and workplaces; programmes of harm reduction for drug and alcohol misuse; the promotion of sexual health and the prevention of HIV infection and AIDS; and community based approaches to healthy nutrition and the prevention of heart disease. This would require recognising the relevance to health of agricultural policy and food production and marketing. A wealth of experience now exists on all these topics.[7-9] The United Kingdom could provide a rational framework as valuable in its own way as *The Health of the Nation* promises to be.

A particular service that the president might perform would be to open up access to the European Community's funds for research. Too often it seems that cliques are able to obtain funding but outsiders cannot. Biomedical research has tended to dominate over epidemiological and social inquiry, which forms the basis of a public health strategy. The British government has tackled much of this at home and is in a strong position to address it in Europe.

A final point about the relationship between the European Community and WHO: WHO is in one of its perennial financial crises. The advent of a public health presence in Europe presents an opportunity to get to grips with an organisation that is still based on a 1948 command model. Our own health service reforms provide the guide here: a drastically slimmed down strategic head office could be linked to member states for policy and to institutions and field programmes for technical support. WHO need not supply this technical support directly: member states have vast skilled networks that could provide it better. WHO and the European Community together playing the role of enabler and catalyst must be the way forward. Unfortunately, some very strong vested interests exist, and secretaries of state are not usually in office for long enough to get to grips with the last of the big bureaucracies. This could be the time to start—with WHO in Europe acting in concert with a slim, strategic minded public health directorate of the community. A red herring that is currently being used to justify the continuation of the status quo is the public health crisis in eastern Europe; this poses a different set of questions, which should be tackled independently by the community.

In its conclusion to the third report on the European Community and health policy the British government's health committee stated, "We recommend that, in response to this report, the government seize the opportunity to lay out its agenda for health during its forthcoming presidency."[3] Much of the groundwork has already been done at home. The United Kingdom's relationship with Europe has not often been a happy one. Yet our record and skill in public health is generally acknowledged to be outstanding: here we have a chance to make a really positive contribution to our neighbours. It would be a pity if we missed our chance.

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Selective serotonin reuptake inhibitors

A modest though welcome advance in the treatment of depression

The selective serotonin reuptake inhibitors are a group of drugs that have been regarded as a major advance in the treatment of depression. Those recently marketed in Britain include fluvoxamine, fluoxetine, sertraline, and paroxetine. Their effectiveness has been shown in placebo controlled trials,[1-4] while comparisons with other antidepressants have sometimes suggested greater efficacy or a more rapid effect—and sometimes the opposite.[5] Conflicting results should be expected; they may be due to methodological imperfections, such as selection bias or unsatisfactory matching, or they may occur by chance. A single trial rarely if ever justifies an unequivocal claim of superiority, and no selective serotonin reuptake inhibitor has been shown consistently to be therapeutically superior to other antidepressants.

Few placebo controlled trials of these drugs have been carried out in depressive disorders in elderly people, and claims for their effectiveness in these patients have been based on the results of comparisons with other antidepressants. Nor have placebo controlled trials been carried out in patients with truly "resistant depression"—a term used in different ways by different investigators. The results of a trial suggesting, for instance, a beneficial response to a selective serotonin reuptake inhibitor in those who have not responded to a relatively short course of a tricyclic antidepressant provides insufficient reason to believe that this group of drugs will benefit most patients with resistant depression. Continued treatment with them may help prevent relapse and recurrence of depression[6,7]—though again not to a greater extent than with tricyclic antidepressants.

Like other antidepressants, selective serotonin reuptake inhibitors are effective in anxiety (and panic) as well as depressive disorders. Anxiety and depression go hand in hand and may be difficult to distinguish from each other, especially in general practice. Doubt persists whether the benefit is due to treatment of any underlying depression or whether the drugs have specific anxiolytic or antipanic effects.[8] Similar considerations apply in obsessive-compulsive disorder, though here there is more evidence that the beneficial effects of selective serotonin reuptake inhibitors are independent of their antidepressant action.[9,10]

Some reports have claimed that fluvoxamine and fluoxetine are more effective than other antidepressants in potentially suicidal patients.[11-13] In one of the studies, however, the difference between the effects of the selective uptake inhibitor and the control drug was not significant,[11] while in all of them reliance was placed on "suicide items" in rating scales for depression. These are not accurate measures of the severity of genuine suicidal intent or predictors of subsequent suicidal behaviour.

The part played by 5-hydroxytryptamine in a wide range of

physiological functions—including appetite, sex, aggression, and impulse control—has led to the selective uptake inhibitors being studied in a variety of neuropsychiatric disorders. They cause less gain in weight than do tricyclic antidepressants,[3 14] while fluoxetine can lead to weight loss; this drug decreases craving for carbohydrate and also the frequency of binge eating and vomiting in patients with bulimia nervosa.[15 16] It has been claimed that they are helpful in substance misuse; for the irritability, impulsiveness, and repeated self harm encountered in disordered personalities; and in many neuropsychiatric disorders[17]—but these claims have not been proved in placebo controlled trials.

Selective serotonin reuptake inhibitors are often better tolerated than tricyclic antidepressants because they cause fewer troublesome anticholinergic effects and less sedation.[3 4 18 19] Their main drawback is the high incidence of gastrointestinal side effects, especially nausea. These are dose related and often mild; they do not usually persist with continued use. Other troublesome effects are increased anxiety, "nervousness," tremor, and insomnia, though these do not affect the outcome of treatment in depressed patients with anxiety. Somnolence occurs but, in general, psychomotor effects at therapeutic doses are less troublesome than with tricyclics.

The selective serotonin reuptake inhibitors have been alleged to precipitate mania, but, as in the case of other antidepressants, the evidence for a causal connection is not entirely convincing. Interestingly, after antidepressants were introduced into clinical practice in the 1950s the proportion of patients who swung from depression to mania did not significantly increase.[20]

Fluoxetine has been said to cause intense violent and suicidal thoughts,[21] but critical evaluation of the evidence suggests more likely alternative explanations such as the personality or psychiatric disorders for which the drug was prescribed.[22] Convulsive seizures have been reported during treatment with selective serotonin reuptake inhibitors, but the incidence is possibly less than that which occurs with other antidepressants.[23]

Isolated cases of akathisia,[24] dystonic reactions,[25] orolingual dyskinesia,[17] and a worsening of neuroleptic induced extrapyramidal symptoms have been published. Clinical anecdotes, however, do not provide good evidence of cause and effect. This applies also to a report of the neuroleptic malignant syndrome said to be induced by fluoxetine[26] and to numerous other alleged adverse drug reactions, including sexual dysfunction.[14]

The selective serotonin reuptake inhibitors, like other newer antidepressants, have fewer effects on the cardiovascular system than tricyclics,[27-30] and this contributes to their safety in overdose.[18 19 31] Future research should focus on the effects of selective serotonin reuptake inhibitors in elderly patients and those with heart disease. Rash occurs on occasion (though probably no more commonly than during treatment with tricyclic antidepressants), and in the case of fluoxetine it has been associated with other features of serum sickness.[32]

There is nothing to suggest that selective serotonin reuptake inhibitors are drugs of misuse or dependence, although at least one woman with anorexia nervosa misused fluoxetine to promote weight loss.[33] Similarly, there have been no reports of withdrawal symptoms, with the exception of one patient who, on stopping treatment with fluvoxamine, became aggressive and hypomanic.[34]

No large scale epidemiological studies have been carried out on pregnant women who have been prescribed selective serotonin reuptake inhibitors, so it is worrying that 24 women were found during a single prescription event monitoring study to have taken fluvoxamine during their pregnancies (J G Edwards *et al*, unpublished findings). Drugs that are not essential, particularly new drugs whose teratogenic properties are unknown, should be avoided during pregnancy, but this important precaution is being overlooked.

Few clinically relevant drug interactions with selective serotonin reuptake inhibitors have been reported. They can inhibit the metabolism of some drugs in the liver and increase plasma concentrations of tricyclic antidepressants. The most serious interactions have been with monoamine oxidase inhibitors, tryptophan, and lithium, leading to restlessness, agitation, gastrointestinal symptoms, hyperthermia, rapidly changing vital signs, rigidity, myoclonus, and hyperreflexia. These symptoms have occasionally progressed to coma and death.[35] Fluoxetine and its active metabolite norfluoxetine have long half lives; this not only is a problem with regard to unwanted effects in general but also necessitates a longer (six weeks) drug free period before the start of treatment with monoamine oxidase inhibitors and other drugs with which selective reuptake inhibitors interact.

In this short overview the selective serotonin reuptake inhibitors have been discussed as if they were all identical. There are similarities, but the four drugs referred to are chemically different, and their clinical differences will be more clearly defined by greater clinical experience and by more and better research—which ought to include more detailed scientific overviews and meta-analyses of the many studies that have been carried out.

Some psychiatrists regard selective serotonin reuptake inhibitors as an important advance in treatment. To justify such a claim a new drug must be shown to be distinctly more effective or to act more rapidly than previously existing treatments, to have less serious unwanted effects, or to be safer in overdose. To what extent do the newer selective serotonin reuptake inhibitors meet these criteria? The evidence published so far suggests that they are no more effective and do not act quicker than their predecessors. But patients who do not suffer nausea tolerate selective serotonin reuptake inhibitors better than tricyclic antidepressants, though not necessarily better than other new antidepressants. The inhibitors are also less toxic in overdose. These advantages do not amount to a major breakthrough in the treatment of depression but represent a welcome though modest advance.

The main uses of selective serotonin reuptake inhibitors would seem to be in clinically depressed patients who are unable to tolerate tricyclic antidepressants and those with associated troublesome obesity or heart disease. They may also play a part in the management of obsessive-compulsive disorder and bulimia nervosa and be considered as alternatives to tricyclics in the prevention of relapse or recurrence of major depression.

Like all new drugs selective serotonin reuptake inhibitors are expensive. Their prices range up to 40 times that of imipramine. Whether or not they are worth the extra cost is something that individual doctors and patients will have to decide.

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London's health care again

This time may be different

Nearly every decade this century someone has tried to solve the interlinked problems of London's health care, medical teaching, and research. Through a combination of unclear direction, vested interests, and lack of political will they have all failed: both the process and the problems continue. This autumn the Tomlinson inquiry will make its recommendations on London to the Secretary of State for Health, and this week the King's Fund London Commission has produced the final report of its £500 000 study into acute care in London.[1] Might the problems be solved this time?

The problems are familiar: an acute sector dominated by specialist services and provided from multiple hospital sites; fragmented teaching and research; and underfunded and underdeveloped primary and community care.[2] One reason for London's high costs is medical staffing levels 30% higher than elsewhere, which have not declined in line with resources or beds. Indeed, one perverse outcome of financial cuts over the past decade is that they have fallen disproportionately on general medical and surgical beds serving local populations. The result is that substantial groups of Londoners do not get as good or responsive health care as many outside London.[2]

The London Commission's final report does not name the institutions that should close—though it thinks that many should. Instead it sets out a vision for the year 2010 of responsive health care and internationally excellent teaching and research and suggests a mechanism and a source of funding for getting there.

The vision is one that will be familiar to health strategists: of a service led by primary care practitioners, who not only provide more services but also orchestrate a whole series of secondary and community services much more than now. Hospitals are fewer because much is done outside them and because highly technological care is concentrated in a few—to use resources efficiently but also to ensure that high volumes maintain high levels of skill. While some hospitals will still have a range of acute specialties to back up accident and emergency departments, others will specialise in day care or short stay elective procedures. The teaching hospital will disappear; research will be based round four university centres, which will contract with many provider units to supply the clinical experience needed by both undergraduates and postgraduates.

The specific recommendations (see p 1651) include reducing the numbers of both medical staff and medical students by a third and reducing 41 acute hospitals in London to no more than 30. The capital and revenue thus released (about £250m) should be used to develop primary and community health services, reshape acute services, and consolidate teaching and research. The mechanism for achieving these aims is a task force answerable to the secretaries of state for health and education (and to the Chancellor of the Duchy of Lancaster for research) that would work with "and direct" regions, district and family health services authorities, provider units, and the university on the details of developing primary care and reshaping acute hospitals.

The London Commission has shown that the traditional pattern of services and teaching in London is unsustainable. In such circumstances the detail of any recommendations becomes almost irrelevant: what is important is that the strategy should be agreed—and then implemented. In fact ministers are unlikely to do anything until the Tomlinson inquiry reports—and clearly the commission hopes its own recommendations might influence what Tomlinson has to say. Although the report's refusal to identify specific institutions that should close seems rather coy, there is sense in not doing so. Firstly, it avoids provoking an immediate defensive response. More fundamentally, no one group can have the wisdom to lay down a detailed blueprint for all of London. One of the London Commission's strong messages is that services have to be tailored to different communities and take into account what their publics want.

The barriers to this vision are, of course, immense. Changing habits and challenging institutional cultures are hard, though already there are signs that the explicitness over activities and costs brought about by the internal market is beginning to force change.[3] Bringing general practice in London up to the standards of the best in Britain would itself be an enormous task—but the commission is asking for more. Building the sort of community based health services that the