Unreliability of reports of hypoglycaemia by diabetic patients

Hundreds of case reports suggest a problem with human insulin

EDITOR,—Simon Heller and colleagues' study of the unreliability of diabetic patients' reports of hypoglycaemia¹ was conducted after my suggestion to John Ward, one of the authors, that both patients' and their partners' views about loss of awareness with human insulin were important. I am therefore surprised that I was not given an acknowledgement. The study confirms my belief that patients' and their carers' views are important.

The authors' suggestion that the validity of previous studies looking into loss of awareness of hypoglycaemia with human insulin is questionable is an understatement. Most scientific studies into loss of hypoglycaemic awareness with human insulin have not included partners as a core factor in the research.^{2,4}

Now that the validity of previous studies looking at problems experienced with human insulin have been questioned we must rely on the hundreds of case reports about human insulin from patients and their carers. These suggest that many patients have problems when using human insulin. The patients and their carers confirm an improvement when the patients change to animal insulin.

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Hypoglycaemia was validated

EDITOR,—Simon Heller and colleagues report significant discrepancies between estimates of the frequency of severe hypoglycaemia and impaired awareness of hypoglycaemia as reported by diabetic patients and their relatives.¹ They conclude that patients' self reporting on questionnaires is unreliable. The hypoglycaemic episodes reported by the patients and relatives were not, however, validated, and no evidence was provided to support the assumption that relatives are more accurate or reliable than patients in identifying hypoglycaemia.

In a study of 100 diabetic patients treated with insulin who were interviewed about hypoglycaemia with a structured questionnaire 24 reported having had no severe episodes and 23 recalled five or more severe episodes.² These 47 patients' histories were validated by scrutiny of their general practice and hospital records. In addition, their close relatives were questioned about the incidence and severity of any nocturnal hypoglycaemia. This confirmed that patients who reported several episodes had documented evidence of multiple treatments for severe hypoglycaemia. Only one of the 24 patients who claimed to have had no severe episodes had documented evidence to the contrary: two episodes of moderate severity had been associated with consumption of alcohol and one had been caused by an intentional overdose of insulin. These episodes were all treated with oral carbohydrate. In addition to performing this validation

exercise we reinterviewed 85 of the 100 patients after 18 months. The test-retest reliability for patients' reported frequencies of severe hypoglycaemia was 0.766 ($P < 0.001$).³

Although the frequency of mild hypoglycaemia can be recalled accurately over a period of only one week, severe hypoglycaemia (any episode requiring external help for recovery) has been shown to be a more robust measure.⁴ While individual patients may have amnesia of a particular hypoglycaemic event, the disruption associated with severe hypoglycaemia usually has sufficient impact on the life of affected patients and their families to be related later. Although prospective recording with witnessed confirmation is superior for epidemiological purposes⁵ and may help to limit underestimation of hypoglycaemia, it is misleading to cast doubt on previous self reported estimates on the basis of a single and limited survey.

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Private prescribing of controlled drugs needs closer scrutiny

EDITOR,—The prescribing of controlled drugs to drug misusers by private practitioners raises some ethical questions.¹ Whether drug users should be prescribed central nervous system stimulants for a fee is particularly controversial. The only accepted medical indications for dexamphetamine are narcolepsy and childhood hyperkinetic syndrome,² and treating stimulant dependence by prescribing stimulants is by no means universally accepted. However, it is common to find drug misusers getting a combination of methadone, dexamphetamine, and benzodiazepines from private sources. The second Brain committee report recommended special licensing for doctors prescribing heroin and cocaine to drug misusers,³ but no such licensing procedure covers the prescribing of amphetamines. In the late 1960s the spread of amphetamine misuse was controlled by doctors voluntarily agreeing not to prescribe it. This case highlights the need for more careful control of current prescribing practice.

A young woman was admitted compulsorily to a psychiatric unit with a three week history of paranoid delusions, auditory hallucinations in the second and third person, and bizarre behaviour including posturing. She was convinced that people were scanning her with a machine, causing her physical pain, and that she was telepathic.

For some years she had been getting a private prescription for 200 mg of injectable methadone, 40 mg of diazepam, and 75 mg of dexamphetamine per day. She was crushing the dexamphetamine tablets and injecting the drug intravenously along with the methadone. After admission she was treated with oral haloperidol, recovered, and was

discharged 16 days later. The following day she returned to the same private practitioner, who prescribed a combination of injectable and oral methadone and 50 mg of dexamphetamine per day. Seventeen days later she was readmitted in a florid psychotic state. There was evidence of self neglect and she had auditory and visual hallucinations and delusions of persecution similar in content to those at her first admission. She required further treatment with antipsychotic drugs.

In view of the known association between amphetamine use and psychoses,⁴ the further prescribing of dexamphetamine to a patient with a documented recent psychotic illness is questionable. Whether this patient's schizophreniform psychosis was drug induced or not, the first episode should have been a contraindication to any further prescribing of dexamphetamine. In this case, prescribing continued. This suggested that private prescribing of controlled drugs needs closer scrutiny than exists at present.

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Drug users' views on general practitioners

EDITOR,—As a result of their survey of drug users' views on general practitioners Charles Hindler and colleagues suggest that general practitioners should adopt a central role in the management of drug misuse.¹ As vocationally trained general practitioners currently working in a substance misuse service, we disagree with this interpretation and suggest that wider issues concerning training and the provision of services need to be considered.

Rather than recommend a central role for general practitioners, the Advisory Council on the Misuse of Drugs suggested that they should share care with specialist services.² To target resources effectively and avoid duplication of services, specialist strategic planning is therefore required. Up to half of vocational trainees in general practice do not undertake psychiatric training posts,³ let alone gain experience in specialist drug units. Day release teaching is no substitute for supervised clinical experience.

Assessing and managing drug users' problems is expensive in medical time. In our district service (population 250 000) we annually assess 70 injecting drug users and provide a detoxification programme for 20; we currently prescribe oral methadone to 64. A recent study of methadone maintenance in general practice acknowledged that "injecting drug users do require a good deal of medical time" in clinics run separately from normal surgeries.⁴ Most general practitioners would find it difficult to take on such extra workload without compromising other commitments.

Users state a preference for counselling by general practitioners. Although most general practitioners have core skills, few have formal training in drug counselling, unlike specialist and voluntary services, which can provide comprehensive programmes to prevent relapse.

Nearly half the sample favoured maintenance prescription of injectable opiates. The inevitable outcome of such practices is illicit selling on of drugs, with accidental overdoses and deaths. Indeed, much prescribed oral methadone ends up on the streets and already seems to play a part in accidental deaths.

The emergence of "dual diagnosis" patients, with both mental disorder and substance misuse, highlights the importance of psychiatric input to drug services.

Although the *Health of the Nation* recommends consultation with users and carers, it does not suggest that services should be designed solely to satisfy consumers' preference or convenience.⁵ Planning of services should be based on good evidence and sound clinical practice.

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Methadone maintenance treatment

EDITOR,—Our review of methadone maintenance treatment¹ elicited a range of views.² Wolfgang Poser and colleagues correctly comment that methadone treatment protects against death due to an overdose of opiates³—an effect that we have reviewed elsewhere.⁴ The problem of deaths due to overdoses of diverted methadone, however, is considerable in Britain and Denmark⁴ and merits further work.

Diversion of methadone is an important if underrecognised problem in Britain. It indicates poor quality treatment and can probably best be addressed through policies and guidelines on the supervision of consumption of methadone, facilities for consumption off site, and attention to lack of compliance with treatment. The issue of compliance is important and poorly studied in Europe.⁴ Kim Wolff and colleagues advocate regular measurement of plasma methadone concentrations.² We do not agree that this is the most direct method of addressing diversion of methadone. The role of urine and blood analysis in addressing poor compliance is unclear, and such tests constitute a substantial cost burden for service providers. On balance, we suspect that the cost of these procedures outweighs the benefits, but further study is needed to clarify this issue.

Frederick H Meyers's comments are not consistent with the research literature, and he cites no evidence to support his opinions.² Steve Kempney² and N J Shaw² express concern about methadone withdrawal in neonates. Methadone treatment for pregnant women who are dependent on heroin has been shown to protect maternal and neonatal wellbeing.⁵ Withdrawal of neonates is often substantially complicated, however, by mothers' use of more than one drug—for example, cocaine and benzodiazepines.

On balance, methadone treatment does have drawbacks, like many interventions in medicine do. Nevertheless, overall, properly delivered methadone treatment confers important benefits

for people who are dependent on opiates and for the community.

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Environmental lead and children's intelligence

Studies included in the meta-analysis are not representative

EDITOR,—Stuart J Pocock and colleagues' meta-analysis of 26 studies of asymptomatic exposure to lead in children concludes that "the evidence strongly supports an inverse association between body lead burden and child IQ."¹ The authors then urge caution before the relation is accepted as causal. They do this on the basis of the following considerations: Are the studies representative? Is confounding adequately dealt with? Is selection bias at work? Is causality reversed: does low IQ cause ingestion of lead?

These questions have been asked and answered before. The criticism of non-representativeness could readily be applied to Pocock and colleagues' analysis, which includes five studies reporting null effects. Three (in Bucharest, Budapest, and Sofia) have not been published independently in peer reviewed journals.² Two had major methodological difficulties severe enough to disqualify them. In one study of small sample size (n=135) half of the mothers of the infants misused a potent neurotoxin, alcohol.³ Another study had serious difficulties in analysing blood lead concentrations and was forced to change the analytical method in the middle of the investigation.⁴ On the other hand, two tooth studies that showed significant effects were excluded for arbitrary reasons.

Pocock and colleagues suggest that there may be many other unpublished and undiscovered studies that find no effect of lead and mention a single case in point. A non-aneecdotal way to deal with this question is to estimate the number of unpublished null studies required to vitiate the observed joint result. This technique, known as "file drawer analysis," has in fact been applied to lead.⁵ The number of unpublished null studies required is between 26 and 82.

In their discussion of confounding the authors ignore the phenomenon of shared variance and assign the decrease in effect size when confounders are controlled exclusively to the confounder. Confounders can have a direct effect on outcome; they can also operate through increasing lead concentration. Poverty affects cognition. It also results in families living in homes with higher lead

content and surfaces that have deteriorated. Lower parental intelligence and poor care taking, in addition to directly affecting the cognition of offspring, may lead to increased absorption of lead. Ignoring this property may result in a type II error.

Selection bias of subjects was specifically evaluated in the two Boston studies and shown not to be consequential.

The issue of reverse causality dissolves under close inspection. Umbilical cord blood lead concentrations, measuring the intrauterine lead burden, are associated with later IQ deficits. Subhuman primates systematically given small doses of lead show clear deficits in learning and attention. To dismiss these studies on the basis of species differences is to ignore one of Bradford Hill's canons of causal inference: biological plausibility. There is no clearer example than the coherence of these two groups of epidemiological and experimental investigations.

Modern critics of the hypothesis linking lead with cognitive deficit should be required to provide fresh reasons for their scepticism and not use worn caveats that have been amply addressed over the past decade and a half.

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Britain must replace its lead pipes to meet WHO standards for drinking water

EDITOR,—As Stuart J Pocock and Marjorie Smith have been members of official British advisory committees, their acknowledgement that there is convincing evidence that blood lead concentrations down to 10 µg/dl (0.48 µmol/l) produce adverse neurological effects in children should have important implications for public policy.¹ The United States government set a target maximum childhood blood lead concentration of 10 µg/dl in 1991, but the British "action level" has remained at 25 µg/dl (1.2 µmol/l). The British government should now lower its target to, or preferably below, 10 µg/dl and then take steps to meet that target.

The problem of raised lead concentrations in drinking water is widespread in Britain. In Blackburn, to cite an extreme example, about 20 000 households receive water containing greatly increased concentrations—some as high as 50 000 µg/l (24 mmol/l) or even 300 000 µg/l (144 mmol/l); in 1990 almost a fifth of samples analysed by British water companies had lead concentrations above 10 µg/l.² If drinking water in Britain is to meet the World Health Organisation's new maximum lead contamination limit of 10 µg/l the only practical solution will be the replacement of all lead pipes.

Too little attention is being paid in Britain to the problem of old leaded paint and the consequent contamination of household dust. The United States has a comprehensive strategy for identifying and reducing housing stock contaminated with lead. In Britain the Department of Health has