mittee and without any of the members having had any formal training in ethical analysis. Ms Jean Robinson, a lay member of the General Medical Council, vigorously argued that there should be a minimum of two lay members on an ethics committee, which should always be prepared to justify its decisions to the public (as it had in this case). Several of the foreign visitors found it peculiar that no national bioethics committee had been established, at least to provide analysis and advice on particularly contentious or difficult medicomoral issues. Such a committee, if also charged to anticipate developments in bioethics, would provide a foothold on the "slippery slope" about which Miss Sims warned the conference.

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Penicillin allergy: how to diagnose and when to treat

The first death from penicillin anaphylaxis was reported within one year of the drug being generally introduced in 1948. "Allergic reactions" to penicillin and its synthetic analogues have since been increasingly recognised, but true IgE dependent anaphylaxis is rare. It has an incidence of about 0·05% and a mortality of 0·0002% in all patients receiving penicillin.[1] Most anaphylactic responses follow the drug being given parenterally, and there appears to be no association with atopy. The remainder of allergic responses to penicillin, which occur in about 1-10% of patients, are accounted for by other immunological processes—for example, haemolytic anaemias, serum sickness, contact dermatitis, and the morbilliform rashes.[2]

Almost everybody who receives a penicillin will develop specific IgG and IgM antibodies.[3] Occasionally penicillin also evokes hapten specific IgE, the antibodies responsible for drug related anaphylaxis. With metabolic cleavage of the β lactam ring a highly reactive penicilloyl group is formed, which covalently links with tissue proteins to form the major antigenic determinant[4]; minor determinants are penicillin itself, penicilloate, and penilloate.[4,5] Penicillin anaphylaxis necessitates the IgE dependent activation of mast cells and basophils with the rapid release of vasoactive and bronchoactive mediators such as histamine, prostaglandin D_2, leukotriene C_4, and platelet activating factor, which together produce urticaria, laryngeal oedema, bronchoconstriction, and hypotension.

On p 1236 Kirk and others describe a young patient with an overwhelming clostridial infection in whom a history of "penicillin allergy" was considered to preclude using this group of antibiotics. But when ampicillin was eventually given as a life saving measure no allergic response occurred. A label of "allergic to penicillin" is common, but it is only the anaphylactic response that is a major contraindication. Moreover, as many as 85% of patients who are allergic to penicillin can tolerate the drug when given it again, since sensitisation may only be temporary.[6]

Usually doctors use another drug in penicillin sensitive individuals, but sometimes it is important to determine the type of allergic response previously encountered, particularly to discover if it was anaphylaxis. Confirmation of IgE related sensitisation to penicillin and its breakdown products may be obtained by standard skin prick testing with a derivative of the major determinant, benzylpenicilloyl polylysine, commercially available at a concentration of 60 μmol/l, and the minor determinants including benzylpenicillin itself, each used at a concentration of 10 mmol/l.[6-8] A wheal and flare reaction after 10-15 minutes of 3 mm or more in diameter and greater than a saline control is considered a positive response. Only about 10% of patients with a history of "penicillin allergy" have positive skin test results, and anaphylactic reactions almost never occur except in patients who give a positive response.[5] Almost all β lactam antibiotics show some cross sensitisation, although it happens little with cephalosporins[9] and almost never with the new β lactam antibiotics such as the monobactan aztreonam[10] and the carbapenem imipenem.[5]

Patients who have a strong history of penicillin anaphylaxis and who need penicillin for an overwhelming bacterial infection should be desensitised.[11] The procedure should be carried out under constant supervision, preferably in an intensive care unit. An intravenous catheter should be inserted and adrenaline should be at hand. One widely used method starts with intradermal injections and is then followed by subcutaneous, intramuscular, and intravenous injections.[11] The starting intradermal dose is 0·1 ml of 100 units/ml benzylpenicillin. The dose is then progressively increased in 15-20 steps at 17-20 minute intervals with the first dose of 10^6 units being given intravenously. A modification is to give all the injections intravenously.[12,13] In an alternative and possibly safer form of desensitisation that takes about four hours increasing doses of benzylpenicillin are given orally with only the last few doses being given parenterally.[14,15] Desensitisation should not be undertaken under the protection of antihistamines and corticosteroids since these drugs may mask a subsequent reaction during the procedure. Once desensitisation has been completed a full course of penicillin or semisynthetic penicillin may be given.

These forms of drug desensitisation work on mast cells and basophils by raising the cellular threshold for triggering by IgE antibody.[16] They do not necessitate inducing blocking IgG antibodies or other immunological responses associated with more classical allergen immunotherapy. Protection is therefore shortlived, and desensitisation will need to be repeated for further drug courses. Despite the current swing away from desensitisation, particularly in Britain, these procedures when applied to penicillin and its analogues may be lifesaving. They are needed, however, only when there is a history of previous anaphylactic reactions and only in the unusual circumstances when an alternative drug cannot be found.

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Tumour necrosis factor

The term "tumour necrosis factor" was introduced to describe a serum protein produced after bacterial infections capable of causing haemorrhagic necrosis of animal tumours, a phenomenon well described in man.[1 2] Two such proteins have now been characterised and are available as recombinant DNA derived proteins, and are referred to as tumour necrosis factor (TNF—predominantly derived from macrophages) and lymphotoxin (also called TNF β—a product of activated T lymphocytes).[3-5] These proteins are important as mediators in immunity and inflammation, although they may also be concerned in tissue remodelling and cell differentiation.[6-9] They have wide ranging effects, including modulation of the properties of vascular endothelium, induction of other cytokines, induction of antiviral activity in cells, stimulation of bone resorption, angiogenesis, and fibroblast mitogenesis.[10-19]

Local and transient production of tumour necrosis factor may therefore benefit the host, but generalised or sustained production may be harmful. For instance, the presence of high levels of biologically active tumour necrosis factor in serum is associated with a fatal outcome in meningococcal septicaemia.[20] In addition, neutralising antibodies to tumour necrosis factor can protect animals from dying of septicaemic shock[21] and prevent the development of cerebral malaria.[22] Systemic administration of tumour necrosis factor reproduces the haemodynamic and metabolic alterations seen in septicaemic shock.[23] Tumour necrosis factor has been shown to play a part in the cachexia seen in animals infected with *Trypanosoma brucei*,[24 25] and as it is produced by some cancer cell lines it may contribute to cancer cachexia.[26]

Is there a role for tumour necrosis factor in treating cancer? So far trials of recombinant tumour necrosis factor given systemically to patients with various types of cancer have yielded low response rates (less than 5%).[27] Higher rates of remission (up to 40%) have, however, been reported after direct injection into the tumour.[28] No deaths have occurred as a result of giving the factor, the most common side effects being fever, hypotension, headache, and occasional disturbances in the central nervous system. More effective regimens will probably exploit the known synergy between tumour necrosis factor and other cytokines such as interferon gamma and interleukin 2.[29 30]

Tumour necrosis factor is part of a network of cell regulatory proteins collectively called cytokines, and its actions cannot be considered in isolation. Understanding cytokine interactions is likely to broaden our grasp of the pathophysiology of many diseases and enable us to use these proteins, or, alternatively, specific inhibitors of their production or actions, as therapeutic agents.

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