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Hippocrates

Maternity care: for better, or for worse?

Because questions of safety and risk in health care often cut across interdisciplinary borders, the various facets of a single issue may be scattered widely and confusingly across the medical, the legal and the public health care literature: complementary facts that deserve to be viewed together may stand alone too long. Anyone reading in this issue of the *Journal* Savona-Ventura's expressions of concern with the effects of caesarian section on a southern European island should also be heeding two voices speaking elsewhere, both on maternity care in developing countries. The one offers an analysis of very real problems caused or aggravated by maternity care itself; the other offers at least some solutions.

T.K. Sundari from India does some masterly scene-setting from a range of countries in his paper: "The untold story": how the health care systems in developing countries contribute to maternal mortality" [1]. It is all too easy, as he makes it clear, to dismiss a proportion of maternal deaths as being due to "patient factors"; so they may be, in a sense, but in those cases where the patient refuses a particular form of treatment, arrives late, relies on an unskilled traditional attendant, or fails to comply with therapy, one is likely to find that the maternity services could have done much better in easing her access, earning her trust and retaining her loyalty. Haemorrhage, sepsis and eclampsia stand out as the main avoidable causes of mortality. Fatal haemorrhage was most usually due to delay, either in the midwife's diagnosis and referral, in locating a supply of blood or plasma, or in removing a retained placenta. Avoidable death from sepsis often followed failure to track body temperature, to carry out bacteriological tests in cases of fever, or to give needed antibiotics. Fatalities from eclampsia were variously due to the hospital's not knowing the history of the pregnancy, failing to monitor, to delaying proper treatment when convulsions were imminent – if indeed the hospital had any clear guidelines on the matters which it could follow.

Clearly, some of these things are directly due to lack of resources; others could be largely countered by training, often of a simple type. These answers are prominent in a "Recommendation on Maternity Care in Developing Countries" which emerged from the 13th General Assembly of the International Federation of Gynecology and Obstetrics held at Singapore in September 1991. Still insufficiently known, the "Recommendation" will be published in full in a future issue of this *Journal*. One may expect disputes to arise around the interpretation of some of its generalities ("each function of maternity care should be carried out by the least

trained persons able to provide that care safely and effectively”) but the right spirit – and a great deal of common sense – is there.

Reference:

- 1 Sundari TK. The untold story: how the health care systems in developing countries contribute to maternal mortality. *Int J Health Serv* 1992;22:513–528.
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Drugs and the camel’s back

As this issue of the *Journal* went to press, a certain Frank Glickman in the United States went to court. Mr Glickman has colonic cancer, and he was suing the drug makers Messrs Johnson and Johnson for charging an “outrageous and unconscionable” price for the levamisole with which he is being treated. As prescribed for him, the drug costs \$6.00 a tablet; sold for veterinary purposes, as he points out, one can buy it for \$0.60 a tablet. Hippocrates might add that when levamisole is purchased generically on the world market a 150 mg tablet can cost as little as one American cent, or something like one six-hundredth part of what Mr Glickman is paying, so the matter may be more extreme than his lawyers seem to imagine.

The counter-arguments are the customary ones. Although levamisole is a very old drug, long used in tropical medicine, Johnson and Johnson were the people who sponsored the clinical studies to determine its value as adjuvant therapy in colonic cancer and examine its safety; such work is expensive and must be paid for. There is talk of “tens of millions of dollars” spent over twenty-five years to determine the usefulness of levamisole in this and other disorders, such as rheumatoid arthritis. The company, as it points out, has a programme to provide the drug free of charge to those unable to pay for it. Mr Glickman’s lawyers, hoping that the case will be considered a class action, present the issue essentially as one of extortion; since patients like their client must have the drug, the company is charging them whatever it pleases, fair or otherwise.

Mr Glickman’s particular case turns on price as a bar to what he believes will be effective adjuvant treatment. In several analogous issues which arose in 1992, excessively high prices were seen primarily as standing in the way of safer or better tolerated treatment; that is the argument as regards certain newly marketed remedies for nausea during chemotherapy and for resistant migraine – remedies which cost a large multiple of the older and less agreeable alternatives. With indications and price differences such as these, the charge of heartless extortion by drug companies is likely to be more than mere rhetoric; it is troublingly likely that we are facing an unhealthy new tactic in the battle for pharmaceutical profits. It is particularly noticeable that where a new drug is intended for a less unpleasant condition and a high price might scare away the potential user, a company generally shows itself capable of marketing it for a sum which falls within the customary range, and presumably of making a profit all the same.

This is an issue on which society still has not got its act together, dealing with individual issues of pharmaceutical pricing ad hoc as they arise and not finding an overall answer as to how a high-risk industry can earn a reasonable reward without throwing an unreasonable burden on those in most desperate need of new drugs. The evident difficulty in facing up to supposed extortion is that no-one can in fact check the company's ledgers and determine what is or is not a reasonable charge; the work has often been spread over many years, a range of countries, and a whole gamma of indications of which some proved more responsive than others; it is clear that someone has to pay for the failures as well as the successes. The solution must lie somewhere in spreading the research burden more evenly across drug users as a whole (which may mean a relaxation of the most severe cost containment systems), promoting competition, and keeping pharmaceutical profits at fair but not excessive levels. They are not easy things to do but provided one gets away from polemics and into constructive negotiation they should be feasible.

The shadow side of whiter teeth

Self-medication and cosmetic medication are fringe areas of medicine which deserve a fresh look. Here and there genuine new opportunities do arise to entrust pharmaceutical treatment to the layman. Releasing loperamide, ibuprofen and hydrocortisone cream for home use in recent years does not appear to have done any measurable harm and has probably done some good. But the shadow side of the story is there too, and some unhealthy innovations slip into the market in the guise of cosmetics while the regulators are looking the other way. It happened with suntan tablets and hair straighteners, and it is happening again with a snowballing promotional effort to persuade the public to whiten its teeth with bleach.

In America, which was faced with the problem earlier than most European countries, the Consumers' Union found that most products of this type were three-step kits. The user first rinses the mouth with a mildly acidic solution to etch away a thin layer of tooth enamel; the solutions tested were mild and probably harmless unless abused. Users then dab a bleaching gel containing peroxide onto the teeth; the American Dental Association has claimed that these can temporarily damage the mucosa, delay wound healing, damage the pulp and perhaps enhance the effects of carcinogens. The third stage involves applying a white pigmented polish which adheres to the rougher parts of the tooth surface.

It *may* be a trivial problem; the difficulty is that no-one can be sure because the risks have not been properly studied. Late in 1991 the Food and Drug Administration indeed told the makers of "tooth whiteners" that they should submit new drug applications, backed by clinical studies, before continuing to market them. To date, as the Consumers' Union notes, the FDA has not "put its muscle where its mouth is"; the untested whiteners are still on sale.

Judges and the right to die

Despite the increasing number of judicial cases around the world which bear on the right of a patient to die, the actual total is still small; any judge handling such a case is, as the American Society of Law and Medicine points out in a recent *Briefing*, likely to be confronted with the issue for the first time; yet the issues are complex, the matter often urgent, and the consequences for the patient as far-reaching as they can be. During the past summer, therefore, trial court judges throughout the U.S. received a set of *Guidelines for State Court Decision Making in Authorizing or Withholding Life-Sustaining Medical Treatment* [1]. The Guidelines are simply presented in the form of twenty brief principles of judgement; each is supplemented by an Appendix, Footnotes and References. The matters which arise are dealt with chronologically, starting with the initial contact with the court and proceeding through the hearing of the case to the formulation of the ruling. Essential issues dealt with include the conditions under which court interference may be improper, the status of "living wills" or other directives given earlier by the patient, the extent to which a curator can take a decision on behalf of an incompetent patient, and the way in which evidence should be taken. The fact that the Guidelines also formulate a series of medical ethical standards which underlie the legal approach makes them particularly valuable for the non-American user; the law may differ, but the basic ethics involved are less likely to do so; at least the reader can verify whether his own basis for judgement is the same as that on which the Guidelines are founded.

Reference:

- 1 Guidelines for State Court Decision Making in Authorizing or Withholding Life-Sustaining Medical Treatment ("DRMLMT Guidelines"). West Publishing Company. Obtainable against payment of postage costs from Ms Carrie Clay, National Center for State Courts, 300 Newport Ave., Williamsburg, VA 23187-8798, USA.
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Cerebral palsy [1]

The greater part of the public believe that damage during birth is responsible for cerebral palsy. Claims for compensation have in some countries become almost automatic, and obstetricians in the United States have had to pay crippling insurance premiums to cover the risk of their being sued for negligence, largely because of this issue. All the same, a recent and critical review of the evidence [2] comes to the conclusion that not more than 10% of cases can be attributed to birth injury. In many children the cause cannot be established; in over half, problems had been encountered before labour; and in premature children cerebral palsy commonly results from brain damage after delivery. What is more, the incidence of

cerebral palsy has not been altered by the trend in many countries towards universal hospital delivery and early intervention by caesarian section. Nor do markers of birth asphyxia, such as foetal monitoring or measurement of the baby's state at birth, predict the risk: in fact, most children with cerebral palsy have not shown signs of birth damage.

The result has been that increasingly strict criteria are being laid down for establishing whether a baby suffered from prolonged hypoxia during delivery, and where "no fault" compensation schemes have been introduced most claims are refused. In Britain, the Spastics Society point out that the overriding need of parents is to know exactly what happened. They are campaigning for the rapid adoption of a comprehensive disability income scheme to support parents and disabled children [3].

References:

- 1 Anon. Cerebral palsy. The Health Summary (London) 1992;IX;13.
 - 2 Lamb B, Lang R. Aetiology of cerebral palsy. Br J Obstet Gynaecol 1992;99:176-178.
 - 3 Discussion paper: available from the Campaigns Department, The Spastics Society, 12 Park Crescent, London W1N 4EQ, United Kingdom.
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Drug exports: Do unto thy neighbour ...

The issue of unhealthy drug exports from rich countries to poor ones has been touched on before in these pages. Repeatedly, action demanded on valid grounds has been delayed and thwarted by protestation; either it has been asserted that the export trade has already been sanitized (which is far from true) or argued that poor countries, being sovereign, must enjoy the freedom to import whatever they wish (which is sanctimonious, for many of them do not have the resources to control the trade). Less than two decades ago, The Netherlands loosened its once exemplary regulations to allow the export of medicines not approved within its own borders. The World Health Organization has its Certification Scheme, but that is a chain which is no stronger than its weakest link, and some countries have been notoriously free in the issue of Certificates where they are not deserved. The European Community, disappointingly, has been largely indifferent to the problems created by its members, proposing standards which are too loose to have much useful effect.

Fortunately, some wealthy countries have woken up to the harm which they are doing. Germany has surveyed its foreign drugs business, Holland is doing so. France is virtually the first country to listen to the call for action and take truly radical measures. On June 30th 1992, a bill was passed by the National Assembly to introduce far-reaching controls. From now onwards, an exporter must seek from the Ministry of Health a certificate to the effect that the drugs which he proposes

to export have been produced in accordance with the well-defined principles of Good Manufacturing Practice. If such a drug is not licensed in France, e.g. because it serves a purely tropical need, the manufacture must explain why he has not sought registration, and the Minister will at the very least pass on this information to his colleague in the country of destination. He can go further, examining such a drug and (if it has an unfavourable efficacy/risk ratio) prohibiting its export. If a drug has been suspended or withdrawn in France it will not be eligible for export at all.

At the time of writing, all these measures had yet to be approved by the Senate, but there was little likelihood of their being challenged. The only reservation one must express is as to the rigorous enforcement of the new rules. The best guarantee for that will be frequent policing by the same well-informed bodies which goaded the government into action in the first place.

Ultrasound and foetal maturity

The American College of Obstetricians and Gynecologists has a tradition of publishing consensus documents of a type at which Americans excel. What results is naturally an American consensus, but a reasoned one, with which others should only disagree if they have equally reasoned arguments to do so.

Now at last reaching the journals is the ACOG's "Committee Opinion No. 98" on the problem of determining foetal maturity in a pregnancy where there is a need to plan for a repeat caesarian section. Essentially the ACOG tries to define what criteria one will have to meet if one is reasonably to conclude that the foetus is mature, without having recourse to amniocentesis.

Here are its alternative criteria – only one of which needs to be fulfilled:

1. Foetal heart tones have been documented for 20 weeks by nonelectronic foetoscope or for 30 weeks by Doppler.
2. It has been 36 weeks since a positive serum or urine human chorionic gonadotrophin test was performed by a reliable laboratory.
3. An ultrasound measurement of the crown-rump length, obtained at 6–11 weeks, supports a gestational age of ≥ 39 weeks.
4. An ultrasound, obtained at 12–20 weeks, confirms the gestational age of ≥ 39 weeks determined by clinical history and physical examination.

As the ACOG adds: "These criteria are not intended to preclude the use of menstrual dating. If any one of the above criteria confirms gestational age assessment on the basis of menstrual dates in a patient with normal menstrual cycles and no immediately antecedent use of oral contraceptives, it is appropriate to schedule delivery at ≥ 39 weeks by the menstrual dates. Ultrasound may be considered confirmator of menstrual dates if there is gestational age agreement within 1 week by crown-rump measurement obtained at 6–11 weeks or within 10 days by the average of multiple measurements obtained at 12–20 weeks."

From the international point of view there may be a little more to be said about the place accorded to ultrasound in this scheme of things. That apart, there is much here that accords with world opinion.

Antibiotic resistance: from threat to crisis

In 1941, to quote a splendidly courageous new paper by Harold Neu from New York [1], 10,000 units of penicillin administered four times a day for four days cured pneumococcal pneumonia; today, a patient could receive 24 million units of penicillin a day and die of pneumococcal meningitis. Some do. The story is a familiar one, but it has too many recent sequels for comfort. In 1984, almost 100% of specimens of *Pseudomonas aeruginosa* tested in the USA, Europe and Japan were inhibited by less than 1 μ /ml of ciprofloxacin; now there are hospitals where a quarter of all *P. aeruginosa* are resistant, not merely to ciprofloxacin but to all the fluoroquinolones. The case fatality of multi-drug resistant TB seems to be between 40% and 60% [2]. What is happening in sophisticated hospitals in East and West is bad enough; turn South and it becomes far worse. In 1990, an epidemic of *Shigella dysenteriae* infection occurred in Burundi, involving a strain which was resistant to all the oral antimicrobial agents available in that country [3]. It is anything but an isolated example.

Anecdotal? Incidental? Pessimistic? That was now precisely the way that some people – representing the antibiotic-producing pharmaceutical industry – reacted when antibiotic resistance was the topic of a preliminary meeting at Bethesda held by the National Institutes of Health, with WHO in tow, in the mid-1980's. The wretched consequence of these tactics was documented by Jill Turner in *The Lancet* at the time [4]; letters went to the Assistant Secretary of State for Health portraying those who were concerned about antibiotic resistance as undesirables and enemies of the U.S. pharmaceutical industry. The N.I.H. hurriedly backed out; WHO remained silent in its embarrassment; and what was to have been the opening of a major campaign against antibiotic resistance petered sadly out in a number of workshops and obscure publications, calling feebly for more investigation. Despite the campaigning of such high-minded experts as Norway's Tore Midtvedt [5], it has been impossible to maintain the sense of urgency which was – and is – so much needed.

The question remains unanswered to what extent the original NIH initiative, had it been carried grandly through, would have significantly slowed down the resistance epidemic and resulted in a less worrisome picture than that which confronts us today, seven years later. Resistance will arise even where medicine is practised optimally. It is an undeniable fact, however, that reckless prescribing of antibiotics – and use of the latest products where something older and simpler would suffice – is among the things which do encourage resistant strains to emerge, both in the hospital ecosystem and in the community at large. We return to Harold Neu, who says the obvious – but unfortunately it still needs saying: “The

responsibility of reducing resistance lies with the physician who uses antimicrobial agents and with patients who demand antibiotics when the illness is viral.... It also is critical for the pharmaceutical industry not to promote inappropriate use of antibiotics for humans or for animals because this selective pressure has been what has brought us to this crisis." As Midtvedt would say: Amen.

References

- 1 Neu HC. The Crisis in Antibiotic Resistance. *Science* 1992;257:1064–1073.
- 2 Iseman MD, Madsen LA. *Clin Chest Med* 1989;10:341.
- 3 Ries AA et al. In: Abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL (1991). Washington DC: Am. Soc. Microbiol., 1991, 1876.
- 4 Turner, J. Antibiotic conference cancelled for second time. *Lancet* 1985; February 8th, 333.
- 5 Midtvedt T. Pencillins, cephalosporins and tetracyclines. In: Dukes MNG. Side effects of drugs annuals 12–16, Amsterdam, Oxford and New York: Elsevier Science Publishers, 1988–1992.