symptoms. As with the other factors that have appeared in prognostic indices, most arrhythmias that occur after infarction are probably an indication of heart disease rather than a direct cause of death.

Furthermore, even if high-risk groups can be identified we have at present little idea how to treat them. The modification of pre-existing risk factors, other than stopping smoking,[19] has little effect. A rise in the blood urea concentration during an acute infarction is a bad prognostic sign[6]—but no one would suggest that keeping the blood urea concentration low would improve the patient's outlook, and there is no fundamental reason to suppose that widespread use of antiarrhythmic drugs will be effective either. Though treatment with β-adrenergic blocking agents may possibly be beneficial,[20] they do not seem to have any useful antiarrhythmic effect in patients after infarction[21] and may therefore be acting through some other mechanism. Sulphinpyrazone is not known to have an antiarrhythmic effect, yet it has been reported to reduce sudden death,[22] which is commonly regarded as primarily due to dysrhythmias.

At present, therefore, epidemiological data are available but clinical trials have not, so far, shown corresponding benefits. If we did have a treatment that really reduced mortality after myocardial infarction its mechanism of action might tell us more about the underlying disease than any prognostic index.


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# Cancer chemotherapy—the inbuilt deterrent

Some 2400 years ago Hippocrates observed that patients with occult cancer did better if they were not treated. Despite undoubted faults, as a generalisation about the patient with disseminated cancer this remained true until the introduction of effective anticancer drugs. There still remain exceptions, for the therapeutic benefits have brought with them all the problems of iatrogenic disease.

Fortunately, the complexity of the newer treatments and the toxicity of many drugs have encouraged the concentration of facilities for cancer chemotherapy in specialist centres. Inevitably much of the emphasis of reports from such centres has been on their increasingly successful results with many tumours. These results have, however, often been achieved only at the cost of highly unpleasant side effects: the intensive treatment necessary to achieve the optimum outcome may cause severe toxicity. Perhaps the greatest problem for the patient receiving cancer chemotherapy is nausea and vomiting, which may be sufficiently severe and prolonged during treatment with adriamycin, mustine, BCNU (carmustine), and platinum diamminodichloride to cause the patient to wish to default. On the other hand, while it is inconvenient, alopecia rarely acts as a deterrent to continuing treatment.

Can the nausea and vomiting be suppressed? There have been few controlled studies of antiemetics, and indeed our understanding of the mechanism of induction of nausea associated with anticancer drugs is poor. Probably there are at least two sites of action: the gastrointestinal tract (particularly the stomach) and centres within the central nervous system. To these must be added a psychological component in patients conditioned to expect vomiting as a consequence of treatment. Direct irritation of the gastric mucosa is of small importance in causing symptoms; thus drugs which speed gastric emptying may reduce symptoms marginally, but little benefit can be expected and little is seen in practice.[1] Sedation with antihistamines, so valuable in motion sickness, is of less obvious benefit in combating the emetic effects of anticancer drugs. Nevertheless, controlled double-blind studies have shown benefits from phenothiazine drugs when compared with a placebo.[2] Sadly, while the benefits may be statistically significant they have yet to impress the patients significantly.

The search for agents that might block the central component of vomiting without producing unpleasant sedative effects has included a study of tetrahydrocannabinol (after anecdotal reports of benefits from marihuana). Tetrahydrocannabinol has antiemetic properties,[3] but substantial doses also cause euphoria and tachycardia in normal volunteers.[4] A new cannabinoid, nabilone, has antiemetic properties in animals[5] and man,[6] and in a double-blind crossover study was found superior to prochlorperazine in patients receiving cancer chemotherapy.[7] Further studies of this promising drug had to be discontinued when unexpected neurological toxicity was discovered in dogs given high doses of nabilone continuously over prolonged periods. None the less, the encouraging results of the earlier study have stimulated interest in other derivatives.

The mixed origins of nausea and vomiting make it unlikely that a single agent will totally control these symptoms. Features that allay anxiety may help to reduce the tendency to nausea and subsequent vomiting. Patients should be seen in restful surroundings and time allowed to answer their questions, which they should be encouraged to ask. Continuity of staff is vital. Within special units a sister experienced with chemotherapy will reduce tensions and as a familiar figure can reassure more effectively than a harried houseman, who may interchange with other junior staff. Frequently other clinicians and other patients condition a patient to expect sickness, whatever the treatment. Time must therefore be found before treatment begins to explain the plans and the possible consequences. Patients are often reassured by having the option of staying in hospital for the first night after the start of treatment. Staff familiar with the problems that may occur may considerably reduce their severity so that later treatments are well tolerated and can be given in the outpatient department. When severe vomiting does occur adequate hydration and monitoring (and, where necessary, reconstitution) of the concentrations of plasma electrolytes are essential. If one antiemetic regimen proves ineffective others should be tried.

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The future of cancer chemotherapy lies in increasing the specificity of treatment and diminishing its toxicity. The lack of specific treatment for many cancers emphasises the importance of the clinical trial in assessing treatment: this will jettison irrelevant or harmful measures, preserving only those of proved value. We must now put similar efforts into identifying those factors, including antiemetics, that can best reduce the one consequence of treatment most often raising doubts in the patient's mind about whether the cure is really worth the discomfort of treatment, however temporary this may be.

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# Tardive dyskinesia

If anyone doubts the continuing truth of Voltaire's claim that doctors pour drugs of which they know little into patients of whom they know even less, the phenomenon of tardive dyskinesia should convince them. Though it was first reported[1] in 1957, for many years psychiatrists were reluctant to accept that tardive dyskinesia was a side effect—all too often an enduring one—of the neuroleptic drugs[2 3] that are their principal weapons against schizophrenia. The syndrome is chiefly characterised by repetitive pouting of the lips and protrusion of the tongue, often accompanied by bizarre facial grimacing and sometimes more widespread choreiform movements. Gibson[4] found that in chronic schizophrenic patients receiving depot neuroleptics the syndrome appeared with steadily increasing frequency and had affected about a quarter of them after three years. Nor is it only schizophrenic patients who may be affected. Paulson[2] reported 14 sufferers who were neither institutionalised nor psychotic but who had all received neuroleptics, some of them for many years.

When many different treatments are recommended for a condition usually none of them is particularly effective. This is certainly the case with tardive dyskinesia. For example, though a recent well-controlled trial[5] showed that muscimol (a structural analogue of γ-aminobutyric acid, GABA) improved symptoms in tardive dyskinesia unfortunately it also caused an increase in psychotic symptoms.

Because treatment is so unsatisfactory attempts have been made to detect patients who may be especially likely to develop tardive dyskinesia. Those with brain damage and the elderly (not necessarily the same people) are known to be vulnerable. Wegner *et al*[6] have recently reported the presence of a characteristic pattern in the electroencephalogram in 95% of patients with tardive dyskinesia, whereas it is found in only 33% of controls; but whether this finding is a precursor or a result of tardive dyskinesia is not yet known.

In our present state of knowledge, the best hope of prevention of tardive dyskinesia remains care and discrimination in the use of neuroleptics. Not all schizophrenic patients require medication, and in those who do short "drug holidays" may reduce the likelihood of tardive dyskinesia—though there is no proof as yet. Most reports suggest that routine anticholinergic medication increases the risk of tardive dyskinesia, though Gibson[4] disagrees. Clearly, neuroleptics should be prescribed for patients with conditions other than schizophrenia only after most careful consideration of the alternatives, especially where long-term use is likely. Early diagnosis of tardive dyskinesia may be important in arresting its progress, but it may also be difficult in a condition which, perhaps surprisingly, often seems to trouble the patients less than it troubles their physicians.[2] In established cases, a gradual reduction or withdrawal of neuroleptic drugs may be helpful, though this sometimes leads to an initial worsening of the dyskinesia. Such a policy may not be practicable if it results in a recurrence of the underlying psychiatric disorder. Paradoxically, *increasing* the dosage may improve matters in some cases. Changing to a different neuroleptic may be worth a try. If that fails, all that remains is treatment with one of the many drugs that have been claimed to relieve symptoms; these include deanol, diazepam, baclofen, alphamethyltyrosine, tetrabenazine, and reserpine.

In the long term the answer must lie in the development of a new class of neuroleptic drugs that will control schizophrenia without producing tardive dyskinesia. A report by Shopsin *et al*[7] indicates that clozapine—a dibenzazepine with some important pharmacological differences from most of the standard neuroleptics—may be such a compound, but psychiatry has seen so many false dawns that it would be premature to cheer. The ghost of Voltaire is there to remind us that, even if further trials confirm the safety of clozapine in respect of tardive dyskinesia, it may turn out to produce other, as yet unknown side effects in long-term use.

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# Systemic sclerosis in old age

Very elderly patients are referred for specialist opinions relatively rarely. Because of this bias, many diseases have been mistakenly thought to be rare in old age. In systemic sclerosis early reports suggested that it was predominantly a disease of middle life and a comparative rarity in old age.[1–3] Before too long, however, the highest incidence was reported[4] to be in patients aged over 65. This revised view was confirmed in a personal series of 15 cases seen by one physician in geriatric medicine in 11 years[5]—representing an incidence of about one per 1000 elderly patients admitted under his care. A recent paper from a department of geriatric medicine[6] has now drawn attention to the ease with which the diagnosis of systemic sclerosis may be overlooked in the elderly because of the minor nature of the skin changes.

What, then, is the clinical picture of systemic sclerosis in old age reported in these two papers? Most strikingly, all the patients were women. Their average age was 80, closely corresponding to the overall average for women admitted to a geriatric department. All had Raynaud's phenomenon affecting the hands, and it was this symptom—otherwise rare in old age—which commonly drew attention to the disease. All the patients had skin changes in their hands, but these were most often not striking. Nevertheless, more than half had evidence of old or recent skin ulceration, whitlows, or necrosis of the pulp.

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