

## Safety and risk in practice

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### Secrecy on drug safety?

Two years ago this Journal published the proceedings of an impressive symposium devoted to the secrecy which often surrounds the drug regulatory process. Undoubtedly that symposium has been one of the elements leading to a current re-evaluation of the extent to which such agencies can reveal the basis of their decisions. Several national bodies have already amended their routines, and at the level of the European Union a series of European Product Evaluation Reports (EPAR's) have appeared since September 1996 to present in brief the factual scientific basis for new drug approvals. A significant sign of progress was the holding of a meeting on 26th June in London where the European Medicines Evaluation Agency discussed assessments of nine of its reports undertaken by the International Society of Drug Bulletins [1].

Helpful though the EPAR's were found to be, ISDB found that they were not consistent in their style or in the amount of information, which they provided, including the evidence from clinical trials which had been provided by the manufacturers. It may be hoping for too much to expect a level of detail in the EPAR's sufficient to enable an outsider to the process to assess the correctness of an agency's decision. What one might however hope for is a text which will indicate more clearly where doubts may still persist as to a drug's long-term safety, so that independent monitoring of a drug's performance in the population can be directed to the issues which really matter.

### Reference

- [1] Press release: ISDB/EMEA meeting on 26 June 1998 in London; also accompanying evaluation materials provided by ISDB to this journal.

### Quality of life: the patient's view

In an eloquent paper by de Graaf and de Graaf-Posthumus appearing elsewhere in this Journal, the point is made that an individual with Down's syndrome may have a much more positive view of his or her own quality of life than an assessment by a third party might lead one to believe [1]. There seems to be a similar discrepancy in some cases of multiple sclerosis. Rothwell et al., in a British paper published last December, found that the elements of life which were determinant for a patient's view of its quality could be rather different from those recognised by his or her physician [2]. In particular, mental health and emotional balance were for patients more central than physical performance. For the practice of safe and sound medicine it is essential to be aware of these things. An obstetrician who believes that a Down's child, once born, will necessarily feel abnormal and unhappy may be too prone to favour termination of the pregnancy. Similarly, a neurologist with too bleak a view of the world of multiple sclerosis may insist on medicinal and other forms of therapy directed exclusively to physician performance and representing an unwanted new burden on his patient.

## References

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- [2] P.M. Rothwell, Z. McDowell, C.K. Wong et al., Doctors and patients don't agree: cross-sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis, *Brit. Med. J.* **314** (1997), 1580–1583.

## Quality of complementary medicines

In an expert report to the Government of South Africa, submitted in March 1998 and since adopted into a draft law, proposals for the reform of the medicines control system included an outline for a new regimen to deal with complementary medicines. While remaining exempt from normal requirements regarding proof of efficacy, they would be assessed like other drug products as regards their quality and safety.

How necessary this is can be seen from a series of cases published in Europe relating to injury by complementary medicines which were either improperly made or had undeclared – and risky – constituents. In the Netherlands, for example, there have over a long period been reports of alternative products, which proved injurious because of constituents ranging from manganese [1] to corticosteroids [2]. A particularly serious report from the same country relates to a woman who developed hyperthyroidism after using "Ader-Rein", also known as "Vascu-Vitaal" for intermittent claudication [3]. The declared composition of the drug admitted to 36 components, including vitamins, minerals, amino acids and tissue and plant extracts. Since one of the components was thymus it seems likely that during the production process thyroid had been used in error; analysis indeed showed the presence of T3 and T4.

## References

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- [3] C.J. Doorenbos, L. Van Aart and S.G.A. Koehorst, Hyperthyreoidie door verontreiniging van het alternatieve geneesmiddel Ader-Rein (Vascu-Vitaal), *Ned. Tijdschr. Geneesk.* **141**(52) (1997), 2572–2575.

## Scabies in hospital

Epidemics of scabies in institutions could and should have been eliminated a long time ago. Yet three physicians who looked into the literature early in 1998 found no less than 44 *published* records of epidemics in recent years [1], most of them apparently involving hospitals in the western world which had both the knowledge and resources to prevent them; the real incidence may be considerably higher. In part this is the typical story of what is all too readily regarded as a nineteenth-century problem and hence overlooked. There are analogies in Europe with urban or geriatric scurvy; and how many young physicians would today think of scurvy – or for that matter scarlet fever – as a diagnosis and recognise it immediately in a patient? In the case of scabies it is readily mistaken for drug rash, dermatitis or senile pruritus, and some senile or mentally incompetent patients may fail to make it known that they are suffering from pruritus. For such reasons, an epidemic may be present for a considerable time in an institution before it is recognised and tackled.

One problem where scabies is concerned is the concentration in specialised institutions of patients at particular risk of infestation. *Scabies norvegica* is an especial risk in groups of patients suffering from dementia, AIDS, incontinence, mental handicaps or poorly controlled diabetes, or subjects being treated with immunosuppressants or corticosteroids. Unlike other forms of scabies it is readily transferred within a group by carriage on utensils and materials, without the need for direct physical contact. However, institutional personnel can easily become infested themselves and transmit the mites which cause the problem from one patient to another.

Where the condition has been recognised, treatment is not always adequate; *scabies norvegica* demands particularly intensive and prolonged therapy in the individual, as well as complete disinfection of the environment – for example, soft furnishings in the ward. Without such measures, the condition is almost certain to recur.

## Reference

- [1] J.A. Van Vliet, M. Samsom and J.E. Van Steenberg, Oorzaken van verspreiding en terugkeer van scabies in gezondheidszorginstellingen; literatuuranalyse van 44 epidemieën, *Ned. Tijdschr. Geneesk.* **142**(7) (1998), 354–357.

## Viagra – do we have a problem? [1]

Sildenafil (Viagra<sup>®</sup>) is surely the drug most widely discussed in the public arena during 1998. Introduced in the United States at mid-year, it was at the same time positively assessed for introduction in the countries of the European Union; formal approval followed in September and the race to market and buy it – by fair means or foul (including the Internet) began. Bearing in mind that the history of aphrodisiacs and products claimed to increase male potency has been one of repeated failures (and some ugly toxicology) the release by critical regulatory agencies of a drug which clearly does enhance the response to sexual stimulation is striking.

The approach is novel. Normally, male sexual stimulation leads to penile erection in a four-stage process. Nitrous oxide is first released into the corpus cavernosum and this in turn activates guanylate cyclase. This induces an increase in the levels of cyclic guanosine monophosphate (cGMP) which relaxes the unstriated muscle of the corpus cavernosum, causing blood to flow in. The process is terminated by the enzyme phosphodiesterase type 5 which causes cGMP to break down. Viagra<sup>®</sup> is a specific inhibitor of this latter enzyme, and is therefore capable of prolonging and perhaps potentiating the effect of cGMP and hence of erection.

To date the enzyme inhibiting effect of the drug seems to be remarkably specific but it clearly does affect to some extent the processes inducing vasodilatation elsewhere in the body. This no doubt explains such symptoms as flushing and headache, as well as Viagra's demonstrated ability to potentiate the blood-pressure lowering effect of nitrates (causing a potentially dangerous interaction). It is, however, peculiarly difficult in this case to decide on the basis of the pre-marketing investigations which delivered these findings whether Viagra<sup>®</sup> will prove to be safe in the field. For *any* drug the pattern of use and misuse inevitably changes once it enters the market and the medicine cabinet. It will be employed by a wider spectrum of users, in all states of health, of differing ages, and presenting a range of unsuspected deviations from the physiological norm, e.g., unusual enzymatic activity or deficiency; in addition a drug in the field will be over-used, deliberately or inadvertently misused, and employed alongside numerous potentially interacting influences. A drug improving sexual performance seems particularly likely to be

used incautiously, notably by those seeking to raise their coital activity to extravagant levels, and those whose state of health imposes a need to limit physical activity. Six deaths known to the manufacturer by May 1998 and reported to the FDA seem most likely to have been attributable either to these factors or to an interaction with organic nitrates. By July, the FDA was aware of 123 reports of death, generally within 4–5 hours of taking the drug; though many of the reports were incomplete, most of the individuals involved had a history of cardiac disorders. With Viagra<sup>®</sup> sales likely to explode in the latter part of 1998 it seemed that much more news was to be expected, and as of October a trend seemed to be emerging. Shah from Los Angeles had described two cases of ventricular tachycardia, in men of 52 and 72, respectively; neither was using nitrates, but both had a history of cardiac disorders. Other writers had reported severe pulmonary haemorrhage in an elderly man with interstitial lung disease, and cystitis in some 15% of the spouses of sildenafil users. All these things suggest that increased sexual exertion is causing sufficient strain for latent weaknesses in the system to become manifest; so far they hardly look like pharmacological effects of the drug.

## References

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- [2] Anon. First oral therapy for erectile dysfunction, *FDA Medical Bulletin* **28**(1) (1998), 2, summer issue.
- [3] Anon. Viagra deaths often occur within 4–5 hours, *FDA Safety Update*. Pink Sheet (Prescription Pharmaceuticals and Biotechnology), 60: 11 August 31st 1998.
- [4] Sildenafil in the treatment of erectile dysfunction. Letters to the Editor, *New Engl. J. Med.* **339**(10), 699–702.
- [5] J. Feenstra, R.J.H.M. Van Druie-Pierik, C.F. Laclé and B.H.Ch. Stricker, Acute myocardial infarction associated with sildenafil, *Lancet* **352**(9132) (1998).

## Clinical trials: the patient's understanding

One aspect of the continuing debate on informed consent to clinical investigations relates to the possibility that the rigid designs for most randomized clinical trials render it impossible to adapt the treatment to the individual patient's needs [1,2]. Individualization of treatment is more crucial in some types of therapy than others, for example, when one is dealing with a drug having a narrow-efficacy safety margin, or a treatment to which individual sensitivity is expected to vary. If in a given trial this risk is truly thought to be present, and the patient is not aware of it, he or she can hardly be said to have given informed consent. Various studies have been directed towards improving the information process so that patients truly are aware of these and other aspects of a trial before consenting.

In a new Danish study on more than 400 out-patients, Kjægaard and her colleagues investigated existing knowledge about randomized trials and the attitude towards clinical research among outpatients, and factors which might influence such knowledge or attitudes [3]. Only 7% of the subjects had ever taken part in a trial, and such knowledge as the subjects had was therefore mostly derived from other sources. The results showed that younger patients tended to have a better understanding of clinical trials and a more positive attitude towards them than older individuals; not surprisingly, a higher educational level was similarly correlated with better understanding. Whereas more than 75% of subjects were aware that participation was voluntary and that a subject had the right to withdraw, well under half understood what randomized trials were and why they were used. Only half understood why placebos were employed. The reader is struck by the fact that forty subjects failed to complete the entire questionnaire (and were excluded for this reason); this could reflect the fact that they were baffled by the topic, in which case the

percentage of positive findings in the study may be inflated. The findings at all events underline the fact that during the recruitment of subjects for a clinical trial, even from a relatively well-orientated North European population, a great deal of general and specific information and explanation need to be given if there is to be a real basis for informed consent. The study still leaves unanswered the thorny question as to how one should explain those risks which could result from failure to individualize treatment.

## References

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## Public health policies – can they do harm?

In an editorial in this *Journal* in 1996, Elisabet Helsing documented the potential of ill-conceived health policies to do harm rather than good, taking her examples from the policies of the former Soviet Union regarding agriculture and nutrition [1]. A new debate, again the field of nutrition, is emerging as regards the harmonization of policies in the European Community. The theory that what is best for one European is necessarily best for another does have some exceptions. The need for vitamin supplementation (or the fortification of foods with vitamins or other supplements) varies not only with climate and nutritional habits but also between population groups. It was shown many years ago that coloured immigrants to Scandinavia brought with them their native habit of shading themselves from the sun; in Nordic conditions this led to deficiencies of vitamin D. The inhabitants of Greenland, by contrast, are over-supplied with vitamin D. The intake of vitamin C in the diet varies very greatly, as does the eagerness of populations to use multi-vitamin supplements. A small debate is currently underway precisely in this field as regards the European Union's belief that infant foods should be vitamins A and D fortified [2]; neither of these vitamins is free of toxicity, and fortifying infant food could readily raise intake to danger levels [3]. Similar debates could readily emerge as regards fortification of the water supply, be it with iron, fluoride or folic acid. It is an area of public health policy which needs to be followed critically.

## References

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## Third generation oral contraceptives and thromboembolism

One of the first issues of the D.M. Davies' pioneering *Adverse Drug Reaction Bulletin*, late in the nineteen-sixties, dealt with the initial evidence that oral contraceptives could cause serious thromboem-

bolic disorders. Thirty years later, issue 191 of the same *Bulletin* stresses the problems which the practitioner still faces in dealing realistically with the issue [1]. The initial calamity of 1969 was perhaps in part dealt with by the hasty and untested replacement of the oestrogen mestranol by ethinyloestradiol. A better documented reaction was the progressive realization that the original oral contraceptives were grossly overdosed, and the rapid development of products offering the same components in much lower concentrations. The problem of thromboembolism never went away, but it was reduced to manageable proportions over two decades.

A new difficulty came to the fore with the introduction of the so-called "third generation" oral contraceptives in the nineteen-eighties. Primarily because patents had expired on the progestagens originally used in the "pill", resulting in a reduction in their marketable value, a series of products with new gestagens (desogestrel or gestodene) were developed and introduced. It has never been clearly demonstrated that these have any real advantage over the earlier oral contraceptives, though claims have been made that their differing effects on the lipid spectrum could prove beneficial. Unhappily, in later 1995 and early 1996 five epidemiological studies concluded that the risk of venous thromboembolism was twice as high with the new products as with their predecessors. The finding was surprising to the extent that the role of the progestogenic component in raising the risk of thromboembolism had earlier been regarded as insignificant. As the *Adverse Reaction Bulletin* concludes, the new evidence of risk has still not been refuted, despite efforts to do so. Further work has merely defined and located the risks more exactly. Public health authorities remain clearly embarrassed by the findings and unable to provide physicians with clear advice on the safest approach to oral contraception in the light of what is now known. In Germany, where the pharmaceutical industry is always quick to demand a legal remedy as soon as its financial interests are threatened, the Federal drug control agency was paralyzed by an administrative court's judgement to the effect that it had failed to prove harm in excess of a "justified level", whatever that may mean [2]. The *Bulletin* itself evidently finds it difficult to advise doctors, as of August 1998, how best to deal with the issue. It considers three options, none of which is fully satisfactory. The first is to inform a woman of the risks of the third-generation products as documented in the literature, but to advise no change in the prescription; this, as the author admits, is likely to spark a difficult discussion with the woman. The second option, to allow the woman to continue on a third-generation product without dwelling on the risks, is unacceptable, since the risk evidence is so consistent. The third option is to advise a move back to the second generation products. The *Bulletin* shrinks from giving this advice, since the new "pills" are effective and the risks concerned are small. At least, however, as the author points out, the prescriber is free to adopt this course; there is no German administrative court to stop him.

What is still lacking in this entire debate is evidence that the new generation oral contraceptives present any positive benefits sufficient to outweigh the additional risks involved in their use. So long as that is absent, it is hard to see why these products should continue in use, except for the occasional patient who, on individual grounds, finds that she tolerates them better than their predecessors.

## References

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