proprietary mixtures with names not betraying their contents. Whereas streptomycin attacks particularly the vestibular branch of the nerve and dihydrostreptomycin the auditory, the other antibiotics in this general group, notably neomycin and kanamycin, affect the auditory branch almost exclusively. Deafness so produced is permanent.

The whole subject has recently been reviewed by W. Leach,[3] who lists nine ototoxic antibiotics. The inclusion of polymyxin B is an error, as is the statement that it is "never used parenterally." It is used in this way and damage to the eighth nerve is not a recognized hazard from it. As the author admits, the evidence against ristocetin is slender and doubtful. That leaves the large group already referred to, including framycetin, which in fact has been shown to be neomycin B,[4] and two others, viomycin and vancomycin. The original material in this paper includes accounts of four patients treated at St. Thomas's Hospital with neomycin who suffered loss of hearing. In one there was renal disease, and another was an elderly man who received excessive doses (6 g. on each of six occasions) by instillation into a thoracic empyema. In the remaining two renal function was considered normal, and the dose was not excessive, though treatment—for bacterial endocarditis—was continued in one of them for six weeks. It must unfortunately be recognized that prolonged treatment with neomycin even in moderate doses and in patients with good renal function entails serious risk. Kanamycin, an otherwise very similar antibiotic, is believed to be less ototoxic, though there are plenty of records of loss of hearing from it in predisposed patients. Some encouragement to its use may be found in a case of bacterial endocarditis recorded by L. P. Garrod and Pamela M. Waterworth.[5] This patient received 1 g. of kanamycin daily together with penicillin for six weeks, and recovered with no sign of damage to the eighth nerve. This patient was a woman aged 42; Leach's patient with bacterial endocarditis was a woman aged 45, and she was treated for exactly the same period with neomycin, and with a dose reduced from 1 to 0.5 g. from the tenth day onwards.

It is usual to recommend that during the use of these antibiotics a careful watch should be kept for signs of damage to the eighth nerve. This should of course be done, and administration stopped—unless the patient's life is at stake—when any such signs appear. Unfortunately this is not an adequate safeguard, because a long latent period—sometimes even of several months—may elapse before the effect becomes manifest. The interval may be such that cause and effect are not connected. Thus it is always worth while to inquire of patients with rapid and unexplained loss of hearing whether they have been given any injections in the recent past. In Leach's patients loss of hearing was first complained of 1, 3, 3, and 4 weeks after the treatment had ended, and he offers no evidence that any tests could have detected what was going on at an earlier stage.

There are much more positive ways of guarding against these disasters. The foremost of these is strictly to reserve these antibiotics for clear and serious indications. The second is always to review the possibility of impaired renal function, for even a moderate degree of this reduces the rate of excretion and produces the climbing blood levels which alone can cause damage during short-term treatment. In Cawthorne and Ranger's series of patients with vestibular damage after small total doses of streptomycin were patients with pyelitis in a solitary kidney, tuberculosis in a solitary kidney, and nephrolithiasis. Diabetic nephropathy was doubtless responsible in the case reported by A. Lustberg and M. Hamburger,[6] a 52-year-old man already blind from diabetic retinitis who was rendered also totally deaf by treatment with kanamycin for boils. Lesser degrees of renal impairment than these are also to be feared. Even those almost normally associated with advancing age may delay excretion, and very serious thought should be given to the administration of these antibiotics to any elderly patient. Thirdly, whenever there is the slightest reason to doubt renal efficiency, the antibiotic must be assayed in the blood and the dose regulated accordingly. A. A. C. Dutton and P. C. Elmes[7] found it necessary to do this at frequent intervals to control the dose of vancomycin in uraemic patients, and devised a method for the purpose which took only five hours. A more leisurely test will often serve, but if facilities for any such tests are not available the clinician using an ototoxic antibiotic in a patient with poor renal function is taking a grave responsibility.

[1] Cawthorne, T., and Ranger, D., *Brit. med. J.*, 1957, **1**, 1444.
[2] Shambaugh, G. E., jun., *et al.*, *J. Amer. med. Ass.*, 1959, **170**, 1657.
[3] Leach, W., *J. Laryng.*, 1962, **76**, 774.
[4] Rinehart, K. L., jun., Alexander, D. A., Goss, W. A., Sohler, A., and Schaffner, C. P., *J. Amer. chem. Soc.*, 1960, **82**, 3938.
[5] Garrod, L. P., and Waterworth, P. M., *J. clin. Path.*, 1962, **15**, 328.
[6] Lustberg, A., and Hamburger, M., *J. Amer. med. Ass.*, 1959, **170**, 806.
[7] Dutton, A. A. C., and Elmes, P. C., *Brit. med. J.*, 1959, **1**, 1144.

HAEMAGGLUTINATION IN VIRAL HEPATITIS

Since Hirst[1] first discovered that influenza virus can agglutinate avian erythrocytes many other viruses have been found with similar activity. Often the agglutination is brought about by the direct action of the virus on the surface of the erythrocyte, and sera from convalescent patients specifically inhibit such agglutination by means of their antiviral antibodies. Since experimental animals are not susceptible to the virus of infectious hepatitis many

[1] Hirst, G. K., *Science*, 1941, **94**, 42.
[2] Rubin, B. A., Kemp, H. A., and Bennett, H. D., ibid., 1957, **126**, 1117.
[3] Havens, W. P., *New Engl. J. Med.*, 1958, **259**, 1202.
[4] —— *Arch. intern. Med.*, 1960, **160**, 327.
[5] Turner, P., Jha, V. N., Crowley, Nuala, and Sherlock, S., *J. clin. Path.*, 1962, **15** 491.

investigators have tried to develop the haemagglutination test as a simple diagnostic procedure for the disease. In 1957 B. A. Rubin, H. A. Kemp, and H. D. Bennett[2] claimed not only that haemagglutination could be obtained with sera from patients with infectious hepatitis but that it was induced by the direct action of the virus itself. Subsequent studies by W. P. Havens,[3 4] though confirming the agglutinating activity of such sera, challenge the view that the virus itself is directly involved. He showed among other things that sera from several subjects known to be responsible for the transmission of viral hepatitis consistently failed in the haemagglutination test.

A recent report[5] from the Royal Free Hospital on haemagglutination in infective hepatitis largely bears out Havens's findings and conclusions. Of 58 cases of infective hepatitis a positive agglutination test was obtained in 21 (36%). This is considerably fewer than in Havens's series, but in patients tested within 14 days of the onset of symptoms the incidence of positive tests was 60%. In both the Havens's and the Royal Free series the reaction in patients with obstructive jaundice was consistently negative. As the combined series included 35 such cases a positive haemagglutination test would appear to exclude this diagnosis. Since positive results are found in 10 to 20% of cases in forms of hepatic disease other than viral hepatitis the consistently negative findings in obstructive jaundice suggested the possibility that in this condition an inhibitor might be present, a suggestion that has been confirmed.[3]

The absence of a positive haemagglutination test in many patients with unequivocal viral hepatitis and the presence of positive tests in some patients with other disease (e.g., rheumatoid arthritis) afford strong support to Havens's original conclusion that haemagglutinating activity revealed by the sera of some patients with infective hepatitis is not due to the causative virus but is a manifestation of one of the serum changes associated with hepatic dysfunction. Similar changes associated with many other diseases would then account for the lack of specificity in this test.

OSTEOPOROSIS IN RHEUMATOID ARTHRITIS

To the clinician osteoporosis is either local, from disuse, or general, the result of senility and perhaps of an endocrine factor. The fact that osteoporosis is an integral part of Cushing's syndrome, in which excessive cortisol is produced, has led many people to assume that the osteoporosis and the vertebral fractures seen in patients with rheumatoid arthritis who receive corticosteroids are of the same nature. McConkey and his colleagues from Cardiff have recently performed a useful act in questioning this view.[1]

Examining 97 patients with rheumatoid arthritis they found osteoporosis in 10 out of 36 (28%) not treated with corticosteroids and in 20 out of 61 (33%) treated with them—a negligible difference. Osteoporosis was associated with purpura and "was largely the result of rheumatoid disease and age, and not of treatment with corticosteroids." However, five cases out of 61 in the treated group had sustained vertebral fractures and none in the 36 not so treated. The authors remark that this difference could have occurred by chance (with a probability of $P=0.154$). Though there was no random allocation to steroid treatment the two groups were similar in regard to age, sex, and duration and severity of disease.

But is this complication due solely to chance? Others have also noted the greater incidence of vertebral fractures in patients treated with corticosteroids. Thus of 216 patients with Still's disease followed up at Taplow between 1947 and 1959 63 were treated by maintenance corticosteroid for three months or longer and 5 of these developed vertebral fractures compared with 2 out of 153 patients who had shorter or no steroid therapy.[2]

The main problem in osteoporosis is the difficulty of assessment. No qualitative method has gained general acceptance. But because something is difficult to assess is no reason for not assessing it. The bold man will step in and produce a purely subjective assessment, and this is valid so long as he includes an estimate of observer error. The Cardiff authors depended on agreement between two observers as to the presence of osteoporosis, but doubt or disagreement occurred in 20 out of 97 cases. These 20 cases they decided to classify as normal without telling their readers what would have happened if they had been classified as abnormal or indeed if a second blind reading had been done to substantiate the first. For these reasons the data, though interesting, do not seem entirely adequate to sustain fully the surmise that "osteoporosis and purpura in patients with rheumatoid disease may be the consequence of the same change in the collagen of bone and skin" and unrelated to corticosteroid therapy.

REPAIR OF RUPTURED INTERVENTRICULAR SEPTUM

Apart from developmental defects, deficiencies in the interventricular septum may result from trauma or myocardial infarction,[1] other causes being of excessive rarity. The commonest acquired perforation of the cardiac wall—post-necrotic rupture of the left ventricle—is not amenable to surgical treatment, because of the rapidity with which it proves fatal; but the comparable lesion of the septum giving rise to a fistula may be treatable, in theory at least, since it is known that a small percentage of patients recover from the episode of infarction and rupture, survival of up to five years being recorded.[2] The ultimate appearances of the lesion differ greatly from those visible in a subject dying, as is the rule, within a week or two of septal rupture. Initially there is a ragged track passing through necrotic haemorrhagic muscle, with a visible opening to the left ventricle and a barely discernible one on the right side of the septum. In the established septal defect, months later, there is a readily seen oval defect (in area about 1 cm.^{2} or more) with a smooth margin of scar tissue and characteristically located towards the apex. (This may

[1] McConkey, B., Fraser, G. M., and Bligh, A. S., *Quart. J. Med.*, 1962, **31**, 419.
[2] Badley, B. W., and Ansell, Barbara M., *Ann. rheum. Dis.*, 1960, **19**, 135.

[1] Schiller, K. F. R., *Lancet*, 1960, **2**, 1322.
[2] Wood, F. C., and Livezey, M. M., *Amer. Heart J.*, 1952, **24**, 807.
[3] Bressie, J. L., *et al.*, *J. Amer. med. Ass.*, 1962, **182**, 1042.