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Transmission of Creutzfeldt-Jakob disease in corneal grafts

Observing the exclusion criteria for donated grafts should ensure the risk is small

The public and political profile of transmissible spongiform encephalopathies has changed dramatically with the identification of a new variant of Creutzfeldt-Jakob disease[1] and continued uncertainty about the size of the threat this may represent. Against this background, the Scottish Office confirmed last month that ocular tissue from a donor who was later found to have classic (sporadic) Creutzfeldt-Jakob disease had been transplanted into three patients. Press coverage of this announcement is certain to stimulate concern among potential recipients of corneal grafts and a reanalysis of measures to prevent iatrogenic disease transmission.

Iatrogenic transmission of Creutzfeldt-Jakob disease was first reported in 1974 in a 55 year old woman who developed symptoms 18 months after corneal transplantation from a donor who was found to have died of the disease.[2] Two similar cases have since been identified,[3] and the potential for transmission of spongiform encephalopathies, including Creutzfeldt-Jakob disease, via transplanted corneal tissue has been shown in animals.[4] As well as being a well identified route of entry for infection, the eye is thought to harbour a relatively high titre of the infective agent in Creutzfeldt-Jakob disease.[5]

Although implantation of any tissue may theoretically introduce infection, all known cases of iatrogenic Creutzfeldt-Jakob disease have resulted from exposure to brain or ocular tissue.[5] Prominent examples are transmission of Creutzfeldt-Jakob disease via human growth hormone derived from cadaveric pituitary pools and in association with dura mater patch grafting.[6] Recombinant technology is now used to manufacture pituitary hormones for therapeutic use, and dura mater patch grafts have not been used in Britain since the early 1990s. For the cornea, sterilisation of tissue for full thickness grafts is not possible and alternatives are not available. Artificial corneas are probably several years away.[7]

No information on infectivity during the incubation phase of Creutzfeldt-Jakob disease is available. Therefore truly accurate advice about the risk of acquiring the disease through an ocular tissue graft is impossible. For classic Creutzfeldt-Jakob disease the risk is vanishingly small. The lifetime risk of acquiring the disease is around 1/40 000 for a potential donor in the general population. Over 3000 corneal grafts are performed a year in Britain alone, and worldwide only three cases of corneal transmission have been reported in the past 20 years.

For the new variant of Creutzfeldt-Jakob disease the current prevalence is also unknown. In the worst case scenario, derived from projections based on mathematical models relating prevalence estimates to possible incubation periods for the new disease, up to 80 000 individuals may be affected,[8] giving a risk for encountering an infected donor in the British population (approximately 55 million) of around 1/700. More accurate risk estimates should be available with time. Meanwhile, it is probably reasonable to emphasise during patient counselling that this figure is based on a worst case estimate. Even assuming that these potential donors were all infective while incubating the disease, genetic susceptibility may be required to develop Creutzfeldt-Jakob disease after exposure.[5]

Since there is currently no method of screening for latent human spongiform encephalopathy the most practical step in risk management is probably to ensure that the exclusion criteria for potential eye donors are well disseminated. In addition to patients diagnosed with Creutzfeldt-Jakob disease and recipients of human pituitary hormones, current guidelines exclude any donors with unexplained neurological disease or central nervous system disease of unknown cause, including multiple sclerosis, motor neurone disease, and Parkinson's disease. Also excluded are patients with active viral disease, some ocular conditions, and haematological malignancies.

Most corneal donor tissue used for transplantation in Britain is stored at eye banks in Bristol and Manchester using organ culture methods. Bovine calf serum used in the organ culture medium is imported from countries free of bovine spongiform encephalopathy. Tissue can be stored for up to one month, and death from an unknown cause is not a contraindication to eye donation if a postmortem examination is pending. Clearly, however, accurate information about the cause of death must be communicated to the eye bank before transplantation.

Most corneal grafts result in a sustained visual benefit and considerable improvement in the quality of life.[9] The possibility of iatrogenic disease transmission in corneal grafts remains real—but a sense of proportion is required. For Creutzfeldt-Jakob disease, including the new variant, the risk may be no greater than that of other hazards associated with the

procedure, such as death from general anaesthetic, which are not normally rehearsed explicitly in preoperative discussions with patients.

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The emerging role of statins in the prevention of coronary heart disease

Statins are effective but we need better ways of assessing risk

See pp 1577 and 1615

The Standing Medical Advisory Committee guidelines for the use of statins have ignited considerable debate in Britain, and similar discussions about the use of statins are, or soon will be, occurring in other countries. The crux of the controversy lies, on the one hand, in earnest efforts to prevent coronary heart disease by any effective means available and, on the other, in fiscal realism. Such controversy has been foreseeable since publication of three clinical trials showing that statins are highly effective in preventing heart disease. The British guidelines conservatively recommend statin treatment only for individuals with at least a 3% annual risk of coronary heart disease events—a threshold selected to minimise costs and focus on patients at highest risk. Ironically, the subsequent *BMJ* editorial criticised the guidelines for being fiscally irresponsible,[1] whereas other issued guidelines and much of the journal correspondence[2] call for the treatment of more, not fewer, individuals.[3]

Three interrelated challenges confront efforts to determine the optimal use of statins: (*a*) sufficient definition of the benefits, costs, and risks of treatment based on data from randomised clinical trials; (*b*) innovative strategies to minimise treatment costs; and (*c*) improved methods for estimating individual patients' risk. It is now clear that treatment of hypercholesterolaemic patients with statins reduces the incidence of fatal and non-fatal myocardial infarctions by 30-35%.[4] These benefits are accompanied by fewer coronary revascularisation procedures and fewer strokes.[5] Additional potential benefits that have not yet been clearly shown include reductions in the incidence of anginal symptoms, congestive heart failure, disability, and unemployment and improved quality of life. Moreover, the cost effectiveness of statins in secondary prevention is comparable to, or better than, other standard preventive interventions.[6]

Nevertheless, several important gaps in our knowledge remain. The quoted reduction in coronary heart disease produced by statins in patients with heart disease was achieved in studies in which many of the participants were smokers and were not receiving aspirin or β blockers. Most of the benefit may have occurred in smokers receiving lipid therapy alone; conversely, statins may have produced additive or even synergistic effects in combination with non-lipid treatments like smoking cessation, aspirin, or β blockers. The incremental benefit from statin therapy in patients already receiving other standard interventions needs to be quantified.

Importantly, the cost effectiveness of statins in the treatment of individuals without clinical signs of cardiovascular disease has not been defined. Primary prevention is clearly less cost effective than secondary prevention because of the lower absolute risk of coronary heart disease, especially in the short term, in overtly healthy individuals. The paper by Caro et al in this issue (p 1577) is the third published analysis on the cost effectiveness of primary prevention with statins, and each comes to different conclusions.[7-9] Such analyses are necessarily complex and employ various models and assumptions at the discretion of the authors.[10] Also, some cost effectiveness research is supported directly by pharmaceutical companies, which have much to gain from increasing statin markets.[6 7] Therefore consensus on this issue will be difficult.

Cholesterol lowering treatment in the elderly, for whom little clinical trial data exist, presents additional questions. Older people are at high risk of coronary heart disease because of age, yet elderly people with low cholesterol values do not necessarily have less heart disease or survive longer than their hypercholesterolaemic counterparts.[11 12] Finally, with respect to safety, deaths from certain non-coronary causes, including cancer, accidents, and suicides, have been increased in some trials, and potential mechanisms are still being investigated.[13-15] Also, non-coronary morbidity outcomes have not been fully reported, and long term follow up has not yet accrued.

The purchase price of statins is the single largest determinant of the cost of lipid lowering therapy. Therefore, when healthcare resources are fixed, drug price very directly affects our ability to prevent

coronary heart disease. If purchasing leverage is used to drive competitive bidding for formulary contracts, considerable costs savings may be achieved (p 1616).[2] For example, the Veterans Health Administration has obtained a price reduction of nearly half [16 17] that of the typical purchase price of simvastatin in America (which is similar to that in Britain).

Clinical decisions about which patients to treat essentially entail estimating the risk of coronary heart disease. That risk is quite high in patients with clinically apparent coronary artery obstruction, and three quarters of such individuals will die from ischaemic heart disease. We agree with the guidelines regarding hypercholesterolaemic patients with atherosclerotic disease outside the coronary arteries (aortic, peripheral, or carotid). Their risk of coronary heart disease is also high and proportional to the severity of their atherosclerosis.[18-21]

Difficulties and differences of opinion arise over the treatment of apparently healthy people, and for them we can and must improve ways of assessing risk. The more accurately coronary heart disease is predicted, the more efficiently our treatment can be targeted, and the more coronary events we will prevent at the least cost and risk. This greater precision can be achieved by systematic and quantitative consideration of multiple risk factors. Total cholesterol is not the best lipid parameter—we recommend the ratio of total cholesterol to high density lipoprotein (HDL) because this single number captures most of the value of the full lipid profile in most patients.[22] Moreover, change in the total cholesterol:HDL ratio with treatment correlates with benefit in coronary heart disease better than other lipid measures.

Commendably, the Sheffield tables do quantify risk and, as well as cholesterol values, take into account age, gender, hypertension, current smoking, diabetes, and left ventricular hypertrophy on electrocardiography. However, we also know that early coronary heart disease in a first degree relative (before age 50 in men or 60 in women) increases an individual's risk and also helps to identify those with familial hyperlipidaemias. Other blood borne factors and genetic markers may soon be added to standard risk assessments.[22 23] Ultimately, the disease we are trying to predict causes morphological changes which may be imaged or otherwise measured, and this should lead us from indirect risk assessment to non-invasive measurement of the disease itself, atherosclerosis. Here, accumulating evidence is establishing the utility of detecting subclinical atherosclerosis by the ankle-brachial blood pressure index, carotid artery sonography, and detection of coronary calcifications.[24-27] The challenge is to offer doctors improved methods of risk stratification to use in their daily practice.

Irrespective of these deliberations, prescriptions for statins have jumped in Britain, and during 1997 in America annual sales of cholesterol lowering drugs increased by a remarkable 29% to $3.7bn (£2.3bn) (International Marketing Services). The great popularity of statins is largely a result of their efficacy and tolerability. However, we should also be cautious with these powerful drugs, for the reasons discussed above. Moreover, the comparable ease of reducing cholesterol concentrations by pharmacological means should not substitute for multiple risk factor interventions, including non-pharmacological approaches to preventing coronary heart disease.

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Management of head and neck cancer in Britain

Plenty of room for improvement

See p 1589

Surgical and radiation oncologists will readily disagree over many aspects of cancer management but one point is widely accepted: patients with head and neck cancer probably present the greatest challenge of all. Apart from the obvious difficulty of assessing a range of treatment strategies for an unusually wide number of primary sites (larynx, pharynx, oral cavity, paranasal sinuses, etc) and the consequent difficulty in comparing outcomes, so many patients have to face devastating treatment consequences as the price of cure. What is more, although the incidence of head and neck cancer is rising,[1] the relatively small number of patients—fewer than 5000 new cases a year in Britain—has slowed cooperative efforts in building worthwhile databases or, better still, mounting prospective clinical studies large enough to provide meaningful results.

The brief report by Edwards and colleagues in this week's issue provides a disturbing overview of current provision for the treatment of head and neck cancer in Britain (p 1589).[2] To discover, for example, that almost a half of consultants had no access to a joint clinic forum (or, worse, chose not to use such an opportunity) is astonishing. How else to decide on a management plan in a patient who might better be treated by non-surgical than surgical means? Or might be suitable for a clinical trial? Or might be best managed by a combination of surgery with planned postoperative radiotherapy? In my own practice I have certainly been aware of patients arriving for a second opinion on the options for management of a locally advanced lymph node positive cancer of doubtful operability. These patients had previously been assessed only in a surgical clinic and been recommended to undergo a radical, mutilating, and demanding operation with virtually no hope of cure by surgery alone.

How much better calmly to assess such a patient within a joint clinic with proper attention paid to the contributions of the surgeon, radiation oncologist, specialist nurses, dental hygienist, speech therapist, dietitian, and other essential members of the group.[3] Many would contend that only by working within such a setting, and seeing a large throughput of patients, can one have any hope of developing enough expertise to provide the best possible advice to these especially unfortunate patients. Yet, as Edwards et al report, the average number of patients encountered by surgical specialists is fewer than 10 per consultant a year, even allowing for joint management. Fewer than half of the consultants returning their questionnaire treated more than 10 cases a year at any anatomical site. The competence of the more experienced consultants was clearly illustrated by the observation that those who treated more cases at any one site were also more likely to record tumour stage[4] —an essential feature of patient documentation crucial to any attempt at treatment comparisons.

Discovering that fewer than half the consultants had access to either nurse specialists (40%) or counselling services (35%) lowered my spirits still further. Few, if any, patients have greater need for the skills of these professionals.[5 6] Which breast or colorectal cancer clinic could manage without either, yet still retain credibility as a top-class teaching facility or service provider? Who oils the wheels in the complex business of rehabilitation after, say, a complex operation such as laryngopharyngectomy with partial glossectomy and radical neck dissection? Operations for head and neck cancer must be among the most demanding undertaken, even for the most well adjusted and well supported of patients. Yet typically patients with head and neck malignancy are often socially disadvantaged, with little or no domestic support, a history of heavy reliance on alcohol, and exceptionally poor general health. Ironically, this type of surgery may often result both in an unusually lengthy hospital admission and a challenging period of home based non-oral nutrition, typically nowadays by percutaneous endoscopic gastrostomy feeding. Recovery in the community will consequently be all the more difficult.

The findings of Edwards et al make for gloomy reading. The clear message is that we need to do far more than pay lip service to the concept of the team approach recommended for so long[6] and that treatment decisions should be far more thoroughly discussed before implementation than is currently the case. We also need much better access to support and rehabilitation services and an insistence that more care be taken in documenting all relevant tumour details, using a standard system such as the recently revised TNM. Better still, as many patients as possible should be treated within a well designed prospective clinical trial such as UKHAN 1, one of a portfolio run by the United Kingdom Coordinating Council for Cancer Research.[7] How can we realistically expect any progress unless we make these simple and professionally rewarding changes?

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Hazardous drugs in developing countries

The market may be healthier than the people

The international pharmaceutical market shows substantial regional differences in availability and promotion of drugs.[1] This variation depends on affluence, health requirements, capacity for local manufacture, and the restrictions which countries may impose to control dangerous or inappropriate use of drugs.[2 3] Because of their limited industrial base, most developing countries import most of their drugs, and transnational corporations are adept at exploiting variations in such markets.[1] Commercial interests may conflict with public health needs in developing countries,[4-6] particularly when people are poisoned due to inadequate restriction of pharmaceutical use, misleading advertising or labelling, or frankly bogus products.

Promotion of unsafe drugs in the developing world has long attracted criticism, particularly when products have been banned or restricted in the country of manufacture.[3 5] Pharmaceutical adverts, labelling, and package inserts in developing countries often show the twin problems of exaggerated indications and minimised adverse effects.[1 5 6] Drug exports from the United States to developing countries were reviewed independently in 1993 and found to have "severe labelling deficiencies," in many cases posing life threatening risks.[7] Locally produced drugs have labelling problems which may exceed even those of imports.[5]

A further problem arises from unscrupulous entrepreneurs whose bogus merchandise mimics acceptable drugs. Whether manufactured locally or imported from the West, such counterfeit drugs can be dangerous,[8] particularly when contaminated. Unethical promotion and counterfeiting are compounded by several factors: inconsistent import, export, and quality controls[3]; the dominance of private pharmacies and self medication[9]; direct advertising to pharmacies and consumers[5 6]; and the fact that promotional material may be the main information available to prescribers.[1 3]

Promotion of expensive brand names increases apparent choice but can also hobble developing countries' efforts to meet pharmaceutical needs by bulk purchase or manufacture of essential generics.[1 3 6] Ironically, "humanitarian" drug donations may serve donor companies (through brand awareness and tax incentives) more than recipient countries, which commonly suffer disposal costs (or toxic consequences) from inappropriate or poorly labeled drugs.[10]

The health impacts of inappropriate pharmaceutical exports have included multiple fatal poisoning,[3 11 12] the spread of antibiotic resistant infections,[3 13] and a host of problems arising from the mismanagement of diarrhoea in children.[4 14] Women and children appear particularly susceptible to the health problems associated with the unrestricted use of particular pharmaceuticals.[3 11 12] Inappropriate promotion of some products (such as stimulants to treat "lethargy" in children) is also lamentable, as it diverts attention and resources away from fundamental public health needs.[1 13]

Control of hazardous drugs is an international imperative. Threats to public health posed by inconsistent control of various chemical hazards have prompted the United Nations to publicise existing regulations, ostensibly to encourage international consensus.[2] A compendium of restricted pharmaceutical, agricultural, industrial, and domestic products has been systematically updated since 1982.[2] Analysis of the pharmaceutical section indicates that a country's capacity to restrict dangerous drugs depends heavily on its wealth, as illustrated by the strong correlation of restrictions with per capita gross national product ($r = 0.65$, $n = 162$, $P < 0.001$). This dismal picture may underestimate the true extent of the disparity, since poor countries with notable restrictions (including Bangladesh, Ethiopia) lack administrative machinery to police these.[3 13]

The gravity of the situation has prompted resolutions from the World Health Organisation, the United Nations, and other corporations against inappropriate export and promotion of drugs. But whether such non-binding agreements help is debatable,[3 5] and an enforceable code is lacking. Despite evidence of progress since the 1970s, some transnationals continue to promote irresponsibly, exploit frail national restrictions on imports, and behave in other unethical ways, for example offering doctors "commissions" for prescribing.[1 6]

Inappropriate pharmaceutical promotion has also been challenged by non-governmental organisations. For example, lobbies such as Health Action International[3] and the Medical Lobby for Appropriate Marketing[1] monitor and publicise improper marketing and use of drugs. These lobbies also encourage governments and industry to invest in the development and appropriate use of antibiotics, contraceptives, and other (generally unprofitable) essentials for developing countries.[13]

With pharmaceuticals as with other technologies, unrestricted market forces do not always work in favour of public health, particularly in countries with the most urgent needs. While sustainable economic development will be necessary finally to relieve the excess burden of illness in poor countries,[13] steps can be taken now to use available resources more appropriately. Rational use of cost-effective pharmaceuticals is an achievable priority, and enforceable agreements are required to control promotion of inessential and hazardous agents.[1 3] The medical community has a role to play in this effort, as it can influence both industry and government policy. Whatever their political leanings, doctors inevitably have a stake both in the control of hazardous technology and in the appropriate use of medicines.

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Developing www.bmj.com

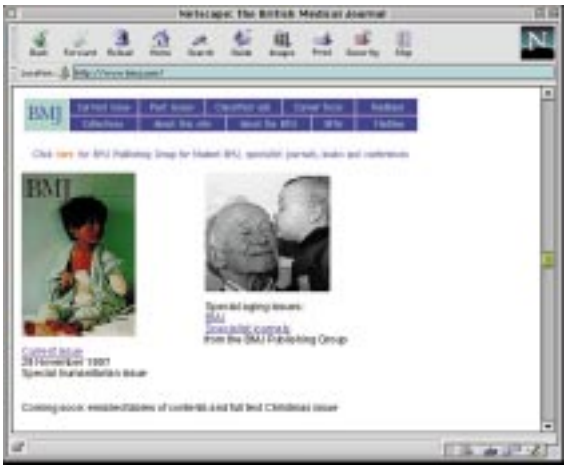
Full text current issues available from the world wide web in March

The world wide web looks like becoming the most rapidly adopted communications medium ever. By next year 25% of American households will be connected to the web—just five years after its creation. Telephones took 35 years to achieve similar penetration of households, television 26 years, and radio 22 years (M Chong, personal communication). The rest of the developed world may be a few years behind the United States, but there is little doubt about the direction in which it is heading. The ability to connect to the internet from the domestic television is likely to accelerate the rate of its adoption.

The number of visitors to the *BMJ*'s website has been climbing steadily over the two and a half years since its inception and, on current projections, will overtake the number of non-member subscribers to the paper journal (17 000) by the middle of next year. The internet gives us unrivalled reach, with readers from 100 countries visiting our site each week,[1] 40% of whom "rarely or never see the paper journal," according to our recent online questionnaire.[2] Some 70% of users come from outside the United Kingdom. One of our original aims—to reach those parts of the world that the paper journal doesn't[3]—has been achieved.

Since we launched our website, massive commercial investment has unleashed a wave of innovations in web technology, many of them directly relevant to online publishing. Lacking the skills to exploit these ourselves, we looked elsewhere for help and have appointed HighWire Press to develop our website. A division of Stanford University's Green Library, the press has a mission to "foster research and instruction by providing a more direct linkage between the writers and readers of scholarly materials."[4] Having watched library budgets fall and the cost of journal subscriptions rocket, its librarian-directors were quick to spot the internet's potential to change the economics and efficacy of publishing.

Within just three years of operation, HighWire has attracted 27 journals to its electronic stable, including *Science* and *Blood*. No single source can boast a more highly cited collection of science, technology, and medical journals, and by mid-1998 another 70 journals will have moved their online versions to HighWire. Paul Saffo of California's Institute for the Future recently described HighWire as "one to watch—certainly one of the most exciting developments on the web."



The *BMJ*'s web site, which last month was the highly commended runner up for the Charlesworth Group Award for Electronic Journals

The *BMJ*'s website moves to HighWire in March. Initially, the site will provide the full text of the paper journal (including links to the classified supplement) and allow users to nominate the topics on which they want to be kept informed. A searchable archive of past issues will be added, as will further features allowing users to customise the site according to their interests. Access to the site will continue to be free, although this policy will be kept under review. (Unexpectedly, publishers have found that giving away electronic versions of paper publications has increased rather than decreased paper sales.[5])

These are fast moving times for the journal and the BMJ Publishing Group. Next year will also see substantial developments in the internet presence of the group's 30 specialist journals and of the BMJ Bookshop.

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1 Web server statistics for *BMJ*. www.bmj.com/stats.html
2 Online questionnaire 13-20 October 1997. www.bmj.com/siteinfo/quest.htm
3 Delamothe T. *BMJ* on the internet. *BMJ* 1995;310:1343-4 (www.bmj.com/archive/6991e-1.htm).
4 About HighWire Press. highwire.stanford.edu/about.shtml
5 Berselli B. Read it and weep: online publishing actually boosts sales. *Washington Post* 1997; 30 Sep:C1-2.