while the traffic club scheme is being planned. This venture must not become bogged down in protracted negotiations; for ultimately it could have a pervasive influence in reducing death and disability well beyond the age of 5.

DAPHNE GLOAG

Staff editor, *BMJ*

- 1 Department of Transport. *Road accidents Great Britain 1986. The casualty report*. London: HMSO, 1987:103.
- 2 Downing CS. Improving parental road safety practice and education with respect to preschool children. In: Foot CH, Chapman AJ, Wade FM, eds. *Road safety research and practice*. Eastbourne: Praeger, 1981:93-101.
- 3 Sadler J. *Children and road safety: a survey amongst mothers*. London: HMSO, 1972. (Government Social Survey report.)
- 4 Transport and Road Research Laboratory. *My traffic book*: 1-5. London: London Residuary Body, 1985-7. (Adapted for "Streetwise Kids" from TRRL material; obtainable from London Accident Analysis Unit, London Research Centre, County Hall, London SE1 7PB.)
- 5 Schioldborg P. *Children, traffic and traffic training. An analysis of the "Children's Traffic Club."* University of Oslo: Psychological Institute, 1974. (English translation from TRRL.)
- 6 Downing CS, Murray G, Durow C. *Trials of a road safety booklet for a pre-school traffic club*. Crowthorne: Transport and Road Research Laboratory, 1981. (TRRL laboratory report 992.)

Antidepressants and skin disease

Many patients with chronic skin problems have depression, which may often be unrecognised, and some will improve when treated with antidepressants. Itch and sleep disturbance, for instance, are common in those with chronic skin conditions and may be helped by antidepressants, particularly trimipramine. Recently, however, it has become apparent that antidepressants may help in some skin conditions even when the patient is not depressed.¹ They have been used with some success to treat chronic urticaria, angioedema and dermatographism, idiopathic cold urticaria, nocturnal pruritus in atopic eczema, postherpetic neuralgia, and the pain of diabetic neuropathy.¹

Imipramine was discovered in the search for antihistamines, as was chlorpromazine. Tricyclic antidepressants, benzodiazepines, and phenothiazines are closely related—like car keys with small variations. How they work is still not clear, but they inhibit uptake of noradrenaline and so potentiate sympathetic activity. They can reduce skin blood flow, lower skin temperature, and reduce sweating. They also are sedatives, antiemetics, muscle relaxants, and local anaesthetics.

So far as the individual drugs are concerned patients with chronic urticaria and dermatographism may benefit particularly from doxepin²⁻⁵; those with postherpetic neuralgia from pimozone and trimipramine⁶; and those with chronic aphthous ulcers from phenelzine.⁷ Emotional factors are important in these conditions. Amitriptyline has relieved unilateral itch after strokes,⁸ and naloxone helps the pruritus of cholestatic jaundice, illustrating that endorphins may have a central modulating effect on itch.⁹

Epiphenomena are part of all chronic illnesses, and when they are not readily explained they are often assumed to have psychological origins. Sometimes this is true, but doctors may overestimate the number of problems that have psychological origins.¹⁰ Nevertheless, antidepressants may often be indicated in patients with skin problems. They may also be indicated for patients whose problems are purely dermatological,

particularly for the urticarias, pruritus, and other pain related syndromes.¹

Antidepressants do, however, have many side effects, and they may interact with other drugs. They should not therefore be used as a substitute for thought and proper evaluation, especially when "waiting and seeing" is an option.

P C H NEWBOLD

Consultant Dermatologist,
Worcester Royal Infirmary,
Worcester WR1 3AS

- 1 Gupta MA, Gupta AK, Ellis CN. Antidepressant drugs in dermatology: an update. *Arch Dermatol* 1987;123:647-52.
- 2 Richelson E. Tricyclic antidepressants and histamine H1 receptors. *Mayo Clin Proc* 1979;54:669-74.
- 3 Sullivan TJ. Pharmacological modulation of the whealing response to histamine in normal skin: identification of doxepin as a potent in vivo inhibitor. *J Allergy Clin Immunol* 1982;69:260-7.
- 4 Guin JD. Treatment of urticaria. *Med Clin North Am* 1982;66:831-49.
- 5 Monroe EW. Chronic urticaria—a review of drug management. In: Champion RH, Greaves MW, Black AK, Pye RJ, eds. *The urticarias*. Edinburgh: Churchill Livingstone, 1985:205-11.
- 6 Duke EE. Clinical experience with pimozone: emphasis on its use in post-herpetic neuralgia. *J Am Acad Dermatol* 1983;8:845-50.
- 7 Rosenthal S. Does phenelzine relieve aphthous ulcers of the mouth? *N Engl J Med* 1982;311:1442.
- 8 Massey EW. Unilateral neurogenic pruritus following stroke. *Stroke* 1984;15:901-3.
- 9 Greaves MW. The nature and management of pruritus. *Practitioner* 1982;226:1223-5.
- 10 Baughman RD, Sobel R. Emotional factors in psoriasis. In: Farber EM, Cox AJ, eds. *Psoriasis; proceedings of 2nd international symposium*. New York: Yorke Medical Books, 1977:180-8.

Drug regulation: evolution or revolution?

The history of drug regulation in Britain has been one of evolution.¹ From the Arsenic Act of 1851 to the Medicines Act of 1968 each legislative step has been prompted by parliamentary, professional, or public concern over particular aspects of the manufacture, promotion, prescription, or sale of medicines. The Medicines Act, stimulated by the thalidomide disaster, created the licensing authority (represented for human medicines by the health ministers) with powers to grant (or revoke) product licences for the sale or supply of medicines and made it an offence to market a drug without such a licence. In discharging its responsibilities the authority obtains advice from committees established under the act, of which the Committee on Safety of Medicines is the most widely known. Although the Committee on Safety of Medicines is only advisory, the licensing authority has rejected its views only very rarely. The committee is thus extremely influential in deciding which drugs should be available on the market.

Recently radical proposals have been put forward by Dr David Green, director of the Institute of Economic Affairs' health unit, who believes that the British licensing system has failed.² He claims that current regulatory requirements impose important additional costs and delays in drug development; preclinical toxicity studies have not proved a wholly reliable indication of safety in man; the licensing system fails to take enough account of the true nature of the risks and benefits of new medicines; and as a result some drugs that might have been effective have been rejected while others have been approved and later found to be toxic.

Green therefore suggests that our licensing procedure should be abandoned and replaced by systems whereby the decision whether a drug should be marketed would rest

with the manufacturer; independent "professional trustees" would publish non-binding "appraisals" of drugs to guide doctors and patients; and patients would have greater access to the courts to take action for negligence where they suffer harm from drug treatment.

Green's criticisms have some merit. A regulatory authority inevitably imposes some delay while submissions are critically reviewed, but, as Green admits, the bureaucratic delays in Britain are slender compared with those in the United States, where commentators have looked enviously at the relative speed with which new drugs reach the market in Britain.^{3,4} Green is also right in pointing out that the development time for new drugs to reach the market has increased substantially over the past 25 to 30 years, but he is wrong to conclude that the increase is necessarily caused by the demands of regulatory authorities.⁵ In truth drug development has become much more complex during the past 25 years because of advances in pharmacology, toxicology, and clinical medicine. And, although preclinical toxicology is unable to detect all the possible hazards that might occur during widespread use with a new compound, modern techniques ensure that most type A reactions are recognised by the time a new drug is marketed⁶; with our current arrangements tragedies such as the sulphonilamide and Stalolin disasters are unlikely to recur. A better solution to the adverse economic consequences of protracted development times might be to extend the patent life of new drugs.

Whether or not the Committee on Safety of Medicines takes "sufficient" account of risks and benefits when making recommendations is more difficult to confirm or refute. For, while benefits and risks can each be scientifically investigated and measured, the trade off between them is usually based on judgment. In circumstances where a drug either cures or produces a worthwhile remission in an otherwise lethal or untreatable condition the judgment is easy: the decision to license zidovudine (Retrovir), despite its known toxicity, for treating the acquired immune deficiency syndrome is a recent example. Risk-benefit assessments are also straightforward where a product's safety profile is clearly out of proportion either with the natural course of the disease for which it is indicated or with other treatments.

Trade offs are less easy for drugs offering modest symptomatic relief for the many at the expense of serious toxicity for the few. Such fine judgment is, of course, part of the daily practice of medicine, and membership of the Committee on Safety of Medicines is drawn predominantly from among doctors engaged in clinical practice.⁷ Without entering into metaphysical arguments about whether the committee's judgments are "sufficient," it is most unusual for drugs that are licensed in Britain to remain unavailable in other developed countries for long. By contrast, there have been instances where drugs denied licences in Britain have been associated with serious problems after marketing elsewhere in the world. The British regulatory system has a good record and international reputation.

The prospect of replacing our licensing procedures with a system based on legal tort would have little appeal to the pharmaceutical industry, doctors, pharmacists, or patients. Leaving aside the real difficulties in establishing causation (as opposed to association) in suspected cases of iatrogenic disease, much of the population—that is, those too wealthy to qualify for legal aid but too poor to pay what may be

enormous costs—would be unable even to contemplate the risks of taking an action. Many cases, moreover, would result in legal wrangles about apportioning responsibility among manufacturer, prescriber, and dispensing pharmacist. The only beneficiaries would, I suspect, be lawyers and clinical pharmacologists (retained as expert witnesses for both plaintiff and defendants). The absence of a statutory licensing mechanism would also remove the present basis for controls on promoting and advertising medicines. The lessons from history,¹ and from those developing countries which lack effective drug regulatory controls,⁸ would have to be learnt again.

There is one practical problem with deregulation which Green ignores. The Treaty of Rome aims at creating a complete "internal market," including pharmaceuticals, within the European Community. Since 1965 a series of directives has been agreed between member states harmonising the broad criteria for granting licences—that is, quality, safety, and efficacy—and the scientific data to support marketing applications.⁹ Although member states retain the power to make their own decisions, Britain could not move unilaterally down the road Green advocates without abrogating its obligations under European Community law.

There may well be a need for evolutionary changes in the administrative arrangements covering drug regulation. Indeed, the Secretary of State for Social Services has set up an inquiry to review the arrangements for processing licence applications. In due course the Medicines Act itself will no doubt need revision to take account of changing scientific, political, and social circumstances. The deregulatory option, however, is in the interests of neither producers, prescribers, nor patients—and it isn't really possible.

MICHAEL D RAWLINS

Professor of Clinical Pharmacology,
Wolfson Unit of Clinical Pharmacology,
The University,
Newcastle upon Tyne NE1 7RU

- 1 Mann RD. *Modern drug use: an enquiry based on historical principles*. Lancaster: MTP Press, 1984.
- 2 Green DG. *Medicines in the marketplace*. London: IEA Health Unit, 1987.
- 3 Wardell WM. The drug lag revisited: comparison by therapeutic area of patterns of drugs marketed in the United States and Great Britain from 1972 through 1976. *Clin Pharmacol Ther* 1978;24:499-524.
- 4 Wiggins S. The effect of US pharmaceutical regulation on new introductions. In: Lindgren B, ed. *Pharmaceutical economics*. Stockholm: Stockholm Institute for Health Economics, 1984:191-205.
- 5 Dukes G. *The effects of drug regulation*. Lancaster: MTP Press, 1985.
- 6 Rawlins MD, Thompson JW. Mechanisms of adverse reactions to drugs. In: Davies DM, ed. *Textbook of adverse drug reactions*. Oxford: Oxford University Press, 1985:12-38.
- 7 Rawlins MD. Risk-benefit decisions in licensing changes. In: Walker SR, Asscher AW, eds. *Medicines and risk/benefit assessment*. Lancaster: MTP Press, 1987:137-42.
- 8 Melrose D. *Bitter pills*. Oxford: Oxfam, 1982.
- 9 Commission of the European Communities. *The rules governing medicaments in the European Community*. Luxembourg: Office for Official Publications of the European Communities, 1984.

Correction

Glasnost on pesticides

We regret that an error occurred in the article "Glasnost on pesticides" (9 January, p 81). In the last sentence of the penultimate paragraph the word patents was misprinted as patients. The sentence should have read: "Perhaps with adequate protection of patents a fair arrangement for the release of data could be agreed."