

Reports on Individual Drugs

Control of *Ascaris lumbricoides*: selective or community therapy?

It is probable that as many as 25% of people throughout the world are host to the nematode, *Ascaris lumbricoides* (1). The large majority of infected persons harbour only one or two worms and — because these do not multiply within the host — they induce no symptoms. The one million cases of ascariasis disease that are estimated to occur each year (2) are the consequence of repeated ingestion of ascariis eggs, which exist in large numbers in endemic areas both in the soil and the environment at large. At greatest risk are children in the exposed communities — particularly those who, because of malnutrition or deficiency of vitamin A, are susceptible to pneumonia and diarrhoeal disease (3–4).

The intensity of this contamination has been claimed to correlate with the quality of sanitation and with broader measures of socioeconomic development (5). However, within these communities, the worm load is considerably greater in some individuals than in others exposed to comparable risk (6). Because of the rapidity at which reinfection occurs, mass chemotherapy has to be sustained for long periods and to be linked with other control measures if tangible results are to be obtained (7). It has consequently been proposed that selective treatment of the intensively infected minority is more rational, notwithstanding the cost of identifying these individuals, than indiscriminate mass treatment (8).

None the less, convincing evidence has recently been obtained to show that selective chemotherapy does not offer a viable approach to control where it is most needed (9). With the aim of studying the prevalence and intensity of reinfection among people living in Dhaka, Bangladesh, a sample of 880 adults and children were treated with a single dose of pyrantel pamoate (11 mg/kg body weight) on 3 occasions at 6-month intervals. This regimen has been estimated to cure 90–95% of ascariis infections (10). After each treatment, the worms expelled by each subject were counted and weighed. The most notable conclusion to emerge from the analysis of the results was that rapid recurrence of heavy infections was common, and

that such recurrences did not tend to develop in the same subgroup of patients after each round of treatment. Indeed, nearly two-thirds of all subjects — and more than 70% of schoolchildren — were shown to be heavily reinfected on at least one occasion within the context of the study.

If this pattern of infection proves to be typical, the absence of any definable subgroup of individuals “predisposed” to heavy infection will imply that selective chemotherapy can never be efficiently targeted. Mass treatment, particularly of children — whose health and development are now recognized to be seriously compromised by intestinal parasites (11) — merits high priority wherever these diseases are endemic. The development of albendazole and other less expensive benzimidazoles as single-dose, broad-spectrum anthelmintics promises to bring a simple and practicable system of community-based treatment to the school-age population in many countries.

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Ofloxacin: promise as an anti-leprosy agent

Antimicrobial resistance has resulted in multidrug therapy becoming standard practice in the treatment of leprosy. Regimens based on rifampicin, clofazimine and dapsone are the most practicable and reliable that have yet been devised. However, since clofazimine and dapsone are only weakly active against *Mycobacterium leprae*, it is important to search for new bactericidal agents with novel mechanisms of action. Their addition to such regimens might not only increase efficacy and further shorten the duration of treatment (1), they might also curb the continued emergence of strains of *M. leprae* resistant to the currently-used drugs, and to rifampicin in particular.

Ofloxacin, which is a member of a new generation of fluorinated quinolones structurally related to nalidixic acid, has been identified as a promising candidate for this purpose. Like other quinolones, it inhibits the enzyme DNA gyrase, which controls supercoiling of DNA in bacteria (2), and it has a broad spectrum of antibacterial activity which embraces most Gram-negative bacteria, many Gram-positive bacteria and some anaerobes. Of three quinolone derivatives tested (ciprofloxacin, ofloxacin and pefloxacin), ofloxacin alone exhibited significant bactericidal activity against *M. leprae* in the mouse footpad system (3-6). This activity has been confirmed in small-scale trials in leprosy patients (7, 8). Indeed, the results have been encouraging to the extent that a large-scale, multicentre, field trial has been organized under the aegis of WHO, with a view to comparing the efficacy, safety and acceptability of combined regimens containing ofloxacin with the regimens currently recommended by WHO in patients with both multibacillary and paucibacillary leprosy.

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Opioids for chronic pain?

There is no dispute that opioid drugs are frequently needed to provide effective relief from the pain of terminal malignant disease. Controversy still persists, however, regarding their place in the management of chronic nonmalignant pain (1, 2). Because of their addictive potential, such use is often portrayed as potentially dangerous for both the patient and society (3, 4). This argument finds support in claims that nonmalignant pain — and neuropathic pain, in particular — is intrinsically resistant to opioids in subanaesthetic doses (5, 6) and in assertions that any relief these drugs may offer is likely to result from elevation of mood and hence to be essentially addictive in nature.

It is important that these claims be further explored. For many doctors they constitute grounds for withholding opioids from large numbers of patients with severe chronic pain who do not obtain satisfac-

tory relief from other analgesics. Yet they are held in contention by others persuaded that morphine and other opioids, given in sufficient dosage and with due caution can sometimes be irreplaceable in controlling severe chronic pain of other cause (7). Various studies are cited by each side to support their viewpoints (5-9) but, for the most part, their design leaves the conclusion vulnerable to criticism (10).

The introduction of patient-controlled analgesia — an infusion technique enabling the recipient to vary opiate dosage on demand within predetermined limits (11) — has created the possibility of obtaining precise dose-response data from patients receiving opiates. The method has recently been used in a small, double-blind study in which the effects of morphine infusions at 2 strengths were compared in 10 patients with severe intractable pain (10). The pain was described as nociceptive (associated with tissue-damage) in 4 patients and neuropathic in 6.

All patients with nociceptive pain and 3 of 6 with neuropathic pain were judged to have obtained substantial relief during the infusions. At first sight these results provide strong support to the thesis that both types of pain are commonly responsive to opioids. However, they must be interpreted with reservation. The author's definition of neuropathic pain is too broad to meet with consensus (12); doubts have been raised about the therapeutic relevance to non-terminal conditions of a treatment that resulted, in some cases, in intravenous doses as high as 300 mg morphine within a matter of hours (13) and, in the absence of a placebo control, observation of a dose-dependent effect in only one of the patients claimed to have neuropathic pain leaves doubt about the extent to which a pharmacological effect was demonstrated (12).

The authors' conclusion that opioids should be considered for relieving severe, otherwise-unresponsive chronic pain of any cause, provided the patient is informed and agrees, thus remains open to question. Given the importance of the issue to countless patients and the difficulties of setting up a decisive clinical experiment within accepted ethical norms, there is a need to learn much more from relevant clinical practice. The WHO international data base of adverse drug reactions is virtually silent on the issue. It would be helpful if experiences were shared as freely as opinions.

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Spermicides and sexually transmitted diseases

Nonoxinol-9, which has been used as a contraceptive for over 30 years, has been shown more recently to have antimicrobial activity *in vitro* against organisms causing some of the most

prevalent sexually transmissible diseases, including gonorrhoea and chlamydial infections, trichomoniasis, genital herpes and syphilis (1). Several clinical studies and surveys have confirmed that commercially-available spermicides enhance the protection provided by condoms against gonorrhoeal and chlamydial infections (2-7).

Since these two diseases may increase the vulnerability of women to HIV infection (8) it has been suggested that nonoxinol-9 should be used routinely by women at high risk of HIV infection (7). However, used frequently, nonoxinol-9 is itself irritant to the vaginal and cervical epithelium (9) and these inflammatory and ulcerative lesions may well operate to increase any risk of HIV transmission (10, 11). Warnings have been sounded that further studies are needed to determine whether such a risk may exist before recommendations for using nonoxinol-9 to protect against sexually transmitted diseases can be accepted (12). Condoms alone, when used correctly and consistently, reduce the risk of transmission of gonorrhoea and are without known significant toxic effects (13).

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Pralidoxime salt: is it really of value in organophosphorus poisoning?

Organophosphorus insecticides, which are widely used as crop sprays, are a frequent cause of poisoning in many developing countries. Some cases result from occupational exposure but it is claimed that more are due to attempted suicide (1, 2). The products are potent neurotoxins which irreversibly inactivate cholinesterase. A potentially fatal acute cholinergic crisis which occurs after some 24 hours is often preceded by muscular weakness, most evident in the neck, the proximal limbs and the respiratory muscles (3). Atropine, which competitively antagonizes the muscarinic action of acetylcholine, and which is cheap and widely available, is the mainstay of treatment. However, the "cholinesterase reactivator", pralidoxime salt — which has been claimed to bind and inactivate organophosphorus molecules (4) — is also commonly employed, when it is available, in cases of moderate to severe poisoning.

The rationale for using pralidoxime is based upon demonstration of an atropine-sparing action in laboratory animals, toxicological evidence that it reverses the effects of organophosphorus compounds in the central nervous system, and a potential to reactivate blood cholinesterase *in vitro* (5-7). However, no controlled trials have ever been undertaken to assess its value in the treatment of

organophosphorus poisoning, and the various uncontrolled studies that have been reported are both inconsistent and inconclusive in their outcome (5-7).

It is generally accepted that more reliable information is needed on the clinical value of pralidoxime, not least because it is costly and is itself toxic. Controlled studies have been precluded on ethical grounds, but opportunity for a retrospective comparison recently arose in Sri Lanka as a result of temporary exhaustion of stocks within the country. The clinical response to treatment of 45 patients admitted to a general medical facility within 24 hours of poisoning with an organophosphorus compound was studied over two successive 6-month periods (8). Pralidoxime, which was infused in a dose of 4 g in the first 24 hours and 1 g daily thereafter, was used routinely in addition to atropine to treat the 24 patients who presented during the first 6-month period, but it was subsequently not available to the hospital. The severity of the cases admitted during each period and the poisons implicated were closely comparable. The majority of cases were attributed to malathion, methamidophos, and fenthion. Slightly less than 30% of the patients within each group died, and no important difference was demonstrated in any other measure of outcome. These included the amount of atropine required to maintain its full effect, the number of days that atropine was administered, the need for intensive care and for assisted ventilation, and the length of stay in hospital.

Because of uncertainty about its therapeutic value, pralidoxime has not held a secure position within the WHO Model List of Essential Drugs. The results obtained in Sri Lanka intensify pre-existing doubts. But, as the authors themselves emphasize, they should not be regarded as conclusive. A severely poisoned adult may require an infusion of as much as 500 mg/hour (9). However, the study is of prime importance, since it both provides justification and demonstrates a need for prospective controlled studies of the clinical efficacy of a very expensive antidote.

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Rubella immunization prevention policies

Rubella infection during pregnancy results in a high incidence of abortions, stillbirths and characteristic birth defects, including serious ophthalmic, auditory, cardiovascular, and neurological lesions, known collectively as the congenital rubella syndrome (1). With the advent of an effective vaccine in 1969, eradication of this risk through mass immunization of schoolchildren became a feasible, if costly, objective which received high priority in the United States in the 1980s (2, 3). In 1984 it was estimated that eradication could in time be achieved — on the assumption that the vaccine was 95% effective — if immunization coverage were maintained year-by-year above 92% (4).

Within a few years of its full implementation, the programme appeared to be on the verge of success. Only 2 cases of congenital rubella syndrome were formally reported within the United States in 1989 (5). Since then, however, more cases have been notified that have tempered early optimism and led to a restatement of national policy (6). A recent cluster of 21 cases in southern

California included both women who escaped immunization at school because of their age and women who had first entered the United States after completing their schooling (7). Opportunity had arisen in more than half the cases for rubella screening and immunization either at the time of marriage, or during previous contacts with the health services.

In contemporary mobile societies, it is suggested, eradication of congenital rubella syndrome cannot be based exclusively on universal immunization of infants with measles-mumps-rubella vaccine. Supplementary antibody testing of women likely to be susceptible to infection needs to be carried out in diverse settings. It needs to be considered during postpartum and postabortion examinations, and during attendances at family planning clinics, student health centres, clinics for sexually transmitted diseases, and drug rehabilitation programmes. A commitment is needed within the health services at large to ensure that rubella screening and immunization is undertaken whenever women who may be at risk to seek medical care and advice.

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Herbal medicines: need for regulatory oversight

The need for cautious oversight of the market in herbal medicines has been repeatedly voiced in recent years (1, 2) and new examples of the inclusion of potentially toxic substances in such products continue to come to light. A herbal slimming product available in the United Kingdom has recently been found to contain a recommended daily dose of approximately 120 mg sparteine (3). This, the authors warn, is a quinolizidine alkaloid with oxytocic properties obtained from Broom (*Cytisus scoparius*) that has been used both as a diuretic and, at an intramuscular dose of 150 mg, for induction of labour. No adverse effects are known to have been reported to the product in question. However, a minority of some 10% of caucasians are likely to metabolize sparteine slowly, since it is oxidized in the same way as debrisoquine (4), and these will be particularly vulnerable to its pharmacological actions. Concern centres upon its potential effect on the gravid uterus, but in excessive dosage it seems that serious acute systemic reactions might also occur to the individual, including circulatory collapse, respiratory arrest, cramps, diarrhoea, diplopia, blurred vision, anorexia, headache and nausea (3).

All national drug regulatory authorities clearly need to maintain and update national listings of substances prohibited for inclusion in herbal products sold directly to the public.

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Vitamin D fortification: the case for quantitative monitoring

At the turn of this century, the vast majority of children living in northern industrial towns were afflicted with rickets. Only in the 1920s was it

appreciated that exposure to sunlight could cure the disease (1) and not until many years later was it realized that adequate stores of vitamin D — which is synthesized in skin from 7-dehydrocholesterol during exposure to ultraviolet light — are vital to normal skeletal growth and mineralization. Deficient stores of vitamin D result in impaired calcium absorption, stunted growth, soft bones, muscle weakness, secondary hyperparathyroidism and pathological fractures. Excessive reserves of the vitamin are also dangerous, however, since they induce hypercalcaemia, extraskeletal calcification, renal impairment and stone formation.

Rickets was rapidly eradicated from western Europe and North America during the 1930s by fortification of milk with vitamin D, but excessive supplements resulting in outbreaks of vitamin D intoxication brought the practice into disrepute in some countries. Withdrawal of fortified products, however, has invariably resulted in a rapid resurgence of rickets in the past (2, 3), and the current preference for low-fat milk products in many countries has rendered reliance on natural dietary sources of vitamin D even more tenuous.

The problem of assuring correct supplementation is not simply a matter of history. As recently as this year, cases of vitamin D intoxication were reported from the United States as a consequence of the distribution of milk from one outlet that contained 500 times the labelled content of vitamin D (5.0 IU per litre) (4). Further investigation of the situation nationally has shown that only 12 of 42 samples of 13 brands of milk and none of 10 samples of 5 brands of infant formula contained vitamin D in amounts within $\pm 20\%$ of the labelled concentration (5). Over 60% of the milk samples contained lesser amounts, and in 3 of these, no vitamin D was detectable. Conversely, 7 of the 10 samples of infant formula contained between 2 and 4 times the labelled amount.

Notwithstanding these findings, the risk of clinically-evident vitamin D intoxication from excessive fortification of foods is probably remote (6), and there can be no doubt that the benefits of supplementation greatly outweigh the risks. The benefits are not realized exclusively in temperate latitudes. Indeed, reports of vitamin D deficiency now frequently emanate from regions with abundant sunshine where people avoid direct exposure to solar irradiation and where there is no fortification of foodstuffs (7-10). There is consequently a strong case for assuring wider availability of fortified

products but, at the same time, provision needs to be made for checking the care and accuracy with which they are prepared. Fortunately, the necessary monitoring technique is now relatively simple since precise chromatographic methods have superseded the cumbersome bioassays that were used in the recent past.

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Ritodrine: does it really prevent preterm labour?

Ritodrine, a β_2 -adrenergic agonist with tocolytic activity, was developed specifically for obstetric use (1), and for the past 15 years it has been used widely in many countries to inhibit preterm labour. The results of both an overview of early published trials (2) and a recent multicentre trial undertaken in Canada involving some 700 pregnancies (3) leave

no doubt that contractions are rapidly inhibited and that the risk of delivery within 48 hours of treatment is substantially reduced. However, in the longer term, this immediate advantage has not been shown in randomized controlled trials to be associated with any reduction overall in the incidence of preterm delivery, low birth weight, or perinatal morbidity and mortality (3-6).

This does not necessarily imply, however, that tocolytic therapy is entirely without value. It is possible, for instance, that its use in threatened termination before 28 weeks' gestation might delay delivery long enough to assure viability. Indeed, the results of the Canadian study support this possibility (3). Later in pregnancy, the rationale for suppressing contractions rests on whether anything else of value can be done in the time saved (3). This might simply constitute the transfer of the mother to a tertiary care facility or, perhaps, the administration of corticosteroids with a view to promoting pulmonary maturation in the fetus (7).

Such use can only be contemplated if tocolytic therapy is essentially without hazard. Concerns were raised in the United States in the early 1980s about an association between use of these drugs and potentially fatal maternal pulmonary oedema. This complication has recently been restated to develop with an incidence of 3% to 9% in treated patients (6). However, this does not reflect the current situation. Adverse reaction reports contained in WHO's international data base show that 66 of a total of 69 reports of pulmonary oedema associated with ritodrine originated in the USA and, of these, 46 were reported between 1981 and 1983. Reports of oedema associated with infusion of terbutaline followed a similar trend. In 1983 a

warning was issued by the manufacturer of ritodrine to doctors within the USA emphasizing the danger of fluid overload during preterm labour and of using saline solution as the diluent for ritodrine infusion (8). Despite continued wide usage of ritodrine, the median annual number of such cases reported to WHO between 1984 and 1988 was 3; since 1989 only one such case has been notified.

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