provide information about medicines,⁸ but both professions are busy and may forget. Furthermore, any verbal instructions may be forgotten, and patients may be confused by technical jargon.^{9,10} Many think that not enough is explained by doctors or pharmacists^{6,7} and would welcome more information. The Association of the British Pharmaceutical Industry (ABPI) has inquired into providing written leaflets, and after reviewing published evidence and consulting the royal colleges and allied faculties, numerous other professional bodies, and consumer groups it has recommended in a discussion document that printed leaflets should be provided with medicines. The definitive document will be available in the autumn.

If the recommendation is accepted various problems will need to be resolved. The first is the type of information to be given. Fortunately, a consensus exists that the information needs to be brief, concise, and comprehensible and should reinforce rather than replace that given by doctors and pharmacists. The items covered should include the name of the medicine, when and how to take it, side effects and what to do about them, precautions such as possible effects on driving, possible interactions with alcohol or other drugs, the purpose of treatment, and how long to take it.⁷ The leaflet might also cover what to do if a dose is missed, how to tell if the medicine is not working, and how to store the medicine safely and dispose of any left over.

The second problem is who should be responsible for writing the leaflets and keeping them up to date? The ABPI working party has concluded that it should be the manufacturer. There are, however, potential hazards in this recommendation as some manufacturers might attempt to include too much information to protect themselves against litigation. Others might use leaflets for advertising. The alternative might be that a professional organisation such as the British Medical Association or the Pharmaceutical Society of Great Britain could produce generic leaflets that could be adapted by each manufacturer. But, whoever undertakes this task, leaflets must be checked for readability as the average Briton has a reading age of only 9 years. Special leaflets may need to be prepared for those who do not speak English and the blind.

A third question is who should distribute the leaflets? It might be either the doctor or the pharmacist. Most patients do not mind who does it so long as they receive the information. Some doctors will prefer to distribute the leaflets themselves, but experience suggests that few will remember to do this routinely.¹¹ The working party considered that distribution by means of original pack dispensing would be the most reliable and economic method. In addition, it has recommended that a compendium of leaflets should be made available to doctors and pharmacists and for patients' reference. This compendium could contain additional, more detailed information on each product.

The ABPI discussion document also examines some legal and ethical implications of giving information to patients. Under the Medicines Act 1968 and the Medicines Leaflet Regulations 1977 this information must include "contraindications, warnings, and precautions" and be consistent with the product licence. Failure to have leaflets approved by the licensing authorities renders the manufacturers liable to criminal sanction. The existing regulations may encourage some manufacturers to put in too much information and therefore confuse many patients. One way of overcoming this problem might be to include a statement that "the information in this leaflet is limited; further details can be obtained from your doctor or pharmacist."

With these and other problems to be resolved doctors are bound to ask "Is it all worth it?" In my view the answer must be "yes." Patients expect more information than they receive now, and there is a clear need for it. Their knowledge about side effects is poor, and many do not swallow their tablets or capsules with either food or fluid. Furthermore, many patients do not know how to store their medicines safely or dispose of those that are left over.^{6,7} Studies have shown that knowledge of these items can be improved with written leaflets,¹² and for antibiotics compliance is enhanced.^{13,14} More importantly, patients' satisfaction with both the information they have been given and treatment in general is significantly improved.^{11,13} At a time when both public expectations and litigation are increasing these improvements in doctor-patient communication should be welcomed.

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Genetic engineering and corneal grafting

There are about 20 million blind people in the world, and the commonest cause of blindness is a scarred cornea, which can often be helped by a corneal graft; but a graft will remain transparent only if enough of its endothelial cells have survived to keep the cornea dehydrated. Now for the first time endothelial cells have been made to replicate in vitro by scientists using a recombinant epidermal growth factor.

Normally endothelial cells stop replicating after birth, and their numbers dwindle from about 5000/mm² at birth to half that number by the age of 40. The cells are frail, and both surgical manipulation and storage may destroy them: about a fifth die in most keratoplasties. If the number of cells falls to a quarter of the initial population then intractable corneal oedema results, and most surgeons are reluctant to use corneas more than a day or two after the donor's death.

The supply of donor eyes is limited and almost non-existent in most Third World countries, where the demand is greatest. The need for a reliable method of long-term storage has thus been great. Over 20 years ago Mueller *et al* first reported a satisfactory way of deep freezing corneal discs.¹

This allows some corneas (stored in liquid nitrogen at -197°C for as long as eight years) to maintain a normal endothelium, which is valuable when tissue typed material is needed—for instance, when the rejection rate is high because the recipient has a heavily vascularised cornea. But the costs of establishing a bank of antigen-labelled corneas are formidable, which, together with the hazards of deep freezing and thawing, have greatly restricted its use. McCarey and Kaufmann then developed a medium for storage above zero, which was widely used, and particularly its most recent derivative K Sol. Corneas have also been stored in a tissue culture at room temperature in Denmark and in Minneapolis,² but this is expensive, requires expert supervision, and inevitably carries a greater risk of infection.

The latest important innovation comes from East Grinstead, where the researchers have used recombinant human epidermal growth factor to produce in vitro replication of endothelial cells in 87 cadaver corneas from patients aged between 6 months and 80 years.³ Clearly defined mitotic figures in all states of cell division are seen throughout the endothelial layer. The endothelial population of donor corneal discs may thus be increased simply by incubating them for about four days in a tissue culture medium that is laced with the growth factor. The growth factor is potentially available in pure form and in unlimited quantities.

Other exciting possibilities suggest themselves. The growth factor might be added to standard short term media and so enlarge the scope for elective surgery: there might be time for HLA matching, which should reduce the many donor eyes that now go to waste. The growth factor might even be used to stimulate the decompensating endothelium of Fuch's dystrophy—perhaps by injecting it into the anterior chamber, and this might postpone or even avoid the need for keratoplasty.

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Red cell antibodies

Since the discovery of the Rh(D) blood group its association with erythroblastosis fetalis (haemolytic disease of the newborn) has become well understood.^{1,2} The introduction of prophylactic anti-D immunoglobulin produced a dramatic fall in the incidence of the disease between 1969 and 1976.^{3,5} The fall has not, however, been maintained because some patients are not being offered prophylaxis and some are not given the anti-D immunoglobulin properly; another problem is spontaneous antenatal sensitisation.⁶

The decrease in rhesus isoimmunisation has produced a relative increase in the number of other red cell antibodies found in the sera of pregnant women.⁶⁻¹⁰ Most arise from the non-rhesus system. In general, they cause only mild haemolytic disease of the newborn but severe disease and stillbirths have been reported in association with anti-c, anti-Kell, anti-f(c), anti-S, and anti-M antibodies.^{6,11-14} Anti-c antibody is the most likely to cause important

disease,^{6,10,15} but other antibodies that may harm the fetus have been listed by Beal.⁸

The incidence of non-rhesus red cell antibodies in pregnant women is difficult to define but seems to be about 2-5%; 65-85% of this group are patients who are rhesus (D) positive. All pregnant women must therefore be tested for the antibodies. Their potential for causing haemolytic disease of the newborn is related to the type of antibody formed and its ability to cross the placenta. IgG antibodies (subclasses IgG1 and IgG3) are the most dangerous, whereas IgM antibodies have little effect. Many of these antibodies arise from previous blood transfusions. Paternal serum should be tested for the antigen, and if it is not found there is no risk of isoimmunisation.

The presence of the antigen in the father's serum may result in maternal antibodies appearing late in pregnancy. Bowell *et al* noted that a third of red cell antibodies, including anti-D antibodies, were not found in the first specimen tested, and often they did not appear until after week 28 of the pregnancy.¹⁰ In this group the resulting haemolytic disease of the newborn was less severe for both anti-D and anti-c antibodies. But preterm infants commonly suffer from jaundice, and any factors that increase the bilirubinaemia—such as haemolytic disease caused by either rhesus or non-rhesus antibodies—will increase the chance that an exchange transfusion will be needed, a procedure that carries its own morbidity.

The most serious risk from red cell antibodies (other than anti-D antibodies) is not to the fetus but to the mothers. Indeed, any patient (not just pregnant women) whose serum contains irregular antibodies is at risk of a haemolytic reaction if given an emergency blood transfusion. Even O rhesus negative blood may be harmful if the patient's serum contains anti-c or anti-e antibodies as the donor serum will contain a double dose of these antigens. Red cell antibodies should therefore be identified well before labour or any elective surgical procedure to ensure so far as possible that compatible blood is available—few district hospital laboratories will hold adequate supplies because many red cell antibodies are now known to exist.

Although the case for testing all pregnant women for red cell antibodies seems proved, the frequency of performing these investigations has to be a balance between the benefit and an acceptable laboratory workload if results are to be obtained within a realistic timetable. A reasonable programme would be to test all patients at their first visit and again at 34 weeks' gestation. If anti-D, anti-c, or anti-Kell antibodies are detected and the consort's serum contains the antigen the tests will need to be done more often. A similar protocol for detecting other red cell antibodies does not seem justified unless regional and international variations dictate otherwise.

Amniocentesis at ultrasound scanning may be necessary for further evaluation of the fetal condition if the serum antibody titre is high or rising, and induction of labour before the expected date of confinement may sometimes be necessary.

The detection rate of red cell antibodies in serum is likely to increase and consequently the number of patients at risk will rise. All doctors who give blood products to any patient, especially premenopausal women, should remember that they are performing a "tissue transplant"—and it should perhaps be afforded the same respect as an organ transplant.

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