benefit and toxicity of treatment but not whether there is an effect. Individual patients should undoubtedly have a role in balancing the potential benefits and side effects of treatment. Several new drugs with substantial activity in patients who are resistant to treatment with fluorouracil, such as Irinotecan (CPT11) and oxaloplatin, are now available for phase II and eventually phase III testing. For the first time there is evidence that monoclonal antibodies may have a role as adjuvant therapy in patients with Dukes's type C colon cancer.¹⁴ Customised treatment according to individual patients' predicted chemosensitivity may soon become a real possibility.¹⁵ The treatment of colon cancer has been transformed from a therapeutic desert into one of the most innovative and fast moving areas of laboratory and clinical cancer research.

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Antibodies to streptokinase

Once is enough

Thrombolysis is established treatment in the early management of myocardial infarction, and it reduces 35 day mortality by about a quarter.¹ The GUSTO study has suggested some advantage of alteplase (rt-PA) over streptokinase with regard to early patency of the occluded coronary artery.² In particular, GUSTO has suggested that patients aged less than 75 years who present within four hours of the onset of pain and with anterior infarction are especially likely to benefit from alteplase. However, the fact that streptokinase is far cheaper than alteplase means that it is likely to remain the most commonly prescribed thrombolytic drug.

Because streptokinase is a foreign bacterial protein it is antigenic. Anxieties have been raised about the role of antibodies to streptokinase in causing hypersensitivity reactions and their potential for neutralising the thrombolytic effect. About 15-20% of patients with myocardial infarction will have experienced a previous myocardial event, and 9% of patients receiving thrombolysis will re-infarct within a year.³ Clearly there is the potential for an important minority of patients to have high circulating levels of antibody to streptokinase, which might reduce the efficacy of subsequent administration of the drug. Most patients will have detectable titres of IgG antibodies to streptokinase because of previous exposure to streptococcal infection,⁴ but these values are low compared to the much higher levels in patients receiving streptokinase. The fact that they fall within 24 hours of administration of streptokinase implies that they combine with streptokinase, raising the potential for impaired efficacy.

Hypersensitivity reactions to streptokinase are uncommon and usually minor—in the ISIS-2 trial only 4.4% of patients suffered allergic reactions to streptokinase¹—and may be encountered more often when streptokinase is administered a second time.⁵ With regard to the efficacy of readministered streptokinase, it does seem probable that high titres of antistreptokinase antibodies would interfere unfavourably with the thrombolytic effect, but there is little clinical

evidence that this is so. In one study of patients previously unexposed to streptokinase and therefore with relatively low levels of streptokinase resistance, there was a small but significant negative influence on thrombolytic efficacy when coronary patency was assessed by angiography; those with occluded arteries at 24 hours had higher streptokinase resistance.⁶ Another angiographic study showed no difference between thrombolytic effect and pretreatment antibody levels, although the levels were relatively low in this population, who had not previously received streptokinase.⁷ However, Brugemann *et al* showed that patients with high levels of antistreptokinase antibodies who received anistreplase (a streptokinase analogue) did not achieve patency of the affected artery.⁸

We know that levels of neutralising antibodies are significantly elevated from four days after administration of streptokinase for an unpredictable period of at least four and a half years⁹; in one series 51% of patients who received streptokinase had titres of neutralising antibodies sufficient to inactivate the conventional dose of 1 500 000 units of streptokinase 48 months later.¹⁰ Lee *et al* reported that neutralising titres of antibodies were detectable up to at least 54 months after administration of streptokinase.⁹ Conversely, one study has shown that neutralising titres returned to control levels after two years.¹¹ The authors acknowledged that their results were at variance with other published data and were unable to explain this disparity. Patients may not be good witnesses of previous streptokinase treatment. Corbett *et al* reported that patients who had received thrombolytic treatment and who had been counselled and given an alert card had poor recollection of the advice that they should not receive streptokinase again within a year.¹² When they were contacted only one week after discharge, only one in 20 patients still possessed the card and none recalled the caution.

We do not yet know the clinical importance of elevated titres of antibodies to streptokinase. The currently available

evidence suggests that it is reasonable to avoid using streptokinase again in patients requiring thrombolysis more than four days after previous treatment. Instead, they should receive a non-antigenic drug such as alteplase or urokinase.

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The European Medicines Evaluation Agency

Moving towards more transparent drug registration systems

The European Medicines Evaluation Agency (EMA) opened its doors for business just over a year ago and, despite a shaky start, is making progress in implementing the new European drug registration system. The aim is to give patients quick access to innovative new drugs, to facilitate the free movement of drugs within the European Union, and to provide rigorous scientific evaluation of new products. The system also aims to encourage cooperation, communication, transparency, and confidence among regulators, industry, health professionals, and consumers.

The system uses two licensing procedures: a centralised procedure via the agency, which is now compulsory for new biotechnology products, although companies can request it for other drugs as well; and a decentralised procedure, which applies to most conventional products and is based on the previous system of mutual recognition of national authorisations. A product licence obtained in one member state of the European Union must be recognised by each of the other states, unless they object to it within a fixed period. Disputed decisions go to the agency's scientific committee, the Committee for Proprietary Medicinal Products, for binding arbitration. Under both procedures, the committee's opinion is passed to the European Commission, which has to reach a decision in 90 days.

Companies seemed initially wary of the new centralised procedure, but by October 1995, 22 new applications had been submitted. Of these, only a third were for biotechnology products, while the rest were for products for which the companies could have opted for the decentralised procedure. By the end of last year, three products had been licensed. For each of them (follitropin alpha, interferon beta-1b, and docitaxel) the agency issued a European Public Assessment Report. The agency has also dealt with 49 multi-state applications that had been pending from 1994 and has given non-binding opinions under the old rules of registration. A permanent group of the Committee for Proprietary Medicinal Products is working to coordinate national monitoring of drug safety, and the agency's electronic communications network is up and running. Documents may be obtained, albeit with some difficulty, from its public web site on the Internet (<http://www.eudra.org>).

How will the EMA's activities affect the still oversecretive regulatory system in Britain? Two changes have important implications. Firstly, the prompt publication by the agency

of European Public Assessment Reports for all products approved under the centralised procedure. The company can request that some data remain confidential, but the committee can refuse this. These reports consist of an abstract, 10-30 pages of discussion, the committee's opinion on restrictions of use, a summary of the product's characteristics (similar to but more detailed than a current data sheet), and the text of the package leaflet. Unfortunately, the report does not identify the studies on which approval is based. The United States Food and Drug Administration's Summary Basis of Approval is more detailed. It describes the salient features of all the studies supporting approval of a drug, with the names of the principle investigators. Other material is accessible under the Freedom of Information Act. The European Public Assessment Report does, however, list what further data the manufacturer has undertaken to provide and when. It also explains what prompted the committee to amend the manufacturer's proposed summary of product characteristics and gives the reasons for the conditions or restrictions of supply and use. As new information becomes available the reports will be updated.

The second change also increases openness. After each committee meeting a press release is issued to summarise important decisions or position statements, such as that on oral contraceptives containing gestodene or desogestrel. However, the nature of applications is not disclosed until a final decision has been made. The agency has shown that it is willing to listen to the concerns of consumers and health professionals, but they remain outside the regulatory process.

Eighteen months ago, in a letter to the Freedom of Information Campaign, Tom Sackville, parliamentary undersecretary for health, stated that the government intended "to seek the same degree of openness in the decentralised procedure as in the centralised one . . . that this should be underpinned by European Union legislation to ensure that all member states are equally open, and that work on this should await the outcome of results from the centralised procedure." Now that many companies have voluntarily submitted applications to the European Medicines Evaluation Agency, and it is evident that its relative openness does not deter them, this statement must be acted on.

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