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Hippocrates

And mothers still die. . .

"Why do mothers still die?" asked this column in Vol. 11, Nr. 2 (p. 144). Rightly, the Program for Appropriate Technology in Health (PATH) has pointed out to Hippocrates that it has at least an overview of the principal answers worldwide and is doing its patient best to alert the world to them [1]. Overall, according to PATH's figures, 585,000 women die yearly from causes relating to pregnancy and birth, and 99% of these deaths occur in the developing world. The figures show that 60–80% of maternal deaths are due to obstetric haemorrhage, obstructed labour, obstetric sepsis, hypertensive disorders of pregnancy and complications of unsafe abortion. Some fundamental approaches to putting things on a sounder footing are being carried through. One simply involves preventing unintended pregnancies, which are so prone to form the prelude to unsafe abortions; in Matlab, Bangladesh, family planning services seem to have contributed significantly to safer motherhood in a test area. In Mexico City, a 24% increase in contraception over five years coincided with a 39% reduction in the abortion figures. Antenatal care services have an evident impact: in the Democratic Republic of Congo development of such services indeed reduced maternal mortality by reducing severe anaemia and cases of obstructed labour. In elevating obstetric care to a level where obstetric complications can be better handled, development of "basic obstetric services" around a better-trained nurse midwife, supported by trained birthing assistants (TA's) has reduced deaths due to direct obstetric causes to a third. All these and other initiatives have for a decade been developed by the Safe Motherhood Initiative, a partnership between governments and international agencies. It is all gratifying: who said that international agencies merely sat around and talked?

Reference

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The perils of not knowing

With the year 2000 just around the corner, as we are interminably reminded, there are still people ready to point a derisory finger at WHO's "Health for All by the Year 2000" slogan; in their view, the fact that people are still ill shows that WHO has failed. WHO naturally never promised that it would be otherwise – the point of the slogan was simply that people should not become ill or remain ill *unnecessarily*. The notion of unnecessary ill-health covers all those conditions which in the present state of knowledge can be prevented, alleviated or cured, yet which persist unabated because knowledge is not put to good use.

One of the many reasons for the gap between knowledge and application is plainly topographical. In a great part of the world, people have no access to the information which could help them; that applies to the medical educator and student as much as to the lay public. Both the printed word and the electronic flow of information are still out of reach. A recent survey showed that 51% of Canadian doctors have e-mail and 47% have access to the Internet with its bibliographic data [1] (which in that country was considered singularly disappointing) but in East Africa and the countries of the former Indo-China the

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figure is still barely 1%. All praise, then, to a programme which the Canadian Medical Association has launched to deliver the *Canadian Medical Association Journal* and the *Canadian Journal of Surgery* to libraries in developing countries. In 1999, thirteen free 3-year subscriptions will be made available to centres around the world. In one of those centres, at the University of Zimbabwe, the *CMAJ* had been regularly received down to 1981, when the collapse of African currencies put the world medical literature out of reach [2]. The Canadian initiative deserves to be emulated widely; the costs, compared with those of providing health aid in other forms, are negligible. Without such initiatives there is a very real risk that the only literature readily available to doctors and students in much of the world will be that distributed – very selectively – by those who have something to sell.

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Pethidine in obstetrics; does it still have a place?

In much of the world, pethidine is still a much favoured instrument in relieving pain on the obstetric ward. Such has been the case for a great many years since the drug came into widespread use in the 'fifties. Is it time to think again?

A thoughtful new paper by Gro Nylander and the late Ingrid Matheson puts the question into perspective against the background of what is currently known about the drug's safety – or lack of it – in this particular situation [1]. Oddly, as they point out, there is little controlled investigation of the drug's analgesic effect in obstetrics; inretrospect a woman may recall that the birthing process was easier to tolerate after she had been given pethidine, but this could reflect the effect of sedation rather than of pain relief. Some work throws real doubt on pethidine's ability (or, for that matter, the ability of morphine) to relieve pain during delivery [2]. The authors' own impression from study on the obstetric ward is that as a rule women actually preferred to deliver without use of the drug. Pethidine is reputed to have value in cases of cervical rigidity, but even that remains an unproven clinical impression.

Like most other analgesics, pethidine can slow labour to some extent though it is not clear that it actually reduces uterine contractions. The mother may experience typical opiate effects; she may complain of a loss of contact with reality and with the birthing process. Some mothers speak of nausea, vomiting or giddiness, and there are occasional instances of hallucinations or bizarre sensations.

A greater problem is that of effects on the child, since the drug readily passes the placenta. It is often suggested that pethidine should be given early (for example, not less than ninety minutes before the expected time of delivery) to avoid sedating the neonate, but several workers have found that it is actually less likely to depress the infant's respiration or derange the acid-base balance or cardiac rhythm if it is given relatively late [3,4]. The depressant effect on respiration can be reversed with naloxon, but there seem to be considerable differences of opinion on whether this should be used routinely, and if so how. Naloxon can in any case probably inhibit the child's own endorphins and impair its ability to withstand post-partumhypoxia. Others have found that pethidine can reduce the infant's reactions to external stimuli, impair muscular tone and generally interfere with neuromuscular function. In line with this is the observation that the infant may be less well capable of seeking the nipple and initiating its own

feeding; the start of breast feeding is likely to be delayed. Taking all these data together, Matheson and Nylander conclude that – however clear the need to provide pain relief in some deliveries – the arguments against choosing pethidine in obstetrics are impressive.

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Compliance in hypertension, once again

One of the most astonishing findings of the drug utilization studies which have been carried out over this last decade is the miserably low level of compliance with treatment [1]; full compliance often only attains only 30–50% and it is sometimes much lower [2]. The problem arises with physical exercise and diet as well, but in some areas of medicinal therapy it is flabbergasting to find that patients who are quite seriously ill simply do not follow the treatment which has been recommended to them and to which they have (explicitly or by implication) agreed. It happens even where the condition has a grave prognosis when it is not treated, or where taking a tablet provides protection from acute and highly unpleasant symptoms (as in epilepsy). Hypertension presents an even worse situation, for here there are commonly no acute symptoms to remind the patient of the need to take the tablets. The 1997 Canadian Heart Health Survey showed that only 16% of adults with hypertension were receiving drug therapy *and* had normal blood pressure; a further 23% had been prescribed treatment yet remained hypertensive [3]. Two very recent papers point to much the same facts in the same country [4,5]. Many residents of Saskatchewan with a diagnosis of hypertension discontinued antihypertensive medication within six months of starting therapy, and compliance declined further over the next four years.

One fact that does discourage compliance is naturally a poor outcome of treatment with the first drug that is prescribed. Another factor that can positively scare the patient away from compliance is the well-meaning provision of information – whether provided by the doctor or the pharmacist – on possible side-effects and interactions [6]. Another is an unnecessarily complicated scheme of treatment; twice-daily drug intake for hypertension is much less well complied with than once-daily treatment, and the results appear to be better. These and other aspects of compliance are unavoidably tied to the effectiveness of the prescriber's own counselling of his patient. It seems to be a fact that a patient can only be expected to comply with therapy if, when he leaves the consulting room, he realizes *firstly* that the treatment is needed, *secondly* that it will not be disproportionately unpleasant or unsafe and *thirdly* that in agreeing to it he has assumed a very real degree of responsibility for his own health.

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Ecstasy: a small sigh of relief?

Hippocrates constantly has to resist the temptation to believe that, at his age, he need not be concerned with the problems which youthful drug users bring upon themselves. If partying with the aid of street drugs remains a significant social phenomenon, the adverse consequences (whatever they may be) will confront the medical profession sooner or later. The possibility of late consequences, and particularly of risks to the second generation, is most disturbing; since these are the effects which are the most difficult to foresee and potentially also most harmful to the community.

Even viewed alongside its fellows on the street, Ecstasy does not look like a nice drug. A tablet of Ecstasy is likely to contain methylene-dioxy-metamphetamine (MDMA) but in view of the way it emerges from obscure kitchen laboratories and an even more obscure trade it is just as likely to contain some other some other amphetamine, to say nothing of additives and impurities. With other amphetamines the literature (including data from experimental animals) suggests the possibility both of brain damage to the long-term user and congenital injury to the second generation, though most of the human evidence so far suggests that when taken in pregnancy these drugs have only a temporary effect on the neonate. With all this in mind, a group of investigators from Holland's Public Health Institute set out to study prospectively the possible second-generation effects of Ecstasy [1].

In their first paper, they present their findings in 43 pregnancies (including one triplet pregnancy) of a total of 49 which they initially set out to study. There were three elective terminations of pregnancy and two spontaneous abortions. All of the forty babies delivered at term were alive. One infant had a congenital malformation of the heart. And that is all.

These limited findings do not seem to give any cause for concern. The children will need to be followed up and the study expanded. To date however the findings do not suggest that there is a greater risk than in any other pregnancy. One may also derive some provisional comfort from the fact that the women concerned delivered such an apparently healthy bunch of children despite their own alternative lifestyle; there was a fair incidence of smoking, use of alcohol, intake of cocaine and of soft drugs. We breath a cautious sigh of relief, and keep our fingers crossed.

Reference

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All our dreams are sold. . .

The risk that the medical literature will be corrupted by the publication of papers which reflect a vested (and particular) a commercial interest rather than those of the patient or of medical science is certainly

not diminishing. It has always been the case that the number of so-called medical journals which publish items paid by the page (or accepted on the condition that a paid advertisement will accompany them) has at least equalled, and probably exceeded, the number of peer-review journals with no axe to grind and no barrow to push. What is now, regrettably, happening is that, with the decrease in community funding for universities and research establishments, many of them are increasingly dependent on commercial funding for their work. That is very likely to affect the nature of the work which they undertake and publish; it will sometimes also adversely affect its quality or impartiality. It is for such reasons, among others, that – where medical and pharmaceutical innovation is concerned – positive findings as regards efficacy and safety attain so much more prominence than negative results or cautions as regards risk or failure. Occasionally, indeed it happens that a researcher is threatened with legal action by a commercial sponsor if he proceeds to publish data unfavourable to a medical product to which his work relates.*

Giovanni Fava of Bologna, a good friend of this *Journal*, recently published elsewhere [1] under the title "All our dreams are sold" a sober review of conflicts of interest in scientific work, particularly relating to his own interest in psychiatric treatment. His review reminds us among other things of a paper by Krimsky et al. who looked broadly at the financial interests held by scientific authors in the matters which they studied [2]. There is also a paper by Zalewski [3] showing, among other things, that when a paper on a new cardiac drug appeared in the *Journal of the American Medical Association* at least thirteen of the researchers involved were stockholders in the company which manufactured it; that finding provides a reminder that even the most eminent of medical publications cannot protect themselves and their readers fully from hidden bias. As the International Committee of Medical Editors has found, such conflicts of interest can also adversely affect both the peer review process and the content of book reviews. Our own *Journal* has frequently requested authors to declare specifically that they have no conflict of interest, or to reveal any interests which could lay their impartiality open to question. On three occasions during the nine years since the *Journal* was founded, papers have been withdrawn as a result. From this year onwards such requests will be made routinely to every author of a paper on medical innovation; it should become a universal practice for all journals and conferences.

As to further steps: it has been proposed for years that a *Journal of Negative Results* is needed to provide a haven for those negative findings which are seldom welcome in the medical journals and the publication of which a commercial sponsor is, to say the least, hardly likely to encourage. The time for that initiative is surely upon us; watch this space.

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Maternal nutrition and pregnancy outcome

It is generally considered that gross malnutrition during pregnancy is likely to have an adverse effect on the child; that may be the case in areas of famine or extreme and chronic poverty in the developing

*See announcement of a study commissioned by the Toronto Hospital for Sick children following the exposure of one of its staff members to such a threat. Anon: Research and conflict of interest: how "truthful" is corporate funded research?, *INFACT Canada Newsletter* **4** (Summer 1998). Also: D. Spurgeon, Trials sponsored by drug companies: review ordered, *BMJ* **317** (1998), 618.

world. Even under those conditions, however, it seems that the mother is more likely to suffer than is the child. Not surprisingly, then, it proves extraordinarily difficult to determine whether more moderate deficiencies and imbalances in the nutrition of pregnant women in the industrialized world are likely to be of great consequence. However anxious some parties may be to sell nutrition supplements for this purpose, the only well documented issue is that relating to folic acid, a relative deficiency of which during the periconceptional period can lead to neural tube defects [1].

As Michael Kramer points out in the *Canadian Medical Association Journal*, the traditional use of birth weight is not a very dependable indicator of neonatal well-being, particularly since perfectly health newborns can have a relatively low body weight if they are born early or are simply small for their gestational age [2]. The "hunger winter" in Holland during the last year of Nazi occupation in 1944/5 did lead to substantial reductions in average birth weights at the time, but it had no perceptible effect on the duration of pregnancy or other pregnancy outcomes [3]. Studies since then of varying levels of intake of iron, zinc, calcium, the polyunasturated acids of fish oils and even folic acid in mid- or late pregnancy have shown no correlation with birth outcomes.

Kramer is critical of Canada's Prenatal Nutrition Program which was set up in 1994 to fund better nutrition during pregnancy in women of the poorer population groups; in his view the chance of reducing the incidence of low birth weight or prematurity in the pregnancy concerned is very small; could some part of the funding not have been spent on examining further the question as to what precisely the importance of nutrition in pregnancy is? The questions which he asks reflect very much the criticism directed towards a similar food aid programme established earlier in the United States [4]. As Kramer points out, no-one can properly condemn any programme which provides better food for the poor, but it is important to ensure that public policies like this are either founded in sound prior knowledge or contribute in some way to extending what we know so that public health activities can be better directed in the future.

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Coronary surgery: variation in risk

In recent years there have been a series of studies showing how markedly the risks (including mortality) of particular surgical techniques can vary from one hospital to another. Finding that there are such differences is the first step, explaining them the second and eliminating them the third.

A recent study continues along this path, looking at the results of the relatively new technique of carotid endarterectomy to overcome carotid obstruction due to atherosclerosis. In 1998, Wennberg and his colleagues took a look at the mortality statistics from a series of US hospitals of different types where this technique was in use [1]. Their data came from Medicare's national data base which covers all patients older than 64 years. No less than 113,300 such individuals had under carotid endartectomy in 1992 and 1993. Of these patients, 6510 had been operated in 86 hospitals which, having been selected

as "centres of excellence" had taken part in the original multi-centre trials in which the technique was first tested and its value confirmed. The remaining 106,790 patients had been operated in 2613 other American hospitals.

The perioperative mortality was lowest – 1.4% – in the "centres of excellence", though this figure was still higher than it had been during the original trial – a fact which could be related to the fact that the original trial extended also to younger patients who were less likely to have any co-morbidity. In the "other" hospitals, the perioperative mortality figures seemed to be related to their degree of experience; the figure was 1.7% in those centres conducting more than 21 operations annually, 1.9% in those carrying out 7–21 operations a year, and 2.6% in hospitals performing the operation less than seven times a year.

The figures could be distorted by various artefacts, but they seem to suggest several conclusions. One is that the means by which "centres of surgical excellence" obtain good results and a low mortality with a new technique to not become sufficiently well known to other centres. A second possible conclusion is that more effort might be made to concentrate certain techniques, particularly those carrying a fair mortality, in a more limited number of centres where experience can be gained and maintained.

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Faults made by junior doctors

Hippocrates recalls how, when he was a very junior doctor indeed, spending time in a casualty department, he gave a patient a ring anaesthesia for a minor operation on the nail of his right forefinger. In error he used not merely a local anaesthetic, but a combination of anaesthetic and adrenaline. Had a more experienced colleague not chanced to look over his shoulder in good time and remove the ring tourniquet, the combination of compression and adrenaline could well have caused the patient to lose his forefinger.

Just how often this sort of thing – and worse – happens because of sheer inexperience is the subject of the well-documented paper which Baldwin, Dodd and Write published from Britain last year [1].

The *Lancet* is accessible to every reader of this *Journal* and we shall not repeat their figures, except to recall that of the junior doctors whose work they studied no less than 43% had in the course of the last year made at least one error of sufficient seriousness to endanger a patient's life – or actually to result in death.

Long hours and overwork were not, in their view, the cause of such problems; it was simply a matter of inexperience; the theory of correct practice may have been inculcated into them in their training, but it had not yet became such a basic part of their professional behaviour that they instinctively did the right thing. It has happened to all of us, and so long as pressures on hospital staffing remain as they commonly are there will continue to be a lack of the patient supervision and continued teaching which a junior doctor needs if he is to exercise his new profession without undue risk to those entrusted to him.

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