Methadone: evidence of accumulation

SIR,—We have recently been exploring the possibility of producing a controlled-release methadone tablet for the treatment of pain in patients with terminal cancer. We have used a controlled-release tablet that we have previously shown to provide a satisfactory bioavailability pattern, with a strong correlation between in-vitro and in-vivo release with aminophylline.¹ This controlled-release tablet formulation has also been shown to provide an effective method of drug delivery for papaverine² and glyceryl trinitrate.³

Methadone created unexpected practical difficulties since, although the drug is an effective analgesic for only some 4 h, the plasma half life has been variously reported to be 15 h⁴ and 25 h.⁵

Our controlled-release methadone tablets containing 10 mg of methadone hydrochloride were prepared and a satisfactory in-vitro release pattern obtained. Three healthy volunteers were given one 10-mg tablet at 0, 12, and 25 h. Plasma methadone levels were measured at 0 hours and at 1, 2, 3, 6, 8, 12, 24, 25, 26, 27, 30, and 32 h.

Plasma methadone levels were determined after extraction on a Perkin Elmer F17 gas liquid chromatograph, using a 3% OV-17 on Gas Chrom Q column, with dieldrin as internal standard. Standard reference solutions used were methadone base and dieldrin at 20 ng/ml and 40 ng/ml respectively. This was modified from a method kindly provided by the Guy's Hospital Poisons Unit. (Further details of the method are available from the address below.)

As can be seen from the accompanying figure a satisfactory plateau level was obtained from the third hour onwards. However, marked peaking occurred 2 h after the third dose and, as can also be seen, there was firm evidence of accumulation. This would suggest that Inturrisi and Verebely⁶ in their original estimates of the half life had considerably underestimated. Indeed, since we completed our study these authors have produced further work on the subject in which they suggest that methadone has a "slow secondary life" of 54.8 h.⁷

For these various reasons we have now abandoned the project. However, we felt that we should briefly publish our findings since methadone is widely used as a cough linctus in addition to its use as a narcotic analgesic and in the weaning of heroin addicts.

Blood methadone concentrations in three volunteers after repeated administration of controlled-release tablets each containing 10 mg of methadone.

Consequently we thought it important to bring this problem of accumulation to the general notice of the profession since it does not appear to be widely appreciated and could give rise to problems in clinical practice.

We have been encouraged to publish our findings by Dr R Twycross and by Professor D Vere and his colleagues Dr T B Binns and Dr A Herxheimer, and we wish to express our gratitude to them for their help and advice and also to Dr D Robinson for his assay method.

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¹ Boroda, C, *et al*, *Journal of Clinical Pharmacology*, 1973, 13, 383.

² Miller, R B, *et al*, in preparation.

³ Ikram, H, *Current Medical Research and Opinion*, 1976, 3, 719.

⁴ Inturrisi, C E, and Verebely, K, *Clinical Pharmacology and Therapeutics*, 1972, 13, 923.

⁵ Inturrisi, C E, and Verebely, K, *Clinical Pharmacology and Therapeutics*, 1972, 13, 633.

⁶ Robinson, D, personal communication.

⁷ Verebely, K, *et al*, *Clinical Pharmacology and Therapeutics*, 1975, 18, 180.

Future of child health services

SIR,—It would be unfortunate if many people were to be misled, as have the Court Committee,¹ by faulty interpretation of the evidence. Dr M A P S Downham (22 January, p 227) is quite incorrect in his belief that epidemiological evidence supports their principles and proposals. Indeed, their use of a comparison of the rate of fall of infant mortality in England and Wales with those of Japan, France, Sweden, and Finland in such a way as to cause the unwary reader to infer that our slower rate of improvement is due to less adequate services is questionable.

The countries selected have enjoyed more rapid economic growth than has the UK. They have not had their infant mortality statistics inflated by substantial contributions from immigrants who have brought with them the mortality rates related to the dietary and cultural practices of their native lands. It may well be that if even half the resources needed to implement the proposals of the Court Committee were spent on improving nutrition (or preventing malnutrition) in girls of reproductive age we might see a greater reduction in perinatal and infant mortality due to a fall in incidence of low birth weight. Even if we accepted that this was a proper aim it has not been proved that "integration of preventive and curative services" contributes in any way to reducing mortality, nor that "continuity of health surveillance from fetal to adult life" would achieve this. Many of the suggestions made in the report have already been tried out in various places and found wanting, but the committee conveniently omits mention of these unpalatable facts.

Many people, however, would dispute their tacit assumption that reductions in perinatal and infant mortality are proper aims. There are good humanitarian grounds as well as sound economic reasons for rejecting them and substituting the "minimising of handicap" as our objective. This would be more appropriate to the needs of society and meet the wishes of most potential parents. The salvaging of damaged babies is an expensive way of imposing a continuing burden on parents, education and social service departments, the NHS, and

the taxpayer, and is currently done in ways which impose additional handicaps on the child.

It is a great pity that this long-awaited report contains so many flaws. Its main recommendations are unsound and impossibly expensive; they are never likely to be implemented in full. Very many of the minor recommendations which are scattered (in italics) through the report are sound and wise. It would be unfortunate if the contempt earned by the rest of the report led to the rejection of the good as well as the bad.

Adoption of some of the minor recommendations combined with encouragement to authorities to experiment with alternative methods of developing and improving their existing service would permit considerable improvement in our services without any massive increase in cost and without the problems which a revolutionary change would inevitably throw up.

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¹ Committee on Child Health Services, *Fit for the Future*. London, HMSO, 1976.

SIR,—I read your leading article (25 December, p 1524) with great interest and found myself wondering how the proposals for the appointment of general practitioner paediatricians would affect my own work as a single-handed rural practitioner. Professor Donald Court's report¹ suggests that I and two or three neighbouring practitioners would be joined by a GPP who would be responsible for the developmental supervision of the children in our practices.

As the care of these young patients is one of the delights and interests of our everyday work I would bitterly oppose such a move, for I would fear that the next logical step would be to relieve me of the care of my elderly patients and that general practitioner geriatricians will be appointed to assist me look after these equally interesting and rewarding patients.

If our standards of care are not up to those deemed proper by Professor Court's committee, surely an easier way to attack the problem is to train or encourage existing practitioners to raise their standards—after all, that is what is suggested for those chosen or who choose to become GPPs.

The attraction of general practice to most of us is that it is truly general and includes the whole family, if not from birth, at least from the cradle to the grave. Any new grade of practitioner would be detrimental to the general practitioners' role in the community and should, I would submit, be resisted.

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¹ Committee on Child Health Services, *Fit for the Future*. London, HMSO, 1976.

Rarity of non-accidental penetrating injury in child abuse

SIR,—Penetrating non-accidental injury as part of the syndrome of child abuse is extremely rare.

A 13-month-old child was admitted with no pulse or blood pressure and not responding to painful stimuli. Bleeding had stopped from a 2-cm stab

wound in the midline of the neck. There were several other lacerations around the main stab wound. Other non-accidental injuries were present. There was recent bruising of the forehead and around the left eye. There were teeth marks with surrounding bruising on both arms. The frenulum of the upper lip was lacerated. Older bruises and signs of a previous lashing injury were present on the back and buttocks. After transfusion of 700 ml of group O negative blood (expected blood volume 1200 ml) over 30 min the child's condition improved and he responded to painful stimuli. During restoration of circulating volume bleeding started again from the main stab wound and the neck was explored. The stab wound was found to extend to the left behind the sternomastoid muscle, and the internal jugular vein was lacerated for one-third of its circumference. The vein was ligated above and below the laceration. The child made an uneventful recovery. A subsequent skeletal survey was normal.

With the exception of road traffic accidents the possibility that injuries in childhood may be non-accidental should always be considered. Penetrating injury is not usually associated with the battered child syndrome. Many children present at accident and emergency departments with lacerations. It is suggested that the same high index of suspicion should exist.

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Surgery for Menière's disease

SIR,—Your leading article on this subject (15 January, p 124) does not reflect the views of all otologists. The natural history of the disease, as seen by those with a special interest, is far from "benign" in 95% of patients. With the passage of years, despite periodic remissions, there is progression of hearing loss, distracting tinnitus, and increasing disability from vertigo in the majority of sufferers. Eventually the disease becomes bilateral in more than 50% and some finish with total deafness.

Rehabilitation in severe cases and prevention of deterioration are the modern aims of surgical and medical therapy. The older destructive operations have little place in the management. We agree with the sentiment expressed in your article that the disease is non-fatal and that surgical procedures which carry a risk of serious complications should be avoided. There is a very limited indication for middle-fossa or translabyrinthine neurectomy and for the subarachnoid shunt operation. Controlled studies on the use of grommets have failed to substantiate the long-term efficacy of this technique. There is also no evidence that, in patients in whom the middle-ear pressure has been measured and who have been proved to have normal eustachian tube function, grommet tubes are of any value whatsoever. Ultrasonic partial vestibular destruction still has a place in the management. Drainage rather than decompression of the saccus endolymphaticus is the surgical intervention which has proved most effective in controlling symptoms and in preservation or improvement of hearing. Bilateral operations are frequently necessary.

Perhaps our main objection to your article is the statement that there is no clear indication for surgical intervention. The results of saccus drainage surgery are excellent when performed on patients whose inner ears show

the features of active hydrops of the cochleo-saccular segment—the pars inferior—and who have not reached a late irreversible stage of the disease. Modern methods of assessment—electrocochleography, glycerol dehydration studies, and appropriate vestibular analysis—can select these patients. The indication for other surgical techniques becomes equally clear when the case analysis is adequate. Conservative surgery is the alternative to medical procrastination and the probable progressive loss of hearing in the ear affected by Menière's disease.

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SIR,—We read with interest your recent leading article on this subject (15 January, p 124). We agree that surgery should not be undertaken lightly and that the indications should be clear; and we would add that there is no place for surgery without adequate and extensive medical treatment.

So far we do not have any operation that consistently results in improvement in the auditory symptoms of deafness and tinnitus. However, in severe cases what most patients want is relief from their incapacitating vertigo. As you state, "radical destruction of the labyrinth . . . may bring speedy relief with comparative safety." Unfortunately, it also brings total deafness in the operated ear. While the patient may see this as a small price to pay, it must never be forgotten that this is a potentially bilateral condition and all useful hearing should be preserved.

Surgical division of the vestibular nerve has the predictability of labyrinthectomy with the prospect of sparing any remaining hearing and, apart from labyrinthectomy, no other operation has success rates for relief of vertigo in excess of 90%. In the series referred to in your article¹ the preoperative hearing was maintained or improved in over 75% and the dizziness abolished in 94%. While your article refers to eight cases of delayed facial paralysis, it fails to record that there was complete recovery in seven, and that in the eighth recovery has been such that the patient is unaware of any residual facial weakness.

While spontaneous improvement of the dizziness may occur even in severe cases of Menière's disease, it often does so at the expense of the hearing. We believe, therefore, that it is unjustifiable for the otologist to stand back and wait, hoping for remission or for the disease to "burn itself out" while the patient remains incapacitated by vertigo. If adequate medical treatment has been tried and has failed and if there is useful hearing in the affected ear division of the vestibular nerve via the middle cranial fossa is indicated in most cases.

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¹ Smyth, G D L, Kerr, A G, and Gordon, D S, *Journal of Laryngology and Otology*, 1976, **90**, 823.

SIR,—Your leading article (15 January, p 124) epitomises the misconceptions and mental confusion which this subject arouses—it certainly provides no help for the practitioner attempting to deal with a case of deafness, tinnitus, and vertigo.

Several careful studies of Menière's disease have suggested that this is an uncommon condition and that a busy ENT surgeon is unlikely to see more than one new case a month.^{1,2} At this rate it will take him over eight years to see 100 cases and during this period he will, according to your article, consider five cases only for surgery—a ridiculous and grossly inaccurate assessment of the real situation. Your article has, quite inexcusably, repeated the common and cardinal error of confusing cases of giddiness with or without hearing loss and tinnitus with cases of Menière's disease. If you had stated that about 5% of all cases prove after careful investigation to have true Menière's disease those with extensive experience of this condition might be more in sympathy with you.

Until I read your article I had been under the impression that the bogus treatment of Menière's disease by myringotomy and the insertion of a grommet drain had been largely and wisely abandoned. It has been shown³ that middle-ear pressures are normal in this condition and that there is nothing to drain. Until some degree of unanimity in the diagnostic criteria of Menière's disease^{4,5} has been reached and until sophisticated units are available regionally where the many conditions simulating it can be eliminated we are unlikely to improve, surgically or otherwise, the lot of the unfortunate patient with these symptoms. In the few units which are properly equipped to diagnose and treat aural vertigo "a bewildering bouquet of procedures" has already been replaced by a small number of skilled surgical procedures, with very gratifying results.

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¹ Frew, I J C, *Postgraduate Medical Journal*, 1976, **52**, 501.

² Wilmot, T J, *Journal of Laryngology and Otology*, 1976, **90**, 833.

³ Cinnamon, M J, *Journal of Laryngology and Otology*, 1975, **89**, 57.

⁴ Wilmot, T J, *Proceedings of the Royal Society of Medicine*, 1974, **67**, 331.

⁵ Wilmot, T J, *Journal of Laryngology and Otology*, 1974, **88**, 295.

Intranasal beclomethasone

SIR,—Your leading article (25 December p 1522) begins with the somewhat sensational title "Intranasal beclomethasone: wonder drug or hazard?" but ends by describing beclomethasone dipropionate aerosol (BDA) as "a powerful and safe weapon in the . . . treatment of allergic . . . rhinitis." Such contradictory statements suggest that comment and updated information should come from the Derby clinic where this treatment was first shown to be effective.^{1,2}

In our long-term surveys of experience with BDA in asthma and in 77 cases of perennial rhinitis³ and seasonal rhinitis⁴ we pointed out that the full dose of the nasal aerosol is localised on a small area. Adverse effects on the nasal mucosa must therefore become evident long before any effects on the bronchi.

Reviews of over five years' experience of using BDA in treating 223 upper and 600 lower respiratory tract allergies, involving about 450 and 850 patient-years of BDA therapy respectively, are in preparation. Suppression of nasal symptoms was almost complete in 68%, the dose could be reduced to four puffs or less in 35%, and treatment was stopped without relapse in 18%.

Dr D Poynter, of Allen and Hanburys