

thromboembolic events by aspirin of 2.7% per year, and the true benefit could be as large as 4% per year. While direct¹ and indirect comparisons suggest that warfarin is better than aspirin, aspirin might still be preferred when convenience and risk are included in the equation. However, this is pure speculation because we now have good evidence for warfarin but not aspirin.

Interpretation of the warfarin trials is helped by the remarkable consistency of their findings, and by the reporting of their results in a way that makes the absolute benefit and risk of treatment easy to understand by ordinary doctors and potential patients. Chronic atrial fibrillation without rheumatic valve disease carries a risk of stroke or thromboembolism of about 5% per year, and this is reduced to about 1.5% per year by warfarin. The cost is the nuisance of taking tablets, a monthly blood test, and a risk of important bleeding of about 0.5% per year. The patients studied seem broadly representative of all those with chronic atrial fibrillation. This is in one sense reassuring, but also means that there is no easy way to stratify patients for baseline risk and therefore potential benefit. Exceptions may be patients below the age of 60 with paroxysmal atrial fibrillation or chronic atrial fibrillation and an entirely normal heart, who seem to be at lower risk⁷ and may benefit less from warfarin.

Since warfarin will prevent stroke and other thromboembolic events in about 3.5% of patients treated per year at a cost of important bleeding in 0.5% per year, patients with chronic atrial fibrillation should probably be offered treatment. This conclusion is supported by the application of a simple decision-analytic expression to these clinical trial data by Caro and colleagues in this issue (p 1381). We are now faced with a daunting problem—how do we find the patients? The prevalence of chronic atrial fibrillation is about 3% in subjects over 60 years and as high as 9% in those aged 80–89 years.⁸ The results of trials such as the ISIS series were easy to implement because patients congregated conveniently in coronary care units, but chronic atrial fibrillation is more like hypertension—patients are “free-living”, may be undiagnosed, and may have few or no symptoms. The offer of effective treatment should not be left to chance, and formal screening for chronic atrial fibrillation will have to be considered. Experience with hypertension is not encouraging: much moderate and severe hypertension remains undetected although thirty years have passed since outcome trials showed a need for screening. Standards of warfarin treatment will have to match those in the trials with respect to heeding contraindications, patient education, and monitoring if the outcome is to equal that attained in the formal studies. To lessen inconvenience patients are best managed in primary care rather than in hospital, so doctors not accustomed to using warfarin may need help to familiarise themselves with anticoagulant treatment. Even the best clinical trials solve few problems—they merely get us to the starting line.

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1. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet* 1989; **i**: 175–79.
2. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with non-rheumatic atrial fibrillation. *N Engl J Med* 1990; **323**: 1505–11.
3. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study: final results. *Circulation* 1991; **84**: 527–39.

4. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med* 1992; **327**: 1406–12.
5. Connelly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *JACC* 1991; **18**: 349–55.
6. Singer DE. Randomised trials of warfarin for atrial fibrillation. *N Engl J Med* 1992; **327**: 1451–53.
7. Kopecky SL, Gersh BJ, McGoon MD, et al. The natural history of lone atrial fibrillation: a population-based study over three decades. *N Engl J Med* 1987; **317**: 669–74.
8. Wolf PA, Abbott RD, Kannell WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991; **22**: 983–88.

RESPIRATORY DISEASE

Transplantation asthma

In this issue (p 1369) Corris and Dark describe four cases that provide further insight into mechanisms of asthma. Two severely asthmatic atopic recipients of normal lungs did not subsequently develop asthma. This observation suggests, first, that asthma is an organ-specific rather than a systemic disease, and second, that donor lungs that are not “primed” to become asthmatic remain non-asthmatic even when infiltrated with recipient lymphocytes and other inflammatory cells. Conversely, the rapid development of asthma in non-asthmatic non-atopic recipients of asthmatic lungs strongly suggests “carry over” and stimulation of the asthmatic predisposition in the donor lung. The histological features of eosinophilic infiltration and epithelial disruption seen in biopsy specimens one week after transplantation are those of the donor lung before transplantation, but the acute appearance of diurnal variability of peak expiratory flow and the persistence of airflow obstruction despite corticosteroid therapy indicate a far more severe asthma in the recipient than in the donor. Asthma developing after allogeneic bone marrow transplantation is likewise characterised by severe airflow obstruction and resistance to treatment.¹ Skin-test reactivity was clearly transferred from skin-test-positive bone marrow donors to skin-test-negative recipients; in 2 of 12 cases, recipients became asthmatic and a third had worsening of pre-existing asthma.² This worsening may relate to increased IgE concentrations associated with reduced number of suppressor T cells in marrow recipients during acute graft versus host disease.³

In some respects we should not be surprised that a lung that has been subject to asthma (whatever that is) for over 20 years should carry that characteristic response pattern into a new host. Atopy in the donor may condition the lung to respond not only to atopic stimuli but also to other triggers of asthma just as sensitisation to an occupational allergen may lead to asthma with both occupational and non-occupational triggers. Even though central to development of asthma in young people, atopy seems to be unnecessary for transplant asthma to persist or to worsen in a new host. Likewise, innervation is not essential to an asthmatic response in transplanted lungs, although this observation does not exclude an important role for neural factors in some (perhaps all) usual asthma cases. Denervation may increase the asthmatic response by depriving the lung of modulatory reflexes and increase the responsiveness of airway smooth muscle muscarinic receptors.⁴ However, airway responsiveness to methacholine was normal in transplanted patients whose lungs showed normal histological features and no evidence of infection.⁵ In that series, none of the

Questa fotocopia viene fornita a scopo di studio e per uso strettamente personale

recipients had a history of asthma and no donor was known to have asthma. One can only speculate about the cellular mechanisms that take place when asthmatic lungs, charged with activated eosinophils and primed T lymphocytes capable of inducing asthma in the donor under normal conditions, are transferred to a foreign recipient. Release of cytokines may be enhanced by the trauma of transplantation; in lungs already conditioned to respond with asthma, these mediators may induce more severe disease than in the donor.

This latest report suggests that transplantation of lungs from a known asthmatic is unwise. However, in practical terms, since many of the younger population have asthma, use of asthmatic lungs may be difficult to avoid. In view of the shortage of donated organs, use of lungs with mild asthma may be better than no transplant at all. Prospective studies of this issue will be difficult, but careful documentation of cases such as those described by Corris and Dark, with detailed information on atopic status, pulmonary function, and cellular and immunochemical studies before and after transplant, may give further clues to the pathogenesis of asthma.

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1. Atkinson K, Bryant D, Biggs J, Concannon A, Dodds A. Obstructive airways disease: a rare but serious manifestation of chronic graft-versus-host disease after allogeneic marrow transplantation in humans. *Transplant Proc* 1984; 16: 1030-33.
2. Agosti JM, Sprenger JD, Lum LG, et al. Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. *N Engl J Med* 1988; 319: 1623-28.
3. Sustiel A, Rocklin R. T cell responses in allergic rhinitis, asthma and atopic dermatitis. *Clin Exp Allergy* 1989; 19: 11-18.
4. Higenbottam T, Jackson M, Rashdi T, Stewart S, Coutts C, Wallwork J. Lung rejection and bronchial hyperresponsiveness to methacholine and ultrasonically nebulized distilled water in heart-lung transplantation patients. *Am Rev Respir Dis* 1989; 140: 52-57.
5. Herve P, Picard N, Ladurie MLR, et al. Lack of bronchial hyperresponsiveness to methacholine and to isocapnic dry air hyperventilation in heart/lung and double-lung transplant recipients with normal lung histology. *Am Rev Respir Dis* 1992; 145: 1503-05.

IMMUNOLOGY

Autoimmunity and insulin-dependent diabetes

All autoimmune diseases, whether organ-specific or non-organ-specific, are characterised by the presence of antibodies to one or more autoantigens. Do these autoantibodies mediate disease themselves or are they merely humoral indicators of an underlying destructive process mediated by T cells?

In some autoimmune conditions—eg, Graves' disease and myasthenia gravis—the disease is plainly mediated by specific autoantibodies. In other autoimmune conditions—eg, Hashimoto's thyroiditis and insulin-dependent diabetes mellitus (IDDM)—the abnormalities seem to be mediated by cytotoxic T lymphocytes.¹ This is cell-mediated immunity. In both Hashimoto's thyroiditis and IDDM the autoantibodies are generally thought to be secondary to the disease process. However, T cells sensitised to antigens of the target organ can also be found. One possibility is that a dichotomy exists between cellular and humoral responses, at least in IDDM. In this issue (p 1365) Harrison and colleagues present evidence that islet cell antibody positive first-degree relatives of IDDM patients, at risk of disease, show a predominance towards either cell-mediated or humoral immunity to glutamic acid decarboxylase (GAD), a

known autoantigen in IDDM.² Those with a cell-mediated immune response progress to disease rapidly, whereas those with only anti-GAD antibodies progress slowly and maybe not at all.

To explain this apparent contrast in the autoimmune response we need to understand the specific role of the helper T-cell subsets involved in the reaction. Mice possess two types of major histocompatibility complex class II restricted helper T cells.³ The first, Th1, produces interleukin-2 and interferon- γ , which, in turn, induce further T-cell activation with the generation and expansion of activated cytotoxic T lymphocytes. By contrast, the second helper T-cell population, Th2, synthesises interleukin-4, a B-cell-targeted cytokine, leading to immunoglobulin synthesis. Furthermore, the two subsets have been shown experimentally to induce contrasting effects. Injection of athymic rats with Th1 cells leads to lymphocytic infiltration of multiple organs and the development of thyroiditis. Injection of Th2 cells causes no such abnormalities; nor does injection of mixed Th1 and Th2. These observations suggest a control mechanism mediated by Th2 cells.⁴ Interleukin-4 is known to suppress the production of interleukin-2 and interferon- γ and this may be a mechanism whereby Th2-cell activation not only leads to a specific antibody response but also suppresses an associated T-cell response. Corresponding helper T-cell subsets in the human immune system were formerly elusive but there is now good evidence of their existence.⁵

We do not know the mechanism by which humoral and cell-mediated responses are selectively activated, but it may be related to the path of antigen presentation. A study in mice showed that antigens presented by B cells stimulate optimum proliferation of Th2 clones, whereas Th1 cells are stimulated maximally by monocytes/macrophages.⁶

The relation between cell-mediated immunity and autoantibody responses to autoantigens has been studied before in an overt autoimmune condition, Addison's disease,⁷ but the report by Harrison et al is the first to detail a dichotomy in the immune response to a known human autoantigen in a predisease state. The data suggest that GAD antibodies in IDDM are not pathogenic per se; but are they good markers for predicting IDDM? This question may be answered by studying individuals who possess GAD antibodies without other markers of IDDM (as we are doing). Secondly, are GAD antibodies pathological mediators in stiff-man syndrome, the rare neurological disorder in which they were first described?⁸ If so, what are the differences between the GAD autoantibodies produced in the two conditions? Maybe the final disease outcome is determined by the precise physicochemical characteristics of different anti-GAD antibodies—ie, antibodies reactive with certain GAD epitopes or of a particular affinity will lead to stiff-man syndrome, whereas others are associated with islet-cell antibodies in the absence of overt IDDM.⁹

What is the role of cell-mediated immunity to GAD in the two conditions? Perhaps cell-mediated immunity is relevant in IDDM but not in stiff-man syndrome mainly because cytotoxic T lymphocytes, even if they cross the blood-brain barrier, are unlikely to be stimulated by neuronal cells, which do not express HLA class I molecules. However, there is no direct evidence that GAD-specific cytotoxic T lymphocytes are pathogenic in IDDM and we await the confirmation that peptides of GAD can be presented to these lymphocytes by HLA class I molecules on beta cells, either in vitro or in vivo. Despite all these unanswered