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Hippocrates

Are you sure you're not depressed?

Endogenous depression is a serious, life-destroying, soul-destroying disorder. If some of the treatments which have to be used to provide relief for it have unpleasant adverse effects, then so be it, so long as we have nothing better. MAO inhibitors, tricyclics and SSRI-inhibitors all have their place and we should be grateful for them. But heaven protect us from those who would persuade us that we need these unpleasant (and expensive) forms of treatment when we are in fact no more than distressed, disconsolate, doleful, uncomfortable, uneasy or just plain miserable. In the western world, the drug peddlers have been at it for many years, with too many doctors in tow. Now the pressure is being stepped up on those unfortunate souls in the developing world who do not realize that they are depressed at all. In the middle of a regional economic slowdown this summer, when plenty of people had plenty of reasons to be unhappy, the *Bangkok Post* published an interview with one Chairat Dejkraisak, managing director of the national subsidiary of a certain multinational [1]. "With an increasing number of Thais under stress from the economic crisis, Organon (Thailand) Ltd. expects its new anti-depressant, Remeron, to become its biggest seller" it began, going on to quote Mr Chairat himself: "Remeron is likely to be our number one product globally by 2000. But in Thailand, it may take a bit longer since most Thais do not consider depression to be a sickness."

The Thais, evidently, are level-headed and optimistic people, but Mr Chairat seems to be rubbing his hands at the prospect that this may change, and he relates to the *Bangkok Post* the list of symptoms which should lead his potential customers to realize that what they think is mere sadness may in fact be a disease. "We are now introducing the new drug to doctors but, by law, the drug must be available on prescription for two years before it can be sold over the counter" he concludes, apparently with some regret. That, at least, gives the health authorities time to engage in a little counter-education of the public before Mr C. gets them entirely in his grasp.

Reference

[1] Anon. Anti-depressant seen as likely big seller, *Bangkok Post*, 20th August 1998.

A new disease – if we believe in it

To pause just a little longer in the corner of psychiatry, it might be worth recalling that the drug industry is not the only entity to devise fictitious diseases: the specialists themselves are up to it. A writer on the Internet in September 1998 has pointed out that according to the DSM4 – the current fourth edition of the American psychiatrist's bible of diagnostic classification – disagreeing with the doctor and hence not following his therapeutic advice also constitutes a disease, classified in axis 5 as "non-compliance with medical treatment". Compliance and failure to comply are complicated matters, with a mass of explanations, but in many cases non-compliance is not a question of failure on the patient's part. One possibility is that the physician has indeed prescribed an unacceptable course of treatment, another that

he has failed to explain to the patient why the therapy is needed or how it should be taken. More generally, non-compliance can reflect the fact that there is something wrong with the patient–doctor relationship. There is indeed something which one might term "intelligent non-compliance" (a sign of health rather than disease) and on occasion we may be thankful that there is.

Classifications of disease never are perfect and ambitious systems like the International Classification of Diseases and Causes of Death have sometimes been held up to ridicule because of their odder ramifications. There was a time when the "accidents" section of the ICDD actually made provision for "falling off a haystack" and "collision between a tram and an aeroplane". But at least these were stark and undeniable calamities, though the latter would seem a trifle unlikely. Non-compliance is in a different category. If it is to be regarded as pathological, may we assume that the next step will be to treat it forcefully, straitjacket and all?

More generally, it does seem that classifications of this type are sometimes overused. Their primary and valid purpose is simply statistical; for the sake of the public health records, one needs to put disorders into pigeonholes, and it is thanks to systems like this that trends in disease incidence can be detected and their causes studied. The risk is that these systems will indeed be regarded as bibles of diagnostic practice. Hippocrates knows of instances where a medical witness in malpractice proceedings found himself under attack because the appalling mental syndrome from which a patient suffered as a result of someone's error did not fit in with any classification in the DSM; therefore, the lawyers argued, it could not exist. That is bad enough; but to argue that an individual is diseased because his behaviour does incontrovertibly feature in the Manual is surely carrying things much too far?

Death in cardiac surgery [1,2]

Back in 1995, Britain's Bristol Royal Infirmary took the unusual step of commissioning an independent expert to examine the mortality rate in its operating theatres for neonatal cardiac surgery. Seven years before, the hospital had been alerted by one of its anaesthetists to the real possibility that something was seriously wrong; it took, alas, all of those seven years to do something about it. The external assessors report was nothing short of horrifying. Of the two surgeons performing neonatal cardiac operations, the elder one had a record 87% mortality when operating for a septal defect, and 13.5% when correcting the tetralogy of Fallot. His young colleague had enjoyed a far better record until in 1992 he set out to correct transposition of the great vessels; of the first 38 children on whom he performed surgery, twenty died – a fact which he himself somewhat lightly attributed to the fact that he was still on a learning curve. So, unhappily, were his patients.

The findings led to legal proceedings being instituted against the two surgeons by the families of children operated at the hospital between 1988 and 1995; of 53 patients, 29 had died and four had suffered permanent brain damage. The legal finesses will be discussed elsewhere in this *Journal.* Professionally the most important sequel to the events at Bristol is an initiative taken by the British Society of Cardiothoracic Surgeons in May 1998 to evaluate critically the operative results of all surgeons working in the field so that measures can be taken where proper standards are not attained. Is this enough? The British popular media have not been uncritical of the fact that only self-regulation is proposed; they also raise the question whether a surgeon's record will be made public so that potential patients or their families can choose their surgeon critically.

It is evident enough that neither all surgeons nor all surgical centres can be expected to attain the same safety standard; the patient population can differ substantially as regards the proportion of high-risk cases. All the same, the world literature provides by now a fair measure of what can be achieved in

terms of survival among neonates operated upon for cardiac defects; it can hardly be difficult to identify professional under-achievers and eliminate avoidable risk.

References

[1] *The Times* (London), 30 May 1998.
[2] *The Independent on Sunday* (London), 31 May 1998.

Artificial insemination and the next generation

Intracytoplasmatic sperm injection (ICSI) is now six years old. It is intended to render artificial insemination possible even where the male partner suffers from greatly reduced fertility; it requires only a single sperm, and where ejeculation is not feasible the material can be obtained surgically from the testis or epididymis. In the Netherlands, some ninety women had been treated with the method up to 1990, at which time the programme was suspended in so far as the use of surgically obtained sperm was concerned. What had happened was that a government commission charged with family planning techniques had become concerned as to risks to the offspring which might ensue if sperm obtained surgically were unripe, abnormal or stale.

Specialist using the method have risen in protest, arguing that the method can reasonably be considered safe provided some precautions are respected. In particular, only morphologically normal and motile sperm should be used, and genetic screening should be carried out in advance to exclude cases where there is a male chromosome disorder. The best evidence that ICSI as a whole does not carry a serious risk of producing abnormal offspring is provided by the largest series of treatments to date. One American study by Palermo et al. presented in 1996 the results of 987 treatments in 751 couples [1]. 578 births resulted; of the neonates, 9 had marked congenital defects and 6 more minor defects. The total incidence of defects (2.6%) was lower than the 3.5% found with conventional *in vitro* fertilization by the same investigators and indeed lower than the 3.7% incidence of congenital abnormalities reported among the population of New York. Within the Palermo series, 94 had involved surgical obtention of sperm; in that sub-series significant congenital disorders had been found in one of 41 children born following use of sperm from the epididymis. In only six cases had sperm been taken from the testis; five live births had followed, and in one of these the neonate proved to have a major congenital disorder. The Brussels group with which the surgical method originated has reported on 29 surgical cases and has seen no increase in congenital abnormalities [2].

Little is to be expected of animal studies in examining the safety of methods like this. Common sense seems to suggest at the moment, however, that where couples seriously want children despite reduced fertility of the male partner it is reasonable to use whatever method is needed to obtain viable and apparently healthy sperm. The prospective parents need to be closelly consulted and counselled since ultimately it is surely they, rather than a government commission, who will have to decide whether the surgical method has a future.

References

[1] G.D. Palermo, L.T. Colombero, G.L. Schattmann et al., Evolution of pregnancies and initial follow-up of newborns delivered after intracytoplasmic sperm injection, *JAMA* **276** (1996), 1893–1897.

[2] M. Bonduelle, A. Wilikens, A. Buysse et al., Een follow-up study van kinderen geboren na intracytoplasmatische sperma-injectie, *T.F.O.* **11** (1997), 13–19.

Clinical trials in mild stroke

Keeping a watchful eye on anything smacking of medical impropriety, the popular media are always ready to pounce on clinical investigation. The notion of the "human guinea pig" makes juicy headlines, but that is all to the good; those of us who venture into this borderline area of medicine should be thankful that the community is concerned that we behave ourselves.

The media in the Netherlands still echo with a thirty-year-old alert; in the late sixties, the State Organization for Applied Scientific Research (TNO) was found to be involved in a placebo-controlled study of the value of anticoagulants in patients with a history or myocardial infarct as a means of preventing recurrence. Since it was generally considered at the time that the treatment was effective, the exposure of patients to a placebo control was duly castigated. Memories of that incident had not entirely faded by March 1998 when an article in the magazine of Utrecht's University Hospital led the newspapers onto the trail of the so-called SPIRIT study ("Stroke prevention in reversible ischaemia") [1]. In a group of hospitals, mostly in the Netherlands, a total of 651 patients with a history of mild stroke had been systematically treated with anticoagulants (INR 3.0–4.5); a comparison group of 665 similar individuals had been treated only with low doses of aspirin. By the time the media realized what had been going on, the study had in fact been terminated and with good reason. In the anticoagulant group, there had been 53 serious cerebral haemorrhages, seventeen of them fatal. In the aspirin group there had been only six such complications, a single one being fatal. It had all been published calmly late in 1997 in the *Annals of Neurology* [2] and early in 1998 in the Netherlands' national medical journal [3]. Was there reason to condemn the fact that the study had been done at all?

According to the study's co-ordinator there had been sound reasons for the investigation. It had been inspired by favourable experience with anticoagulant treatment in cases of cardiac dysrhythmias accompanied by transient ischaemic attacks. Might the same approach not work in cases of mild stroke? In retrospect some critics argued that the two conditions were so entirely different that the investigators should never have extrapolated from one to the other. The physicians concerned pointed out in self-defence that, at the time the study was planned, earlier work had provided reason to believe that anticoagulant treatment following stroke was indeed superior to aspirin; the study had been well-planned to test the hypothesis, and had been carried out in a proper manner; as soon as a routine intermediate evaluation showed that aspirin (despite the modesty of its own effect) was more effective the study was terminated. Thanks to the investigation, the use of anticoagulants in mild stroke had now virtually been abandoned.

All the same, the controversy leaves some questions unanswered. If it is true that widespread use was already being made of anticoagulant treatment in mild stroke, without proper evaluation, it was defensible to look at it scientifically; the publications do not make it clear whether it was indeed being employed more than incidentally. If not, the view of some critics that giving anticoagulant treatment to certain cases of mild stroke is asking for trouble, surely ought to have prevailed. At all events, a European–Australian follow-up study (ESPRIT) is now under way, but notably using lower doses of anticoagulants.

References

[1] Newspaper reports in *De Telegraaf* (Amsterdam), March 19th and 20th and *NRC Handelsblad* (Rotterdam), March 19th and 24th.

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[3] J.W. Gorter, Preventieve behandeling van patienten na niet-invaliderende cerebrale ischemie door vermoedelijk arteriële oorzaak, *Ned. Tijdschr. Geneesk.* **142** (1998), 306–312.

Do you have a serotonin inbalance?

At any given time, the community has usually had a number of favourite labels for obscure disorders. Two centuries ago it was "The Melancholy", and people regularly died of it. The latest in the series is a "serotonin inbalance" which provides not only a label but also an excuse for prescribing a whole range of drugs which are supposed to modify the serotonin system, one would hope in an appropriate manner. The difficulty is that we still have only a limited insight into what serotonin does, how, where and why; as with the blood clotting system, the more we learn about it the more complications we encounter. Where serotonin is concerned, that is particularly evident from a sober paper by Dennis Murphy and his colleagues which came out within the last few months [1]. Hippocrates himself is awed by it, and gladly leaves comment to a particularly sensible Alaskan psychiatrist, Dr Douglas Smith, who is more expert than most at detecting medical fictions in his particular field. Dr Smith comments to us:

> "This humbling article describes the 15 known 5-HT receptors, the different projection pathways, the differential effects of 5-HT transmission on various areas of the brain, the multiple and complex cotransmitters and co-modulators, and the different actions of 5-HT as a neurotransmitter, neuromodulator and neurohormone. I like the conclusion; "even partial understanding of the final mechanisms involved in the therapeutic effects of drugs like the SSRI antidepressants continues to be elusive"."

So what is Dr Smith's advice? Listen:

> "The next time your psychiatrist tells you have a serotonin imbalance ask him (1) Is it too high or too low? (2) Is it imbalanced in the dorsal, medial, or caudal raphe nuclei? (3) Is it affecting the hippocampus, the basal ganglia, the cortex, or the cerebellum? (4) Are you talking about serotonin in its role as a neurotransmitter, neuromodulator, or neurohormone? (5) How will the drug restore the balance? (6) How will the drug be smart enough to know when the balance is restored? (7) What will the drug do to all the other serotonin subsystems that aren't out of balance?"

That, surely, should discourage him from meddling lightly with your serotonin.

Reference

[1] D. Murphy et al., Brain serotonin neurotransmission: an overview, *J. Clin. Psych.* **59**(Suppl. 15) (1998), 4–12.