and a high incidence of uncertain scan findings, to be used as the only method of search for secondary deposits. The greater accuracy of ^{99m}Tc polyphosphate makes it more suitable as the principle means of search though in one patient of the 61 investigated with this isotope we were unable to identify metastases which were clinically and radiologically evident. Care also needs to be used in the interpretation of positive results since an isotopic "hot spot" is a non-specific indicator of abnormal metabolic bone activity and can therefore be produced by any metabolically active lesion, such as are seen, for example, in Paget's disease. We do not envisage that polyphosphate scintigraphy will completely replace *x*-ray examination in the identification of bone metastases, but we do feel that it should be used as the principle "search weapon" both in the initial assessment of the patient with prostatic cancer and in the continuing management of the disease.

We thank Drs. J. J. Stevenson and T. Sherwood, consultant radiologists at St. Peter's Hospitals, who reviewed and reported on the *x*-ray pictures of the patients in our study, and we are indebted to Dr. Sherwood for the first suggestion for the polyphosphate study. We thank also Mr. J. P. Williams, subdean, Institute of Urology, Mr. J. C. Park, consultant urologist at Greenwich District Hospital, and the consultant urologists of the St. Peter's Hospitals who referred many of their patients to us. This work was supported by the St. Peter's Research Trust.

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MEDICAL MEMORANDA

Development of Heart Valve Lesions during Methysergide Therapy

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Methysergide is a pharmacological antagonist of serotonin and is used mainly for the prophylaxis of migraine. Unwanted side effects on normal therapeutic doses occur in 10-15% of cases and retroperitoneal fibrosis is likely to occur in about 1% of all cases treated continuously for more than a year (Neleman, 1972). The fibrosclerotic side effects causing retroperitoneal and pleuropulmonary fibrosis have been well documented (Graham, 1964, 1967). During 1968-70 some 50,000 E.C. 10 prescriptions of methysergide were issued in England and Wales, and during that time four cases each of peritoneal fibrosis and pleural fibrosis were reported to the Adverse Reaction Register (Committee on Safety of Medicines, personal communication). The yearly number of E.C. 10 prescriptions in England and Wales fell from 23,000 in 1968 to 800 by 1972, probably due to the recognition of these side effects. Valvular insufficiences due to methysergide appear to be less widely known (Graham, 1967). This paper describes a case involving the tricuspid and mitral valves.

Case Report

A 48-year-old aircraft mechanic with hemiplegic migraine had been taking methysergide 2 mg twice daily for four years. This was the only drug able to control his attacks though it did not affect his gradually progressive dementia and extrapyramidal disorder. Investigation showed no retroperitoneal fibrosis, no cardiac symptoms and no murmurs. Blood pressure was 140/80 mm Hg and the E.C.G. was normal. There was no history of rheumatic fever. A 24-hour urine sample contained less than 10 mg 5-hydroxyindoleacetic acid. He became bedridden as a result of dementia and extrapyramidal ataxia and died with an intercurrent pulmonary infection.

At necropsy death was found to have been due to lobar pneumonia. The brain showed areas of cystic degeneration of white matter. The heart was normal externally and weighed 370 g. The mitral valve showed mild stenosis, admitting only two fingertips (2 cm diameter) and feeling stiffer than normal. There was a strikingly uniform, glistening white thickening of the chordae tendineae with some fusion which extended on to the ventricular aspect of the valve leaves, producing fan-shaped ridges. Slight diffuse thickening was present on adjacent parts of the cusp surfaces (fig. 1). The anterior and septal cusps of the tricuspid valve were similarly but less severely affected (fig. 2). The aortic and pulmonary valves were normal. The only other endocardial lesion was a 5-mm white fibrous thickening on the septum below the aortic valve resembling a "jet" lesion caused by turbulence. The myocardium and pericardium were normal. The abdominal organs were normal and there was no obvious retroperitoneal fibrosis.

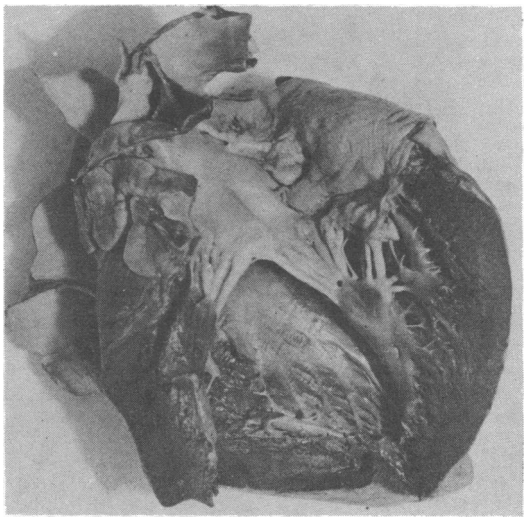

FIG. 1—Mitral valve after four years of methysergide therapy. Chordae tendineae are covered with smooth white fibrous tissue.

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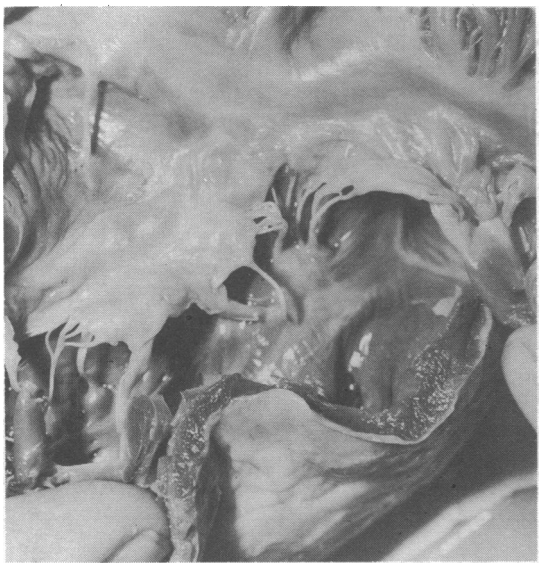

FIG. 2—Tricuspid with affected septal and anterior valve leaflets.

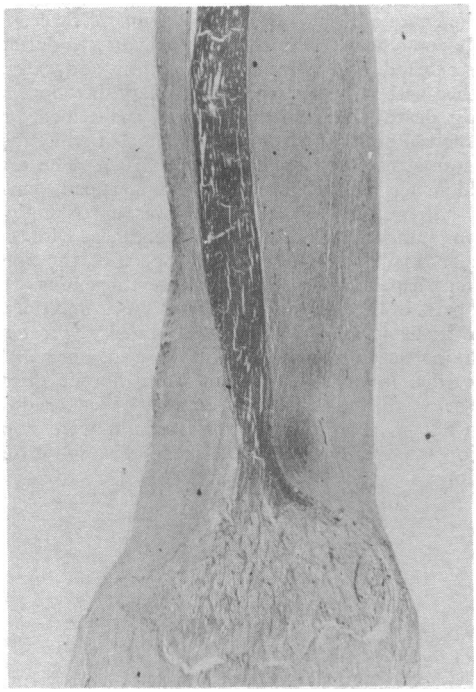

FIG. 3—New fibrous tissue surrounding chorda of mitral valve. Apex of papillary muscle at base of photograph. (Verhoeff and van Gieson. □ × 20)

Histologically the heart showed a uniform layer of avascular, poorly cellular fibrous tissue covering the affected chordae and valves. This was free from elastic fibres and was clearly demarcated from the underlying endocardium of the valve cusps and chordae, which were otherwise normal (fig. 3). Fibrin could not be shown with special stains (phosphotungstic acid and haematoxylin and Lendrum's Martius Scarlet Blue method). No abnormalities were found in the myocardium and pericardium.

Comment

Many patients develop systolic and diastolic murmurs during methysergide therapy and these usually disappear or diminish on discontinuing treatment (Graham, 1967). Some cases have progressed to cardiac failure and two of Graham's patients required valve replacement. In one case, after six months of methysergide the aortic cusps were found to be thickened and incompetent. The patient had rheumatoid arthritis. The other, treated for four years, showed thickening of the aortic and mitral valves by plaque-like deposits of new fibrous tissue. Munroe *et al.* (1969) described a further case in which the mitral valve was replaced because of gross mitral incompetence after four years of methysergide 9 mg daily. Kunkel's (1971) case 9 was not clear-cut because of a rheumatic history and pre-existing murmurs. The excised valves in all these cases showed the same features as in the present case—namely, thickening of the chordae and valve cusps by a layer of avascular fibrous tissue. They differed from rheumatic valve deformities on the absence of vessels and absence of elastic fibres in the newly laid-down fibrous tissue and the "normality" of the architecture of the underlying valve. In contrast the similarity to the endocardial lesions of the carcinoid syndrome was striking though in that condition they are predominantly right-sided. In view of its structural similarity to serotonin it is not surprising that methysergide produces related pathological changes, especially as it appears to have some agonistic as well as antagonistic properties to serotonin.

The mechanism of the fibrotic lesions, whether cardiac, pleural, or retroperitoneal, is unknown. Attempts to reproduce these fibrotic lesions in animals have been unsuccessful (Hodal and Griffiths, 1973).

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