and/or fibrinoid necrosis are unusual and, when present, are often at the base of an ulcer, suggesting that they are a secondary phenomenon.

**Aetiology and pathogenesis**

The aetiology and pathogenesis of Behçet's syndrome remain poorly understood. It seems likely that the enhanced inflammatory responsiveness and vascular endothelial dysfunction that characterise the condition are triggered by infective and/or immunological insults occurring in genetically predisposed individuals.

**Genetic associations**

Behçet's syndrome is associated with the histocompatibility locus antigen (HLA) class I antigen B51, although in Japan the syndrome occurs in only about one per 1,000 HLA-B51 positive individuals. In Turkey, the frequency of HLA-B51 is higher in hospital patients than in those studied in the community, suggesting that it may be a marker of more severe disease. HLA-B51 also appears to be particularly linked to eye involvement. It is not yet clear whether the true genetic association is with HLA-B51 itself or with another gene closely situated on chromosome 6. On the one hand, neutrophils generate enhanced amounts of free radicals not only when derived from HLA-B51 positive individuals but also when obtained from HLA-B51 transgenic mice; on the other hand, markers situated centromeric to the B locus maybe more strongly associated with Behçet's syndrome than HLA-B51. One such candidate gene is the major histocompatibility complex I chain-related gene A (MICA), the gene product of which is predicted to interact with γδ T lymphocytes.

**Infections**

As the title of his original paper indicates, Behçet proposed that the syndrome was caused by a viral infection. At present there is no evidence indicating that Behçet's syndrome is caused by a specific infection. However, it is likely that infections play an important secondary role in triggering disease flares or possibly in stimulating secondary autoimmunity. Most interest has focused on the possible involvement of *Herpes simplex* virus type 1 and strains of streptococcus.
Autoimmunity

There is evidence that autoimmunity may play a role in the pathogenesis of Behçet's syndrome:

- There are scattered reports of transient neonatal Behçet's syndrome in babies of mothers with the syndrome.37-40
- Patients frequently respond to immunomodulating agents (eg cyclosporin A).

Recent studies have found that γδ T lymphocytes from patients with Behçet's syndrome show enhanced proliferation to peptides derived from the mycobacterial 65 kDa heat shock protein.41

Significant homology exists between the 65 kDa microbial and 60 kDa human heat shock proteins. It has therefore been proposed that microbial heat shock proteins initiate an immune response that can result in the production of T cell clones able to react with endogenous heat shock proteins.45 Intriguingly, injection of these peptides into Lewis rats induced uveitis.42 The 65 kDa heat shock protein is also present in streptococci strains implicated in the pathogenesis of Behçet's syndrome (eg S. sanguis and S. pyogenes).43 Patients with Behçet’s syndrome also tend to have circulating antibodies to the 65 kDa peptides, but the difference between patients and controls is not as striking as for γδ T lymphocyte proliferative responses.41

Management

The management of Behçet's syndrome is difficult because of the heterogeneity of the condition, lack of reliable laboratory markers of disease activity and the paucity of controlled clinical trials. In devising a treatment plan, it is vital to establish clear clinical objectives and to discuss treatment options fully with the patient.

Mucocutaneous lesions

Mild mucocutaneous lesions can often be managed adequately by local application of corticosteroids. We tend to prescribe a beclomethasone inhaler, instructing the patient to spray ulcers as soon as they are felt to be developing. Established oral ulcers may also be helped by applying topical corticosteroids in the form of triamcinolone acetonide in an adhesive base (eg Adcortyl or Orabase) or hydrocortisone lozenges (eg Corlan). Another approach is for the patient to prepare a solution of betamethasone 500 μg and doxycycline 100 mg and hold this in the mouth for 10 minutes before discarding. More severe mucocutaneous lesions may require systemic corticosteroids, ideally given in short courses.

Colchicine is frequently used to treat mucocutaneous disease that does not respond to local measures.44-47 In our experience, colchicine seldom eliminates oral ulceration completely, but may reduce to an acceptable level the frequency and severity of ulcers. There is some evidence that adjunctive penicillin therapy may enhance the clinical response to colchicine therapy for both orogenital ulceration and arthritis.48

Thalidomide is often highly effective at reducing the frequency and severity of mucocutaneous disease resistant to colchicine.50-52 However, because of the teratogenic effects of the drug, it is our policy to prescribe thalidomide only to men, postmenopausal women or women who have undergone tubal ligation or hysterectomy. Unfortunately, peripheral neuropathy is relatively common, and baseline nerve conduction studies should be performed before starting therapy and at regular intervals whilst on treatment.53 The risk of developing neuropathy appears to increase with total exposure, so it is important for patients to take as low a dose as possible (50-100 mg) and to try taking the drug only every second or third day. In view of its sedative effect, thalidomide is best taken at night.54

Ocular involvement

Treatment of ocular inflammation in Behçet's syndrome should be conducted in close collaboration with an ophthalmologist. Episodic attacks of anterior segment disease in the absence of sight-threatening posterior segment inflammation may be treated with corticosteroid topically or via orbital floor injection alone. More significant acute flares are treated with short courses of high-dose prednisolone (up to 1 mg/kg/day). Immunosuppressant agents are often required to control recurrent inflammatory activity. Clinical trial data indicating efficacy exist for azathioprine and cyclosporin A.55 Studies performed to date indicate that FK-506 (tacrolimus) has a similar efficacy in uveitis to that of cyclosporin A, but the role of this agent in treating ocular disease has yet to be clearly defined.56 Another promising agent for the control of resistant ocular inflammation is mycophenolate mofetil.57

Other manifestations

The controlled trials conducted so far in Behçet's syndrome have tended to focus on ocular inflammation, and there are no hard data on the relative merits of different drugs in treating other manifestations such as vascular and neurological involvement. In practice, these tend to be treated along the same lines as ocular disease. Patients with severe acute neurological involvement may require cyclophosphamide or chlorambucil.

The use of anticoagulants to prevent thromboembolism syndrome is controversial, because of a perceived greater risk of bleeding from gastrointestinal ulcers and, rarely, from ruptured aneurysms. Moreover, as discussed earlier, pulmonary embolisation of deep vein thrombosis is uncommon. In view of the underlying inflammatory pathogenesis of thrombosis in Behçet's syndrome, immunosuppression appears to be a more appropriate and safer approach. In patients with confirmed venous thrombosis, our policy is to initiate anticoagulation on a temporary basis.
whilst immunosuppressive therapy is established. The decision when to withdraw anticoagulation needs to be based on the individual clinical situation.

Isolated aneurysmal disease should be treated, where feasible, by surgical repair because of the high risk of rupture. However, as with all surgery in Behcet's syndrome, control of inflammatory activity prior to surgery is highly desirable to prevent postoperative complications. Immunosuppressive treatment, in combination with corticosteroids, is indicated postoperatively to prevent relapse.11

Conclusions

Behcet's syndrome is an uncommon, but intriguing illness in which the central abnormality is enhanced inflammatory responsiveness. Further study into the nature of this unusual inflammatory response will teach us not only about its pathogenesis but also about inflammatory responses in general. There is no diagnostic test, and diagnosis thus depends on recognition of its typical clinical manifestations. Finally, the internationally recognised classification criteria should enable large multicentre controlled clinical trials to be performed, which in turn will provide improved, evidence-based management strategies.

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Clinical pharmacology and therapeutics in a changing world

A report of a working party of the Royal College of Physicians

The role and influence of specialists in clinical pharmacology and therapeutics in the health service, medical education, government policy and the pharmaceutical industry needs to be more clearly understood and recruitment to the specialty strengthened. Changes in the NHS structure, less flexible training programmes and lack of a clear career structure have led to uncertainty about the role of the specialty—both among employers and those who wish to follow a career in clinical pharmacology—and also to a deficit in training opportunities.

This report describes in detail the work of clinical pharmacologists in the NHS, in academia and the pharmaceutical industry which include: the clinical care of patients; clinical toxicology; the use of medicines in the community (pharmacoeconomics); drug safety (pharmaco-vigilance); the economics of prescribing (pharmacoeconomics); advice to government agencies on the licensing and use of medicines; the teaching of undergraduates and postgraduates; research; and new drug evaluation within the pharmaceutical industry. Many of these activities have particular relevance and importance at a time when the cost and efficacy of new drugs is high on the health care agenda. Strong recommendations are made including that clinical pharmacologists should have a major role in cost-effective prescribing and by creating joint appointments and training opportunities between industry, universities and the NHS.

This report will be informative to managers in the health service and the pharmaceutical industry and to those responsible for teaching in medical schools and at postgraduate level. For those practising or contemplating a career in clinical pharmacology and therapeutics, this report will also provide much useful guidance.

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