six. Eight patients had had congestive heart failure. Two of these had mitral incompetence, and at necropsy were found to have extensive lesions in the papillary muscles. Recurrent pericardial effusions had preceded death in two cases: in both there were granulomas in the left ventricular myocardium as well as the pericardium.

By contrast, in the nine cases in which there had been no symptoms attributable to cardiac sarcoidosis, the heart lesions had consisted of small granulomas, visible only microscopically in eight. Seven had shown evidence of cardiac dysfunction from other causes: cor pulmonale due to extensive pulmonary sarcoidosis in four, valvular disease (presumably rheumatic) in two, and myocardial infarction in one.

The frequency of myocardial sarcoidosis is difficult to estimate. Some reports have stated that a high proportion of patients with sarcoidosis show electrocardiographic changes suggestive of myocardial lesions,[7 8] and that these changes may return to normal with regression of the sarcoidosis.[8] This suggests that in the active phase scattered granulomas may be present in the myocardium in some cases but resolve—as they do in other organs—with the spontaneous regression of the disease that occurs in most cases. Whether or not that is so, few patients with sarcoidosis develop symptomatic cardiac disease.[5] The difficulty of diagnosis varies greatly with the mode of presentation. Sudden death, presumably from ventricular fibrillation or heart block, in individuals who have had no symptoms leading them to seek medical advice is a problem for the pathologist rather than the clinician. Cases of this sort may be expected to be over-represented in studies based on necropsy reports, but they are frequent in all reported series: there were 12 in the 50 cases of cardiac sarcoidosis collected by Fleming[3] from clinical records in Britain. In a patient known to have sarcoidosis, the appearance of a ventricular dysrhythmia or heart block of any degree must be strong presumptive evidence that the heart is affected, particularly if there is no reason to suspect any of the commoner cardiac diseases; and in the exceedingly rare event of the sudden development of mitral incompetence sarcoidosis of papillary muscles is a leading possibility. At least one case of this sort has been treated successfully by replacement of the mitral valve.[9]

Diagnosis is much more difficult when the problem is the coexistence of myocardial dysfunction and sarcoidosis. Coronary angiography may help but may be inconclusive. Direct evidence of coronary artery disease does not exclude the possibility of myocardial sarcoidosis; and, while finding normal vessels supports a diagnosis of cardiac sarcoidosis, it cannot exclude other cardiomyopathies. Extensive lung lesions may complicate the diagnostic problem; but Roberts *et al*[4] found that, both in their 26 cases of cardiac sarcoidosis causing cardiac dysfunction and in 63 similar cases reported by others, the initial symptom was most often related to the heart, and symptoms related to other organs were infrequent.

Cardiac sarcoidosis extensive enough to cause symptoms has a poor prognosis. Sudden death, though fortunately it is rare, is frequent, either as the first and only manifestation or after an illness which is generally not prolonged. Of the 26 patients described by Roberts *et al*,[4] 19 died within 12 months of the first cardiac symptom. Moreover, as with all the persistent chronic forms of sarcoidosis, the results of treatment are unsatisfactory. The suppressive effect of corticosteroids on the granuloma may help in controlling some of the features of the active phase of the disease: arrhythmias, conduction defects, and electrocardiographic evidence of myocardial dysfunction may be favourably affected. But treatment is in no sense curative. Granulomas tend to recur when corticosteroids are withdrawn, and there is no reason to suppose that the proportion of cases in which such recurrence does not occur is higher than might be expected from the lapse of time in the natural course of the disease. Furthermore, corticosteroids are unlikely to have any effect on the fibrotic scarring which is the end point of persistent granulomatosis.

Effective treatment of sarcoidosis in general must continue to await the elucidation of its aetiology. Even when such treatment becomes available, cardiac sarcoidosis will present special problems, both from diagnostic difficulties and from the occurrence of cases in which the first symptom appears only when the changes are extensive and irreversible, and may be sudden death.

1 Delaney, P, *Annals of Internal Medicine*, 1977, **87**, 336.
2 Israel, H L, and Goldstein, R A, *Annals of Internal Medicine*, 1973, **79**, 669.
3 Fleming, H A, *British Heart Journal*, 1974, **36**, 54.
4 Roberts, W C, McAllister, H A, and Ferrans, V J, *American Journal of Medicine*, 1977, **63**, 86.
5 Scadding, J G, *Sarcoidosis*. London, Eyre and Spottiswoode, 1967.
6 Mitchell, D N, *et al*, *Journal of Clinical Pathology*, 1977, **30**, 395.
7 Stein, E, *et al*, *Proceedings of VI International Conference on Sarcoidosis*, p 360. Tokyo, University of Tokyo Press, 1974.
8 Mikhail, J R, Mitchell, D N, and Ball, K P, *Proceedings of VI International Conference on Sarcoidosis*, p 365. Tokyo, University of Tokyo Press, 1974.
9 Raftery, E B, Oakley, C M, and Goodwin, J F, *Lancet*, 1966, **2**, 360.

Self-poisoning with beta-blockers

Self-poisoning with beta-blocking drugs is uncommon. The main clinical features include bradycardia, hypotension, low-output cardiac failure, and cardiogenic shock. Airways obstruction may also occur and respiratory depression develop as a result of severe circulatory impairment or of a central drug effect.[1] In severe overdosage the myocardium may become relatively refractory to pharmacological and electrical stimulation and death occurs in asystole.

Variations in the pharmacological properties of the different beta-blockers affect their therapeutic action and predictable adverse effects,[2] but we do not know how important these individual features are in serious overdosage.[1] Patients have tolerated therapeutic doses of up to 4 g propranolol daily[3] and deliberate overdosage of both practolol[4] and propranolol[5] without serious adverse effects. Conversely, circulatory collapse may occur in patients with pre-existing cardiac failure when sympathetic drive is inhibited by even a small dose of a beta-adrenoceptor antagonist. This observation was originally made in a patient given propranolol intravenously,[6] but it has also been reported after a single 20-mg dose of oxprenolol by mouth.[7] Apart from the problems posed by the individual drug, other factors that may complicate management include age, obstructive airways disease, diabetes mellitus, and renal or hepatic insufficiency.

Gastric lavage may allow the tablets taken to be identified but is unlikely to be sufficient to prevent serious poisoning unless performed early, because all beta-blocking drugs are absorbed rapidly. Estimating the blood concentrations of beta-blocking drugs may confirm the self-poisoning, but this is of limited value in immediate management. Haemodialysis is unlikely to rid the body of propranolol,[8] although it has not been tried in gross overdosage. It may be possible to dialyse beta-blocking drugs which are more water soluble and less

protein bound than propranolol,[9] but the value of this procedure has not been assessed.

The optimum management of these patients requires intensive supportive care with facilities for continuous cardiac monitoring and ventilatory support. Transvenous electrical pacing may be useful,[10] though it is not always successful,[1] and ideally all patients with serious overdosage from beta-blocking drugs should have a pacing catheter inserted. Intravenous atropine, 2-3 mg in divided doses, should be given to reduce unopposed vagal activity, and isoprenaline should be given by intravenous infusion with the dose monitored according to the response of the pulse and blood pressure. Because beta-blocking drugs are competitive antagonists of isoprenaline, massive doses may have to be given: in one recent report a total of 115 mg was infused over 65 hours.[10] The effects of beta-blocking drugs on the body last longer than their chemical half life in the plasma, and so intensive care may have to be continued for several days. Theoretically, other catecholamines such as dopamine or dobutamine[11] may have some advantages over isoprenaline, especially in poisoning with selective drugs such as atenolol or metoprolol—when the haemodynamic effects may be modified by beta-receptor selectivity, unopposed alpha-adrenoceptor stimulation, and baroreceptor reflexes.[12] Further developments of specific beta-adrenoceptor agonists are awaited with interest.

Intravenous glucagon may also be of value in treatment[13 14] and in severe overdosage with beta-blocking drugs it should be given early. Glucagon is thought to activate myocardial adenyl cyclase by a different mechanism from the beta-adrenergic catecholamines,[15] and its inotropic effect is not blocked by propranolol.[16]

Individual clinicians are unlikely to gain much experience in treating self-poisoning with beta-blockers, and hence these emergencies require close collaboration between the cardiologist and the clinical pharmacologist.

[1] Khan, A, and Muscat-Baron, J M, *British Medical Journal*, 1977, **1**, 552.
[2] Petrie, J C, *et al*, *Postgraduate Medical Journal*, 1976, **52**, suppl 4, 63.
[3] Boakes, A J, and Boeree, B H, *British Medical Journal*, 1973, **4**, 675.
[4] Karhunen, P, and Härtel, G, *British Medical Journal*, 1973, **2**, 178.
[5] Wermut, W, and Wojcicki, M, *British Medical Journal*, 1973, **3**, 591.
[6] Stephen, S, *American Journal of Cardiology*, 1966, **18**, 463.
[7] Brooks, N H, *British Medical Journal*, 1975, **4**, 24.
[8] Lowenthal, D T, *et al*, *Clinical Pharmacology and Therapeutics*, 1974, **16**, 761.
[9] Harvengt, C, *et al*, *Journal of Clinical Pharmacology*, 1975, **15**, 605.
[10] Lagerfelt, J, and Matell, G, *Acta Medica Scandinavica*, 1976, **199**, 517.
[11] *British Medical Journal*, 1977, **2**, 1563.
[12] Herwaarden, C L A van, *et al*, *European Journal of Clinical Pharmacology*, 1977, **12**, 397.
[13] Kosinski, E J, *et al*, *New England Journal of Medicine*, 1971, **285**, 1325.
[14] Ward, D E, and Jones, B, *British Medical Journal*, 1976, **2**, 151.
[15] Parmley, W W, *New England Journal of Medicine*, 1971, **285**, 801.
[16] Glick, G, *et al*, *Circulation Research*, 1968, **22**, 789.

Plasmapheresis

Removing of antibody from the circulation of patients with antibody-mediated hypersensitivity diseases sounds a rational remedy. In practice, however, it is not quite so simple. Sudden withdrawal of antibody from the circulation stimulates a brisk compensatory increase in its synthesis, and subsequent antibody concentrations may exceed or even double those before plasmapheresis.[1 2] Plasmapheresis needs to be combined with treatment with immunosuppressive drugs such as cyclophosphamide or azathioprine to suppress this response. Even then such a regimen achieves only partially suppression of antibody synthesis.[3]

Plasma exchange has been used with success in the management of Goodpasture syndrome,[4-7] an autoimmune disease in which antibodies are formed against glomerular and pulmonary basement membranes.[8] Removal of these antibodies may not, however, be the factor that induces remission—for improvement has been reported in other forms of acute glomerulonephritis associated with renal failure[7] and in patients with the Goodpasture syndrome in whom antibodies are not detectable in the serum.[5] Plasmapheresis certainly produces profound defibrination,[4] and fibrin deposition is well established as part of the renal lesion in the Goodpasture syndrome and is also thought to play a part in crescent formation.[9]

In systemic lupus erythematosus the clinical manifestations are caused by immune complexes (made up of DNA and anti-DNA) becoming deposited in the kidney, blood vessels, and skin. Plasmapheresis is an effective way of reducing the amounts of circulating immune complexes, and may be associated with clinical improvement.[10] Plasma exchange is also an effective way of lowering anti-D concentrations in Rhesus immunised women,[11] though the authors could not conclude that it contributed to the successful deliveries.

Myasthenia gravis has long been suspected of having an immune basis, and recent animal studies in which the disease was reproduced by immunisation with purified acetylcholine receptor[12] gives this hypothesis strong support. Furthermore, circulating antibodies specific for the acetylcholine receptor are found in nearly 90% of patients with myasthenia gravis.[13] Further evidence that the circulating antibodies might be the cause of the neuromuscular disorder has come from studies in which the passive transfer of serum fractions from patients with myasthenia gravis induced the disease in mice[14] and from experience with plasma exchange, which shows that there is an inverse relationship between the clinical state and the antibody titre.[15 16]

What, then, is the place of plasmapheresis in the treatment of myasthenia gravis? Pinching *et al*[17] described improvement in two patients during a series of plasma exchanges and Finn and Coates[18] noted transient improvement in one patient. A larger series has recently been reported from the United States.[16] Combined with corticosteroids and azathioprine, plasmapheresis produced striking improvement in five patients who were still severely disabled despite thymectomy, corticosteroids, and optimal doses of anticholinergic drugs. The drop in the titre of antibody to acetylcholine receptor was steep during the first three plasma exchanges, falling to about 40% of the initial value, but the maximum clinical response was delayed for a further several weeks. Possibly since the neuromuscular junction had been subjected to antibody attack for several years the resulting structural damage might take time to recover. Alternatively, the response might be the effect of the administration of azathioprine. Dau *et al*[16] believe that plasmapheresis offers a valuable new treatment for myasthenic patients with major disability or life-threatening weakness. Nevertheless, such a conclusion is premature, and the warning of Pinching *et al*[17] against the premature acceptance of uncontrolled results in only a few patients is pertinent. Controlled studies are under way,[19] and these may provide a more secure basis for recommending the use of plasma exchange in myasthenia gravis.

In general, the applications of plasma exchange are limited. It is time consuming, expensive, and cumbersome, and there may be practical difficulties in gaining access to the circulation. Though the procedure seems to be reasonably safe,[20] an