steadily or is heavy from the outset penicillamine has to be withdrawn—all too often when patients are enjoying remission of their symptoms.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. 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 (crescentic) 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the 24 hour protein loss should be measured, while if haematuria is definitely present then penicillamine must be withdrawn.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, 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 Some never really feel well on it and are glad when it is withdrawn.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 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 unremitt ing 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.

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 histologically 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.
with no discomfort to the patient, and for the foreseeable future all visitors to tropical Africa and tropical America should be vaccinated.


Rationing N.H.S. Resources

Rationing is simple enough when everyone can be given the same fixed amount, but rather more difficult within as complex an organization as the N.H.S. While the current economic crisis has forced everyone to recognize the need for economies, there is no consensus of opinion on the form they should take. Those parts of the Service that have been underfinanced in the past argue that a simple percentage cut would perpetuate injustices; yet the redistribution of resources presents many difficulties, as became clear last week at a symposium on the problem at the Centre for Studies in Social Policy in London.

The social scientists, N.H.S. administrators, and Department of Health experts present agreed that some reallocation was urgent. One effect of the reorganization of the N.H.S. has been that statisticians can see and the general public can notice inequalities between regions and within them. At the same time the economic recession has spelt the end of the policy of using the ‘new’ money available each year from real growth in N.H.S. expenditure to correct the inequalities and satisfy pressing demands. Depressed areas have been told for years that all would be well when their new district hospital was built; now that these new hospitals have vanished over the horizon to become no more than castles in Spain, some more realistic approach is needed.

Yet while differences can be identified their interpretation is far from agreed. Variations in per capita expenditure on health, in the provision of beds, in their occupancy, in discharge rates, in perinatal mortality—all these can be extracted from the flood of statistics pouring into the D.H.S.S.—but what do they mean? To some extent they only reflect the truism first voiced by Mr. Enoch Powell, that within a free N.H.S. demand will always rise to absorb all the resources made available. Are the people living in underfinanced regions such as Trent noticeably less healthy than those in the rest of the country? Should the aim be to level up or to trim the excess off the fat cats? The health indices in current use are of very little help in attempting to answer such questions.

Assessments of health care are still in their infancy. Patients as consumers have strong views on the length of waiting lists and the physical conditions of their hospitals, but the quality of medical care provided can be measured only by some form of audit—which can be carried out only by the medical profession. Standards might then become apparent for investigation, treatment, and the outcome of treatment, to provide an objective measure of one part of the service given to patients.

Meanwhile, decisions have to be made on the basis of the data available. Rationing is acceptable only so long as it is seen to be fair, and much of the time at the C.S.S.P. symposium was spent in attempts to devise a fair solution. No one seemed very optimistic that radical measures would be possible: these doubts stemmed from a general disbelief in any political will to press unpopular decisions. Is there, for example, any prospect of cutting beds and making doctors redundant in the prestigious London teaching hospital groups? Their costs are inflated by high metropolitan salaries; their patients may have to travel as much as 40 miles for an outpatient consultation; their concentration into a small, expensive part of Britain makes neither medical nor economic sense. Nor are they excusable as unavoidable relics of the past—several are brand new.

Perhaps the most promising scheme was that put forward by Drs. P. H. Gentle and J. M. Forsythe, who suggested that revenue should be allocated on the basis of population, with some weighting to take account of factors such as size, age, and sex of the population, teaching commitments, and movements of patients across administrative boundaries. Once such a “fair” system of allocation has been agreed the areas and districts could then be allowed to adopt their own policies on the spending of their resources, with the incentive—absent in the current system—that any savings made would benefit the community concerned rather than the region or the N.H.S. as a whole. These twin themes of fairness and incentives to encourage self-help are essential if any scheme of rationing is to be widely acceptable.

4 British Medical Journal, 1974, 1, 255.

Diagnosis of Malignant Carcinoid Syndrome

Carcinoids are small yellow tumours, usually less than 2 cm in diameter, arising in cells in the crypts of Lieberkühn. The commonest site of the tumour is at the tip of the appendix, where it was formerly regarded as benign—hence the term carcinoid.1 Pearson and Fitzgerald, however, in reviewing a large series4 found metastases in 38% and emphasized that all carcinoids should be considered malignant. Some cause blood loss or obstruction due to intense fibrosis in surrounding tissues, and those in the rectum should be recognized on sigmoidoscopy, but in other areas the correct diagnosis may not be made before laparotomy. Morgan and his colleagues5 found that 26% of their patients had associated malignant neoplasms, judged to be responsible for more deaths than the carcinoids. Even then the prognosis is good; one-half of 106 patients submitted to surgery survived 10 years.

The full carcinoid syndrome of flushing, intestinal disturbances, and right-sided heart disease develops in about 5% of patients with an intestinal carcinoid tumour. With few exceptions,4 it occurs in patients who already have hepatic metastases. Substances secreted by the tumour are metabolized in the liver, and so long as they remain confined to the portal circulation systemic effects are curtailed. Lembeck6 isolated 5-hydroxytryptamine (serotonin) from a carcinoid, and for years it was accepted that 5-hydroxytryptamine (5HT) caused flushing, diarrhoea, and bronchoconstriction. However, serum 5HT levels correlate poorly with flushing attacks,6 suggesting the presence of some other vasoactive agent. Oates and others7 showed that the tumours contain a proteolytic enzyme, kallikrein, probably released by catecholamines to produce a vasoactive polypeptide, bradykinin, from the alpha globulin fraction in blood. They also showed that infusion of bradykinin reproduced the characteristic flush. Probably 5HT is concerned in causing gastrointestinal symptoms, for the drug parachlorophenylalanine, an inhibitor of tryptophan hydroxy-