These feeding techniques do not prevent the inhalation of secretions; and when respiratory weakness does not allow adequate coughing fluid can be excluded only by the cuff of a tracheostomy tube or by surgical closure of the glottis.[10] Respiratory weakness is invariable in the terminal stages, and once a tracheostomy tube has been introduced the time will inevitably come when assisted respiration needs to be considered for the patient's respiratory distress. A decision to withhold treatment at this stage can clearly be influenced by factors other than the interests of the patient, notably the natural emotions of the family and the morale of the nursing staff. With modern methods and an experienced team a patient with motor neurone disease can be kept alive for a prolonged period, alert and with intellect and insight usually intact, but helpless and without hope of recovery. Rosin[8] concluded that on humanitarian grounds the respirator should not be used, and few would disagree. Death is sometimes sudden and unexplained, but usually results from pneumonia or respiratory failure. Distress, as well as pain, responds to opiates.

Far more attention should be paid to relieving depression, isolation, and fear, and some alleviation of dysphagia can be achieved, preferably without tracheostomy. Nevertheless, the full resources of intensive care are inappropriate.

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Pills for pimples

Ten heads are better than one: so runs the idea behind any committee. Some who work in the NHS have learned to doubt the universal truth of this belief, but it is still a mark of respect for any clinical problem to have a national committee set up to examine it. Everyone who treats acne vulgaris with systemic antibiotics, and this must include many general practitioners, should be grateful for the careful report[1] on the topic by an ad hoc committee on the use of antibiotics in dermatology (part of the American Academy of Dermatology).

In many patients acne can be controlled adequately by topical measures and may not need antibiotics, but the problem is still huge. In the United States, for example, 10% of all the tetracycline produced for human use is prescribed by dermatologists for acne. Yet many of the clinical trials on which this use is based can be faulted easily enough on technical grounds. The committee discarded all investigations which were not adequately controlled and found itself left with only 12 studies; these contained 14 drug treatment trials comparing one or other tetracycline with a placebo. Of these, six trials showed the tetracycline to be significantly better than the placebo at the 5% level; a further six trials showed no significant difference; and the final two trials were not presented in a form suitable for analysis. Despite this apparently even balance, the committee was in no doubt that tetracyclines are effective in acne, believing that the lack of statistical significance in five of the trials was due to factors such as small sample size and short duration of treatment.

Could the widespread use of tetracyclines, based on rather scanty data, be harming patients? The committee also considered reports on this question, but found no reports of definite abnormalities in kidney or liver function in a study of prolonged treatment with oxytetracycline in 170 patients.[2] Patients with acne tend to be young and in good health and may consequently suffer fewer side effects than debilitated patients given the same doses. The presence of renal disease should swing the choice of antibiotic towards one mainly metabolised by the liver, such as chlortetracycline, doxycycline, or erythromycin, rather than oxytetracycline and tetracycline. Allergic reactions to tetracyclines are rare, and phototoxicity is seen chiefly with demeclocycline. Massive infections with resistant organisms have not been a problem, and the main microbiological effects have been an increased incidence of vaginal candidosis and Gram-negative folliculitis of the face. The American committee's final verdict on tetracycline treatment in acne was that it is "rational, effective, and relatively safe."

Some patients with bad acne are not helped by systemic tetracyclines. The committee found evidence that erythromycin, clomocycline, and the trimethoprim-sulphamethoxazole combination are roughly as effective as tetracycline. Erythromycin is relatively non-toxic; hepatic dysfunction is seen mainly with erythromycin estolate, but not with the ethyl succinate or stearate, which may offer reasonable and effective alternatives to the tetracyclines. Clindamycin is also effective, but there have been reports of patients developing pseudomembranous colitis.[3] In two recent studies of long-term clindamycin in acne,[4,5] enough patients (nine of the 130) developed diarrhoea to make the drug unsuitable for routine use.

Perhaps the future management of severe acne will depend on first checking the antibiotic sensitivity of the patient's own strain of *Corynebacterium acnes* before choosing the right antibiotic. This may then be used topically in a vehicle designed to enhance penetration. Preliminary studies of this approach, using clindamycin in a vehicle containing N-methyl-2-pyrrolidone, have shown some promise[6]—but no doubt this technique will create problems of its own for another committee to pounce on.

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Migrants and cardiovascular disease

International comparisons of cardiovascular death rates show considerable differences among countries. Though the different age structures of populations can be taken into account fairly easily, such studies are often hampered by diagnostic differences and varying practices of death certification. Surveys can be done of different populations with a uniform clinical procedure, and these have proved that differences in vital statistics

can reflect true differences in the incidence of cardiovascular disease. For example, Reid *et al*[1] reported the prevalence of angina, possible myocardial infarction, and electrocardiographic abnormalities in middle-aged men in England and the eastern United States. They used a standard cardiovascular questionnaire,[2] read and coded electrocardiograms using the Minnesota code conventions,[3] and confirmed an excess of cardiovascular disease in American men. The Americans also had higher blood pressures, but this could be explained by obesity and the authors concluded that "factors associated with the excessive adiposity of the Americans are the more likely explanation of their adverse experience." These unknown factors could be genetic or environmental; and it has become usual to remove the genetic component by comparing migrants to a country with the population in the country from which they came. As might be expected, British and Norwegian men migrating to the United States have death rates from coronary heart disease intermediate between those of the country of origin and America.[4] Problems arise, however, if the migrant population is observed shortly after migration[5 6] as they tend to be physically fitter, to have a higher incidence of psychoses, and to have death rates affected by childhood exposure to risk factors.

In 1957 Gordon first showed that Japanese men who went to California had a higher death rate from coronary heart disease but a lower risk of stroke than Japanese who had not migrated.[7] Migration had occurred mainly in the late 19th and early 20th centuries and the problems associated with recent migration were not present. It had to be proved, however, that the differences were real and that low death rates were not due to early elimination of susceptibles—a problem common to all cross-sectional studies of this nature. A recent series of papers has answered most of these doubts. Firstly, the death certificates were compared with the results of necropsies carried out on about 33% of the Japanese men living in Japan and 67-70% of those living in California.[8] The differences did not appear to be due to differences in certification. Furthermore, the same techniques as those used in the Anglo-American comparison[1] showed that the American Japanese had twice the prevalence rates of angina, possible myocardial infarction, and electrocardiographic abnormality as those found in Japanese living in Japan.[9] The Japanese Americans also had a higher average serum cholesterol, glucose, uric acid, and triglyceride concentrations[10] and higher average blood pressures.[11] After adjusting for weight there was, however, no difference in blood pressure between the communities, and the American Japanese had less electrocardiographic evidence of left ventricular hypertrophy.[9] The authors suggested that hypertension might lead to coronary heart disease in the presence of other recognised risk factors, while in the absence of these recognised factors hypertension in Japan led more commonly to stroke.

Perhaps the most important conclusion from this recent research is that conventional risk factors cannot fully explain the differences between the populations. After allowing for blood pressure, age, and cholesterol the relative risk for coronary heart disease in America was 2·1 times that in Japan. Longitudinal studies such as the Framingham Study[12] are required to confirm the effects of additional risk factors such as smoking, since prevalence studies may be biased by their effect on survival. Possibly studies of migrants may suggest which factors to examine. So far no simple explanation has emerged for the differences between the experience of migrants and the population of their country of origin. Blood pressure, serum cholesterol concentrations, and current smoking practice are only partly responsible, and much research remains to be done on the possible effects of obesity and changes in diet and way of life on cardiovascular disease in migrants.

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Glutethimide—an unsafe alternative to barbiturate hypnotics

CURB (the campaign on the use and restriction of barbiturates) is trying to speed the rate at which the use of barbiturate hypnotics is already declining.[1 2] One of the main reasons behind this campaign is the number of deaths—about 2000 per year—from acute barbiturate poisoning. Most result from determined attempts at self-destruction, but a few may be episodes of manipulative self-poisoning that have misfired. In 80% of these tragic deaths the victims never reach hospital to benefit from modern intensive medical care.

Restriction of the use of barbiturates will not necessarily mean an overall decrease in the demand for, or prescription of, hypnotics; so that any alternative drugs should be safer when taken in overdosage. Glutethimide (Doriden) is a possible alternative which has been available for many years, but if the frequency with which it is taken in overdose in this country is any guide[3] it can never have held a major share in the hypnotic market.

It would be unfortunate, however, if glutethimide gained popularity with the decline of barbiturates, since several recent reports make it clear that severe glutethimide poisoning is an even greater danger to life than comparable barbiturate overdosage. An American investigation[4] of the drugs ingested in suicide attempts and the associated outcomes showed the overall mortality from glutethimide and barbiturate poisoning to be 13·9 and 0·7%, respectively, while a study from Copenhagen[5] reports corresponding values of 14·1 and 1·8%. Yet another US study[6] found glutethimide to have the highest mortality of all drug-induced comas (17%). This experience is by no means uniform. The most recent British report[7] of 31 patients with acute glutethimide poisoning gave a mortality of only 6% in patients who were unconscious, and in another series of 70 patients[8] there was only one death, and this occurred well after consciousness was recovered.

The reasons for the special toxicity of glutethimide are not difficult to find. Respiratory depression and hypotension are probably no commoner than in severe barbiturate poisoning, but pulmonary oedema,[6 7] cerebral oedema,[7] convulsions,[5] and sudden apnoea[6 7 9] are encountered more frequently with gross glutethimide overdosage. The depth of coma tends to fluctuate, and this and some of the other features may be due to the accumulation of a potent, toxic metabolite, 4HG (4-hydroxy 2-ethyl 2-phenyl glutarimide).[10] These features and a high potential for inducing dependence make it impossible to