advantages in various vascular emergencies and can safely and effectively solve difficult clinical problems.

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The fish odour syndrome

The problems are psychosocial

The fish odour syndrome is characterised by an offensive body odour of rotting fish and abnormal excretion of trimethylamine in the breath, urine, sweat, saliva, and vaginal secretions. Since its recognition in 1970[1] some 35 cases have been reported, the largest series being that of Ayesh *et al* (p 655).[2,3] The smell is usually apparent in childhood, although it may be noticed first in infancy[4] or adulthood. It may be intermittent, and puberty, sweating, menstruation, and a high dietary intake of sea fish or foods rich in choline exacerbate the smell.

Three cases have been described in patients with serious physical disabilities,[1,2,5] but these were probably chance associations. All other patients with the condition have been healthy; their problems have been psychosocial.[6] Most have had low self esteem. Some were ostracised or ridiculed at school. Schoolwork suffered, and they became lonely and withdrawn. Those unable to detect their own odour had added anxiety.[3] Diagnosis was often delayed because doctors were unaware of the condition.

The underlying problem is a reduced ability to oxidise trimethylamine, an amine derived from the diet. The two major sources of this compound are choline and trimethylamine oxide, which is present in many salt water fish. Bacterial degradation of these precursors in the bowel releases trimethylamine, which is readily absorbed from the gut and, normally, oxidised almost completely by the liver to trimethylamine N-oxide. This compound is excreted by the kidneys and does not smell. The combined urinary excretion of trimethylamine N-oxide and trimethylamine of normal adults is around 40-50 mg a day, with more than 90% as the oxide.[3,7] In the fish odour syndrome the oxidation of trimethylamine is impaired.[3] Unoxidised trimethylamine is increased in urine, breath, sweat, and other secretions, causing the fishy smell.

Reports of trimethylaminuria include pairs of siblings,[3,4,8] suggesting that the defect is inherited. Smith *et al* have now investigated five affected families.[3] On a normal diet all the asymptomatic parents had normal urinary excretion of trimethylamine and trimethylamine N-oxide and no body odour. When stressed with an oral load of 600 mg trimethylamine, however, all showed reduced oxidising capacity. These results indicated carrier status for the defect and are strong evidence that it is an inherited autosomal recessive condition. From a study of 169 healthy volunteers a carrier frequency in Britain of at least 1% was proposed.[7]

The molecular defect is unknown. Trimethylamine is oxidised by liver microsomal mono-oxygenases containing flavin. These have broad specificity and also catalyse the oxidation of many pesticides, foreign compounds, and drugs.[9] The oxidation of trimethylamine has been studied in liver from only one affected patient. The oxidation system was defective, with a K_m for trimethylamine five times greater than normal.[10] Better understanding of the condition may come from genetic studies of flavin coding mono-oxygenases.[11-13] Further work is needed to define the relation between the various isoenzymes of these oxygenases and their relative importance in oxidising trimethylamine and to pinpoint the defect in trimethylaminuria.

The disorder is diagnosed by showing increased free trimethylamine in urine, with reduced trimethylamine N-oxide. Common problems causing body odour—poor hygiene, gingivitis, urinary infections, infected vaginal discharge, advanced liver and renal disease—and rare, inherited organic acid defects with a characteristic but non-fishy odour should be excluded. Samples should be collected into strong hydrochloric acid during an exacerbation, with the patient taking a normal diet but without fish for 48 hours. The analyses are technically difficult, and in Britain are available only through interested research groups. Nevertheless, establishing the diagnosis is essential. Patients and parents are helped by understanding what is wrong. A low choline diet (avoiding eggs, liver and other offal, peas, and soy beans) with the exclusion of sea fish reduces the excretion of trimethylamine and sometimes, but not invariably, reduces the odour. Measures to minimise sweating help. Short courses of antibiotics active on the gut flora (for example, metronidazole or neomycin[3]) or lactulose[8] may allow some dietary relaxation for important social occasions.

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Drugs: from prescription only to pharmacy only

The benefits are clearer than the risks

The range of medicines available over the pharmacy counter is set to increase.[1] The Medicines Control Agency has revised its procedures to speed up the reclassification from prescription only medicine (POM) status to pharmacy only (P) status. In addition, the Medicines Act has recently been revised to ensure, by five yearly review, that the prescription only status of a medicine continues to be justified.

Economic and philosophical considerations underlie these moves. Economic considerations include an escalating growth in spending on health care, which includes a drug bill, growing at around 12% every year. One solution is to shift more of the financial burden to individuals by encouraging them to treat themselves with non-prescription drugs. What is more, the current controls on drug spending have constrained profits in the drug industry, so more companies are moving into the over the counter market.[2] The government's philosophy on health care is that individuals should take greater responsibility for their health[3]; trends towards less medical paternalism and more consumerism favour greater freedom to choose self treatment for palliation and cure.

All drugs have some potential to cause harm, and reclassifying some from prescription only to pharmacy only increases the community's exposure to hazard: although the secretary of state for health claimed that patients' safety would be a prime consideration,[1] how good are the data on safety? Clinical trials are usually done on a restricted range of patients under controlled conditions and may not predict what happens in general use. Postmarketing surveillance studies are often poorly planned and executed,[4] and the Committee on Safety of Medicines collects only a small proportion of adverse effects.

It can be difficult to extrapolate from similar changes in other countries. For example, in Denmark cimetidine was made available without prescription in 1989 and the pattern of adverse reaction reports did not change.[5] Changes in reimbursement and advertising controls complicate interpretations of the change in status, and the amount of the drug sold over the counter was small, with much of it probably bought by patients who had previously been prescribed it. The true effect on the community will not be seen until the drug is widely purchased by people who are taking drugs with which cimetidine may have clinically serious interactions—such as phenytoin, warfarin, and theophylline.

In Britain the Medicines Control Agency has the task of assessing these data. Are the mechanisms to prevent inappropriate use and detect adverse effects sufficiently robust to support a substantial shift in policy? The main checks to stop patients misusing a drug are restricting its sale to a pharmacy (where the pharmacist need not speak to the customer) and the inclusion of a readable patient information leaflet. The effectiveness of a leaflet will depend not only on the purchasers' ability to read and understand it but also on whether they heed any warnings. Having spent their money, customers may well choose to take the drug despite the leaflet. How sensitive the yellow card system is for detecting serious adverse effects of self medication is unclear. The risk of an adverse effect depends on the drug, the population exposed to it, and how it is used. Both the population and method of use may change with a change of status.

New approaches to managing risk should accompany the increase in drugs available without prescription. A strategy based on gatekeeping, informing, and monitoring is needed. In Australia pharmacists can fulfil these roles because of their legal obligation to give advice and elicit information before some drugs can be sold over the counter; while not perfect, this approach has some merits. Perhaps all drugs that change from prescription only to pharmacy status should be sold in person by the pharmacist for the first three years. Information would be given and elicited at each sale, depending on whether the sale was for a first or repeat supply. Patients with excessive use or suspected adverse effects would be referred to their general practitioner. Gatekeeping could include the pharmacist recommending only self medication from a list of nationally agreed "preferred medicines."[6]

Overall, the shift from prescription only to pharmacy only medicines should be welcomed as it gives greater freedom of choice to patients and allows them to treat symptoms quickly. But there are risks that patients may delay consulting about serious conditions and that an unacceptably high incidence of adverse effects may result from the way that the general population uses the drug. In this risk-benefit equation only the benefits are clear; the risks, and the burden of harm that may accrue, are hard to predict. The push from prescription only medicine to pharmacy only medicine needs to be supported by further research, including anthropological studies, and the new approaches to managing risk.

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