be cautious when making promises lest they turn out to be like those heard at election time and soon rescinded. Advances in the treatment of leukaemia and solid tumours in children, and a few tumours such as Hodgkin’s disease in adults, cannot be used as a camouflage to draw over the mortality statistics (such as those for cancer of the lung, gastrointestinal tract, ovaries, and bladder) which have remained virtually unchanged since the advances attained 20 years ago as the result of improvements in anaesthesia and operative techniques. Our public face need not be too pessimistic, however, for about half of patients with some common tumours will survive for five years, lung cancer being a notable exception, and for many of them this survival to five years will be because they have been cured. This is something positive about cancer that the public should be told; maybe we should not overstress the fact that it is not until some time has gone by that we can be sure that a cure has been achieved, for this only causes unnecessary anxiety.

To put too much stress on the details of any particular cancer in an education programme may do more harm than good. Levine found that the fear of an illness was increased with the individual’s knowledge of the disease. Cancer education programmes should be quite clear about the extent to which detailed information on normal and abnormal function of the body is germane to the message. Some groups need special advice—for example, on normal variations in the menopause and the indications for seeking medical advice. Here the audience is ideally composed of women in the relevant age range and the information is best given in the small group setting. The special requirements for workers in potentially hazardous industries must not be overlooked, though as a rule management is all too aware of the problems once it has been warned by the Factory Inspectorate. But the unions sometimes seem more interested in compensation than in prevention, and workers may disregard preventive measures if they are inconvenient. The onus lies heaviest on the foremen and work supervisors; if they can be convinced the precautions are worthwhile then there is a reasonable chance they might be brought into force.

Information about specific forms of cancer as they affect particular individuals is a daily requirement for the relatives of cancer patients; their interest is real and anxious. The task is often easiest when the eventual outcome is predictable, and it is a delicate point of judgement what to say when the prognosis is uncertain. It is unlikely that a reference bureau on cancer would be able to deal with the specific needs of giving the appropriate answers to questions put by a patient’s relatives. Opinions vary on just how much the patients themselves should be told; circumstances differ so much from one patient to another that generalizations are impracticable. If anything, we in Britain err on the side of reticence which may result in the patient becoming isolated from his relatives by a conspiracy of silence. However, to swing over to a “brutally frank” style of doctor-patient relationship (as seems at first sight to be demanded by some of the protocols of American cancer chemotherapy trials) would require the patient to have been conditioned by several years’ living in the U.S.A. for it to produce reassurance and not acute anxiety.

Penicillamine: More Lessons from Experience

When in 1973 we reviewed1 the place of penicillamine in the treatment of rheumatoid arthritis the drug was new to most rheumatologists. Those who began to prescribe it did so with the caution due to a drug which has so many similarities, both therapeutic and toxic, to gold; and as a result, despite a high withdrawal rate because of drug intolerance, there have been very few deaths attributable to penicillamine. This drug is now being prescribed more widely, and non-rheumatologists may not all be aware of the precautions which have been developed2 by hard won experience. Penicillamine treatment was the subject of a well-attended workshop and an unofficial colloquium at the VIII European Rheumatology Congress in Helsinki in early June. What further lessons are to be learnt about management from the experience reported there? The most important have to do with dosage. The trial which showed the activity of penicillamine in advanced and recalcitrant rheumatoid arthritis3 had used two-weekly increments of 250 mg up to maintenance doses of 1000-1500 mg daily, and that was the regimen recommended in 1973. No drug can restore a ruined joint, and some rheumatologists have been using penicillamine at an earlier stage with good effect and at maintenance doses of 500-750 mg daily, with increments at four-week intervals from a starting dose of 250 mg. These lower doses have cut down intolerance to the drug without noticeably reducing its benefits.4-7 A few patients respond well to as little as 250 mg daily; some need as much as 2000 mg. Thus the policy of gradually increasing the dose from small beginnings, originally advocated by Jaffe as a means of diminishing early intolerance, also enables the clinician to work up to the optimum maintenance dose for each patient, this being the least amount that appears to be bringing about a remission. Response to penicillamine is delayed for several weeks, so that the rate of increase of dose must be slow even if this somewhat lengthens the latent period of therapeutic effect—during which other treatments must be kept up.

The rule that the starting dose of penicillamine should be 250 mg daily or less is absolute, because a few patients react even to this dose by high fever, acute dermatitis, persistent vomiting, thrombocytopenia, or neutropenia. Violent reactions like these preclude further use of the drug by such hyper-sensitive patients. The blood changes occur quite unpredictably, but if detected promptly they respond rapidly to withdrawal of penicillamine, without other treatment; if ignored they can be fatal. Platelet and white cell counts must be carried out every 7-14 days for the first few weeks and monthly counts, continued indefinitely, are obligatory in maintenance therapy. Disturbing reports have recently been received about patients who have died when these basic precautions were omitted.

Thrombocytes are now often counted by machines. Occasionally, because of some clumping, a falsely low count may be recorded, and a visual check should always be made before the decision to withdraw penicillamine is taken. The incidence of severe and early haematological disturbances and other side effects has been much reduced by the adoption of lower dose regimens,8 but one characteristic penicillamine reaction, proteinuria, has not. At some stage after the first few months of treatment almost one-third of patients taking penicillamine for rheumatoid arthritis or cystinuria (but not Wilson’s disease) excrete protein in their urine. When this increases

1 The Times, 10 May 1975, p. 5.
6 Davis, A. C., Columbia Journalism Review, March/April 1975, p. 61.
8 Knoopp, A., Changes in Opinion after 7 Years of Public Education in Lancaster, 1974, Manchester Regional Committee on Cancer.
steadily or is heavy from the outset penicillamine has to be withdrawn—all too often when patients are enjoying remission of their symptoms. The immune complex nephritis which causes this protein loss slowly resolves, and ultimately a further course of penicillamine may be tried. Proteinuria will, however, recur more often than not. A single attempt to reintroduce penicillamine after recovery from an episode of thrombocytopenia or neutropenia is also reasonable, and has a better chance of success, but it is imperative to start again with not more than 250 mg daily. A second failure is final.

Sternlieb et al.3 have published an account of three patients with Wilson's disease who died from Goodpasture's syndrome precipitated by penicillamine; and at Helsinki Dr. H. Burry described a rheumatoid patient severely affected by renal failure and haemorrhagic pneumonitis attributed to penicillamine. Jaffe has long urged that frequent testing of urine for blood is even more necessary than for protein because this may herald the onset of a more severe form of (vesicant) glomerulitis. Provided that they have been adequately instructed in the storage and method of use of the appropriate dip sticks, these tests may be done by patients at weekly or twice weekly intervals. If proteinuria is detected the 24 hour protein loss should be measured, while if haematuria is definitely present then penicillamine must be withdrawn. A sudden unexplained rise in the sedimentation rate or a fall in the platelet count sometimes immediately precedes the onset of penicillamine nephropathy—the chief disadvantage of treatment by this drug. Myasthenic reactions have also been reported,19 most responding to withdrawal of the drug but some not. Penicillamine may, perhaps, precipitate true myasthenia gravis, though it should be borne in mind that rheumatoid arthritis and myasthenia gravis do, though rarely, affect the same patient.

All these and several other reactions render penicillamine a drug which can be handled confidently only by clinicians who have a great, if not infinite, capacity for taking pains. Even they will encounter other problems. Some patients derive no benefit from even large doses of penicillamine. Some never really feel well on it and are glad when it is withdrawn. Yet others, responding well for some time, later show signs of reactivation of their arthritis. Jaffe distinguished two groups; one relapsed at about 9 months, and these patients usually respond to an increase in dose; others relapsed after about two to five years, and these do not respond to such an increase. This late acquired resistance to penicillamine does not occur in Wilson's disease or cystinuria, so the cause presumably does not lie in any change in the rate of metabolism of penicillamine.

When and how should treatment with penicillamine be stopped when a remission appears to have been achieved? Dr. H. F. H. Hill's policy is to wait for six months and then reduce the daily dose by 250 mg at intervals of two to three months. This allows time for symptoms to reappear, if they are going to, before the drug is finally withdrawn. Patients who have responded once to penicillamine usually respond again. Jaffe's clinical observations and advice about the use of penicillamine have thus, in essence, been reaffirmed by general consent of the many who now have personal experience with the drug in the treatment of rheumatoid arthritis. Its benefits can be purchased safely only at the cost of unremittant vigilance and painstaking follow-up of the patients given it. Some clinicians have organized special penicillamine clinics to ensure this. Of one thing there should be no doubt: if a patient is unlikely to adhere to the time-consuming programme of supervision or a clinician cannot provide it, then each would be wise to try something else.

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2 Lancet, 1975, 1, 1123.
4 Hill, H. F. H., Current Medical Research and Opinion, 1974, 2, 573.
6 Dixon, A. St.C., et al., in press.
9 Sternlieb, L, Bennett, B., and Scheinberg, I. H., Annals of Internal Medicine, 1975, 82, 673.

Yellow Fever

Yellow fever is a disease of tropical Africa and tropical America due to a small virus transmitted to man by mosquitoes; *Aedes aegypti* is the vector in man-to-man urban transmission, while other species of *Aedes* may transmit to man from monkeys, among which the infection is enzootic. Serological surveys have shown that the infection is more widespread than clinical illness might suggest, but both natural infection and inoculation with the 17D vaccine prepared from attenuated living virus give solid immunity.

In those people with symptoms the manifestations range from a transient febrile illness to a fulminating one fatal in a few days. Basically the infection is a hepatitis with renal lesions in those seriously ill; clinically there is little to distinguish yellow fever from viral or spirochaetal hepatitis or relapsing fever, though historically characteristic features may be present, and the bleeding tendency may be more marked in those with severe yellow fever. Jaundice may, however, be absent in patients dying early—and in some outbreaks in those surviving also. It is therefore likely that in the past other infections have been diagnosed as yellow fever and that yellow fever has been missed.

Diagnosis depends on the demonstration of complement fixing or neutralizing antibody, for virus itself is much less commonly isolated from the blood. A rising (or falling) titre should be obtained, so that the diagnosis is usually retrospective. Yellow fever may appear in a new locality or in one apparently free from infection for years; this happened on the Benue Plateau of Nigeria in 1969 producing a widespread outbreak, the first in Nigeria for 17 years. A further outbreak occurred in a neighbouring area in 1970 with an attack rate of 40% and a low case fatality of 2%. Using the complement fixation test as an indication of recent infection surveys were carried out at distances up to 400 km from the outbreak, and these showed that yellow fever infection had occurred in other areas during the same period. The epidemiology was not understood; non-human primates were scanty in the area, and the virus is present in the blood of man for a few days only. Introduction from outside the area at a time when ecological and entomological factors were favourable may have been responsible.

There have been recent reports of yellow fever in South America1; in Colombia 16 patients with jungle yellow fever were reported in November and December 1974 and all died. In 1974 there were 29 fatal cases all confirmed histologically; in 1968-73 there were 53 cases; the last was reported in January of this year. During the past four weeks there have been reports from Bolivia, Ecuador, and Peru and from Sierra Leone in West Africa; and of these 86 patients, 44 died. Previous to this the last reports from Ecuador had been in 1967 and 1951. Clearly there can be no relaxation in inoculation, which gives solid immunity for at least 10 years.