

RSM 00015

## Hippocrates

### **Pharmaceuticals and political upheaval**

No country can claim to have attained the ideal in national pharmaceuticals policies. Most have struggled along in the hope of providing as much assurance as possible that the medicines on the market are effective, safe and properly made; these are things which the individual doctor cannot usually assess for himself, and the various institutes and committees which handle drug regulation effectively try to act on his behalf. There are differences in national view as to how stringent such regulation should be; among western countries policies range from the frugality of Norway (some 900 compounds on sale) to the prolixity of Italy (with something approaching 2000).

All the same, national drug administrations have in the thirty years since the thalidomide disaster edged towards their various ideals, making errors on the way, but generally getting better, and largely uninfluenced by swings in party politics. They have done a lot to prevent the reckless marketing of potentially dangerous products.

Two recent trains of events could upset that steady progress. One is the attempt to attain a single internal market in the European Community by 1992; which as far as the pharmaceuticals market is concerned might mean riding roughshod over much that has been achieved in the interests of safety and caution, ending up with something like the lowest common multiple of the national drug lists. Just as some compromises on that particular issue seemed to be emerging, however, the eastern part of Europe erupted politically, raising the question as to what that will mean for pharmaceuticals policies in a further seven countries.

Very obviously, a great part of Eastern Europe has for forty years lived with isolation, restrictions and shortages on many fronts; the West came to be seen by many as a land of milk and honey, the free economy as the solution to every problem. Is it? In a field such as pharmaceuticals, the West has itself experienced the necessity of constraining pharmaceuticals in the interests of public safety. The East has done something of the same, but its policies have been generally overshadowed by the much greater constraints imposed by bureaucracy and weak currencies. The risk now is that, with the relaxation of political ties, pharmaceutical regulations will be cast aside as just one more vestige of a past which people are anxious to forget; that would leave the road wide open to the sort of commercially dominated extremes which the West has been trying to abandon.

The German Democratic Republic may present the greatest challenge to moderation. The Medicines Book of the G.D.R. reflects some sensible and well thought out policies; there is a fair choice, yet little in the way of unnecessary risk. Drug information is dull, but generally reliable. The Democratic Republic was the first country on earth to institute a compensation scheme for vaccine injury. In various respects one might consider it ahead in terms of public policy of the Federal Republic, where a massive industrial lobby has impeded achievement and where *Die Rote Liste* – the medicaments handbook – is a vast compendium containing a great many nonsensical products (how many fixed combinations with digitalis can you imagine?) and very little prescribing information. The trouble is, as a correspondent from the F.R. reminds us, that “it might prove difficult to convince the citizen of the G.D.R. of the quality of his health system, since he has experienced it only in a situation of penury. What use are well formulated medicines if they cannot be delivered? The danger exists that western health systems will be uncritically adopted, in the first place because the Western pharmaceutical industry with its economic potential is bulldozing its way into the market, and in the second place because the population wants the “good” medicines of the West. After the opening of the frontier between the GDR and the FRG in November 1989, in some Berlin pharmacies the entire monthly supply of Aspirin tablets was sold out in a day, and the customers were not to be convinced that the substantially cheaper generic equivalent was essentially as good.”

Weld GDR and FRG into one on equal terms, taking the best from the practice of each, and you might be on the way to some sort of policy ideal. Will it happen? A recent WHO visitor to East Berlin returned shaking his head sadly: “They are simply waiting” he said “to be colonized.”

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### **Two doctors, one patient**

As recent cases from Sweden and The Netherlands remind us, medical disciplinary tribunals can easily find themselves in trouble when handling cases of possible fault in which the patient has been seen by more than one physician. The Dutch case involved a not uncommon situation; the hospital to which a woman had been admitted for hip surgery suspended the uninspired long-term drug therapy (nitrofurantoin, carbachol and two diuretics) which she had been receiving from a urologist for a urinary disorder. Her urological condition was nevertheless treated adequately while she was in hospital and the hospital took steps to ensure that the general practitioner would follow it up. Nevertheless the Central Medical Disciplinary Council admonished the hospital physician for interfering with the treatment prescribed by a colleague, partly because the hospital physician had no special knowledge of urology. The Council has now in turn been berated for its decision by the clinical pharmacologist Offerhaus in Holland’s national medical journal [1] and pilloried in the *Lancet* [2]. Clearly it is very often wise to suspend existing therapy when a patient is admitted for surgery, and in this case (even though it was polypharmacy of dubious merit) it was done with due care.

Sweden's Council for Medical Responsibility (HSAN) has been in trouble on a rather different issue, involving a boy of 14 with testicular torsion who presented with his symptoms at a health centre [3]. The duty physician A missed the diagnosis but arranged for the boy to be seen at once by his administrative superior B who was also the district medical officer of health; he too missed the diagnosis and the boy was discharged on antibiotic therapy only. The HSAN held both physicians liable. Correctly? As the senior physician Rudolf Schlaug points out in a recent *Läkartidningen*, the patient himself had never consulted B; nor was B involved because he was A's administrative superior; A had consulted B, who had the same medical rank, simply because he wanted the opinion of an experienced elder colleague. The fact that neither physician succeeded in diagnosing this fairly rare condition is not the issue of principle here; the problem is, as Schlaug puts it, that disciplinary decisions like this could cause doctors to become very cautious about giving advisory opinions at all; the HSAN, in his view, sometimes tends to have more regard for formal administrative structures than for the demands of good medical tradition.

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### **Placebo comparisons: when enough is enough**

In conducting a clinical study, when do we become so certain that drug therapy is effective that it becomes improper to continue to use placebo? The question arises often enough in the individual study of a life-saving drug, but Bonfils and Rene in France have raised it on a broader front (4). We now have quite a range of symptomatic therapies for peptic ulcer, including the H<sub>2</sub> blockers, prostaglandin treatment and drugs of the omeprazole type; all of them result in healing of the ulcer, though none cures the underlying disorder. For new entrants to these classes, all that one needs to know medically is how they rank with respect to those we already have. The scientific value of many of these double-blind placebo-controlled trials is for a number of reasons very limited: the more rigid the conditions of study, the less they will resemble those of daily practice; results of meta-analyses are distorted by national variations in normal ulcer healing rates, bias in patient selection and the non-publication of negative results. To continue to perform vast numbers of placebo-controlled trials with these new drug variants merely so that they can meet regulatory requirements and earn their marketing licences represents a vast waste of energy, money and research capacity. And, one would add, placebo exposure.

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### **Antibiotics: talking and doing**

How serious is the problem of antibiotic overuse? Six years ago, a large NIH/WHO meeting at Bethesda, MD, sought to come to grips with the problem;

despite palpable resistance from some quarters, the work at that meeting (and the follow-up undertaken at its instigation) was published by Levy et al. in 1987 [5]. The picture is not complete but it is clear enough that resistance has in some areas of the world developed very fast indeed, and that this correlates with reckless selling and prescribing, including the generous use of those newer agents which in fact should be prescribed very restrictively. A 1990 report on a 1988 WHO symposium [6] provides a much smaller but newer sketch of what is happening. So far, development of newer drugs has generally kept pace with emerging resistance, but these sophisticated replacements are not cheap. For the developing world, it is of concern to note the conclusion here that “estimates of resistance of *E. coli* and *Shigella* spp. to ampicillin, tetracyclines, nitrofurantoin, and first-generation cephalosporins often exceeded 50% . . . . Particularly troublesome were reports of resistance of *Str. pneumoniae* and *H. influenzae* to penicillins, tetracyclines, chloramphenicol, and TMP-SMZ.” Laudably, the meeting showed how antibiotics should be used in some selected clinical conditions; it noted what a series of organizations have done to address the overall problem; but it also noted realistically that at the primary health level people are still neither informed nor concerned. It is excellent that a meeting like this calls for a global WHO surveillance programme on antibiotic use and resistance; the difficulty is that WHO itself is rarely given the financial means to do more than echo the exhortation; in the two years since the meeting precisely nothing seems to have happened. In the meantime, antibiotics have remained on over-the-counter sale in half the world’s pharmacies. Shall we have to await a massive tragedy before we are prepared to change our ways?

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### Doctors, sleep and night duty

The expectation that medical students and junior doctors will work impossible hours is deeply rooted in medical apprenticeship; like most initiation ceremonies it is defended stoutly by many who have survived the ordeal and see no reason why others should escape. All the same, it is now being questioned for the good reason that tired people make mistakes. Orton and Gruzelier [7] opened a phase of the current debate in Britain by showing cognitive changes in house officers who had been on night duty; in that same country, a study commissioned by the health authorities had found junior doctors in paediatric departments on duty for an average of 91 hours per week, with a period of rest which never exceeded four hours [8]. There had been similar findings in the USA although most of the other evidence as to tiredness (such as that provided by Cashman et al. in a study of anaesthetists [9]) identified only to subjective feelings of fatigue (which do not necessarily mean impaired performance). A Minnesota group who studied the way in which house officers on duty spend their nights has called for reconsideration of the question as to whether “the experience of continuity provided by night call is essential to the development of young physicians” [10]. And now in 1990 the AMA, in taking a critical look at some of the less happy experiences of medical students, has devoted

attention to sleep deprivation as a real problem [5,6]. Here, tradition may not be in the interests of good medicine.

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### **Medication errors – a partial view**

Read only the summary of last summer's paper by Raja et al. on "Medical errors in neonatal and paediatric intensive-care units" and you may be left with some lopsided impressions. Having examined prospectively four years of work in a 17-bed NICH and a seven-bed PICH, they noted in summary that "... 315 iatrogenic medication errors were reported among the 2147 neonatal and paediatric intensive-care admissions, an error rate of 1 per 6.8 intensive-care admissions (14.8%). The frequency of iatrogenic injury of any sort due to a medication error was 66/2147 (3.1%) – 1 injury for each 33 intensive-care admissions. 33 (10.5) error were potentially serious. 32 (10.2%) causes mild patient injuries and 1 patient had acute aminophylline poisoning... [13]".

Part of the reserve with which one must regard such figures is brought forward by the authors themselves: people do not always admit to or report their errors and "it is likely that the frequency of errors was much higher than reflected in the incident reports". Beyond that, however, the figures relate only to errors which arose after the drugs had been prescribed, i.e. they reflect such matters as giving the wrong dose or administering it at the wrong time; they therefore relate largely to the acts or omissions of pharmacy staff and nurses, and only secondarily to doctors' errors since the physicians were at this stage usually no longer involved. All these same, these are some of the figures which we need to build up a proper picture of errors in health care. The important thing is to look at the detail, trying to determine what the sites and causes of error were, and only with great reserve totalling the work from different studies.

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### **Un-quality of life?**

Another shiny new volume has arrived with evidence that pharmaceuticals improve the quality of life; by now we should all be convinced. One goes on hoping, all the same, that someone will turn up to bring rather more balance into the discussion, setting the debit items alongside the credit rating, so that a mere prescriber knows where he is. That some widely used classes of drugs do make people feel dreadful is perfectly well known, and when one looks into the matter as thoroughly as has been done for the credit side one can uncover a lot of preventable misery. The oral contraceptives have making some women feel disconsolate since 1960, though some (male) doctors have pooh-poohed the notion. The mood problems and vague headaches which are familiar enough to some users come to the fore again in an Australian study last November [1] which showed that half the women

who discontinue the “pill” do so because of adverse effects, many of them quite minor or subliminal ones of this type. Malaise, or whatever one wishes to call it, is a known cause of poor compliance with treatment, which is as good an indicator as any that the quality of life has been lessened. Not so surprisingly, the best emphatic work on impairment of quality of life caused by certain drugs has been engineered by those who have competitive products to sell. Beta blockers for hypertension? In the early nineteen seventies people became very upset if you suggested that they deranged mood, driving or sex. But then came the ACE inhibitors, and without anything exciting to say for themselves they clambered to success on the basis of claims that the beta blockers were so very awful. *Sic transit gloria mundi*. (One did hope to keep Latin out of this Journal but it must have the last word.)

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