A decline in coronary mortality

Even given the changes in diagnostic accuracy, death certification, and classification, there has been an alarming rise for most of this century in mortality from ischaemic heart disease in the developed countries of the world. Perhaps the tide is beginning to turn, however, for even a pessimistic observer would have to allow that a recent decline in coronary mortality has been reported—3 from two countries, the USA and Australia. Advocates of health education have claimed that this change reflects efforts in the last two decades to increase public awareness of the dangers of tobacco and overeating and the merits of physical exercise: but there is no clear evidence to justify such claims. Indeed, the first question which must be raised is whether the decline, which is far from dramatic, may be considered real.

In the United States mortality from coronary heart disease, after increasing up to the early 1960s, was stable until 1968—after which all race, sex, and cohort age groups have experienced a small but appreciable decrease.1 In 1968 there was an important change in the International Classification of Diseases affecting coronary heart disease and related causes of death, and there is a theoretical possibility that the recent decrease is an artefact. Gordon and Thom2 have recently examined that question, and they concluded that as mortality from other cardiovascular causes has declined even more in the same period it is implausible to ascribe all of the decrease simply to the assignment of coronary deaths to other causes. Furthermore, they also noted parallel decreases from non-cardiovascular causes of death: in fact the only causes which showed an increase were cancer, violence, and hepatic cirrhosis.

Welcome though this fall in coronary mortality is, its lack of specificity weighs against its being due to improved treatment of myocardial infarction. Gordon and Thom believe that they have identified at least two relevant factors. Firstly, there has been a steady decline in mortality from hypertension, an important factor in most cardiovascular diseases—though mortality from hypertension was declining before the recent change in coronary mortality. The main reason, they suggest, is a decline since 1968 in mortality from influenza and pneumonia—diseases known to influence the death rate of coronary disease.3 Support for this view comes from the finding that the decrease in coronary deaths has been mainly in the months November to February, the peak months for mortality from respiratory disease.

In Australia the decline in coronary mortality has been virtually confined to men. Unfortunately, in England and Wales coronary mortality overall is still rising, though in men aged under 45 the rates have shown only a slight upward trend4 since 1965. Death rates from influenza and pneumonia have not been falling here in the same way as in the USA, so that these British trends in coronary mortality do not conflict with the suggested explanation for the fall in N America.

Among women the smaller decline in coronary deaths in Australia as well as the greater increase in England and Wales as compared with men is consistent with an effect of smoking, which has been increasing recently more in women than in men. Other factors however may also be relevant, such as oral contraception.5 Trends in the next few years should clarify some of these uncertainties. Nevertheless, at present the prospects of an appreciable improvement in coronary mortality rates do not seem bright.

The pill and raised blood pressure

Most practitioners, and many women too, know that taking oral contraceptives may lead to a rise in blood pressure. The risk appears to be higher in women who are heavier or older or who have a history of hypertension in previous pregnancies or in their families—in other words, those who are more likely to become hypertensive anyway. Severe hypertension seems to be rare, but one recent report1 described a patient who developed malignant hypertension and irreversible renal failure when given an oral contraceptive. Hypotensive drug treatment was unsuccessful, and bilateral nephrectomy and later transplantation became necessary in this previously normotensive 27-year-old woman.

Changes in the cerebral2 and coronary3 circulation are known to occur in some patients given hormonal contraceptives. Changes in the renal circulation have recently been investigated in a remarkably thorough (albeit small) study of nine patients.4 All had developed either hypertension or renal failure (or both) when given oral contraceptives, and all underwent selective renal angiography and renal biopsy. Five patients, normotensive before and after contraceptive therapy, but whose mean blood pressure during its administration was substantially raised (mean 198/123 mm Hg) were shown on angiography to have definite attenuation of peripheral renal vessels with luminal irregularities. In three patients these vascular findings were confirmed on renal biopsy, when all five were
found to have periglomerular thickening and degeneration of renal tubular cells. Two other patients who were hypertensive before oral contraceptive administration suffered deterioration of renal function which improved on contraceptive withdrawal. Both showed evidence of diffuse intravascular coagulation—namely, raised blood concentrations of fibrin degradation products, and intrarenal microthrombi at renal biopsy. These have been recorded before in patients given combined oestrogen-progestogen pills.\(^5\) Two patients resembled the woman described by Zech and his colleagues,\(^1\) in that acute oliguric renal failure was apparently precipitated by oral contraceptives (again with evidence of intravascular coagulation) and there was no improvement on withdrawing the pill. Both had previously had apparently normal renal function. It is tempting to attribute these changes to the process of hypertension, but, as the authors point out, the short period of raised pressure and the dissimilarity of the pathological changes to those found in essential hypertension militate against that particular argument.

This grisly collection of contraceptive-induced disease reinforces the opinion held by many doctors that administration of these drugs must be as closely controlled as that of any other potentially hazardous therapeutic agent. Moreover, it should also provide thought to those paramedical groups who wish to remove the prescribing of oral contraceptives into their own hands.

As to the management of contraceptive-induced hypertension, as a first step no women with moderately or severely raised blood pressure should be given conventional combined oestrogen-progestogen oral contraceptives. In those with mild hypertension a dogmatic statement of policy is not possible. Many practitioners will advise other forms of contraception, and they will find justification for this attitude in the studies reported here. It remains to be seen whether the recently introduced oral contraceptives with a very low oestrogen content will prove less likely to precipitate hypertension. In any case, periodic monitoring of blood pressure is mandatory. For the patient already on these agents and whose blood pressure is found to be raised the counsel of perfection is to review the method of contraception and when possible to find an alternative means. The practitioner must then weigh the undoubtedly greater chance of pregnancy when other contraceptive methods are used against the dangers of hypertension and the side effects associated with hypotensive therapy. A combination of oral contraceptive therapy with antihypertensive therapy is particularly unhappy: every effort should be made to avoid using one drug to treat disease induced by another.


### Antirheumatic drugs: plenty is not enough

Musculoskeletal pain is so prevalent that perhaps not surprisingly we are confronted with an ever-rising flood of new antirheumatic drugs. Yet do we still need new drugs for relief of pain in inflammatory joint disease? Probably we do. Aspirin has long been recognised as the sheet anchor of drug therapy, but nearly one-third of patients find full doses unacceptable on account of dyspepsia;\(^4\) and it also causes acute gastrointestinal haemorrhage in a small proportion of patients, as does indomethacin—which may also cause chronic peptic ulceration. Phenylbutazone and oxyphenbutazone induce bone marrow depression once in every 80 000 prescriptions.\(^8\) Chloroquine and hydroxychloroquine cause irreversible retinal damage in one in every 1-2000 patients on long-term treatment.\(^9\) In Britain gold has the undeniable reputation of being responsible for more deaths per million prescriptions than any other drug.\(^2\) Practitioners still too readily resort to corticosteroids, which were responsible in a Glasgow study\(^6\) for 5% of admissions to hospital and 12% of deaths in patients with rheumatoid arthritis. Even if it cannot be curative there is a very definite need for an effective and safe anti-inflammatory analgesic drug for rheumatic pain.

How good are the new drugs? One of the advertising claims made for ibuprofen is that it is “the best tolerated of the available anti-rheumatic agents,” and experience in Britain supports this claim—though the drug is not quite as effective as indomethacin.\(^7\) Other propionic acid derivatives naproxen, fenoprofen, and ketoprofen have been shown in short-term clinical trials to be effective in relieving pain, but no more so than aspirin or indomethacin. Benorylate is a condensation product of paracetamol and aspirin and is a palatable but expensive form of aspirin. The fenamates are useful anti-inflammatory agents, but have the disadvantage of producing diarrhoea in 10-15% of patients. Other compounds currently undergoing clinical trials include azopropazone, tolmetin, diflalone, niflumic acid, feprazone, aclofenac, and flurbiprofen. Alclofenac has recently been reported as a possible cause of vasculitis,\(^8\) and Cutbello\(^10\) has recently reviewed the side effects of nonsteroidal analgesics reported to the Committee on Safety of Medicines in the United Kingdom.

There is unlikely to be much to choose between the nonsteroidal anti-inflammatory analogues in terms of pain relief; nor is it likely that using combinations of these drugs, such as aspirin and indomethacin, will provide any more relief than using them singly.\(^11\) A recent study\(^8\) has shown that about one-third of patients with rheumatoid arthritis treated in hospital receive two or more non-steroidal anti-inflammatory agents at the same time; but (in view of the increasing evidence of pharmacokinetic interactions between these drugs) pain should, whenever possible, be controlled with single drugs rather than with combinations.

We should think again about education in the use of anti-rheumatic drugs (and presumably other classes too). At present this is left too much to the pharmaceutical industry.\(^13\) Much of what is done is excellent, especially with the recent trend to publish symposia, but it is difficult for the busy doctor to obtain reliable comparative data between new and existing drugs. Specialists in pharacotherapeutics seem to be engrossed in drug kinetics,\(^14\) the minuitae of drug interactions of dubious clinical relevance,\(^15\) and the use of brand names. They should concern themselves more with educating doctors how to use drugs properly.\(^16\)