ventricular rate of 68. The P wave was of normal shape; the QRS complex was of normal duration (0.08 second); the S-T segment was slightly depressed in leads I, aVL, and V₆; and the T waves were flattened or inverted in I and aVL. The pattern indicated heart-block and suggested anterolateral ischaemia and left ventricular strain. The patient died within six days of admission from cerebral haemorrhage and heart failure.

Post-mortem Findings.—**Brain:** There was a recent haemorrhage into the white matter in the right parieto-occipital region, while an old apoplectic cyst was found in the left putamen. The larger arteries were atherosclerotic. **Heart:** This weighed 360 g. The left ventricle was moderately dilated and hypertrophied, the parietal and valvular endocardium was smooth, and the myocardium was brownish yellow. No macroscopical changes were found around the outlet of the coronary sinus or around the pars membranacea septi. The coronary arteries were moderately atherosclerotic. **Aorta:** This was atheromatous, with some ulcerated plaques in the abdominal part. The remaining viscera were congested and the lungs were oedematous.

Microscopical Findings.—A single block comprising the base of the interatrial septum and the upper three-quarters of the inter-ventricular septum was fixed in formalin and embedded in paraffin. Serial sections were cut 50 μ apart and stained with haematoxylin and eosin, azan, or orcein. The region adjacent to the central fibrous body, which is normally rich in fatty and soft connective tissue, was found to be diffusely and coarsely fibrotic (Special Plate, Fig. 1). The atrioventricular node and its connexions with the right atrium showed sclerosis and severe atrophy. Within the predominant fibrous strands and interlaced with elastic fibrils there were several channels, scattered or in groups, lined by thick layers of swollen endothelial cells often occluding the lumen. A few channels were slightly dilated and lined by a single layer of endothelial cells which sometimes protruded into the lumen (Special Plate, Fig. 2), and some of these were empty while others contained acidophilic debris. The sections, however, did not have a cystic pattern. Perilymphatic infiltration with round cells was often seen (Special Plate, Figs. 3, 4, and 5). A small amount of calcium was deposited among the fibrous strands. The area of abnormal histology involved a few square millimetres on each of the sections from the base of the inter-atrial septum to the upper border of the bundle of His, but it was never very well demarcated. Distally the right bundle branch was normal but the roots of the left were partially damaged. Sections from the walls of both ventricles showed no areas of myocarditis.

DISCUSSION

Five cases of heart-block ascribed to lymphangio-endothelioma of the heart have been reported (Armstrong and Mönckeberg, 1911; Lloyd, 1929; Perry and Rogers, 1934; Rezek, 1938; Mahaim, 1945). The diagnosis in these cases was made on the necropsy findings of whitish nodules and of cysts, and confirmed by the histological demonstration of cells

aggregated in columns or clusters and of numerous cysts in a "honeycomb" pattern (Perry and Rogers, 1934), with little or no evidence of an inflammatory process (Rezek, 1938). The diagnosis of lymphangio-endothelioma was challenged, however, by Rezek (1938), who suggested that the "tumour" in these cases had arisen in ectopic endodermal, probably foregut, epithelium. This hypothesis has been put forward, too, in other cases where the cystic element was prominent but the conducting system not involved. It has also been suggested by Mahaim (1945) that the "tumours" may have a mesothelial (coelomatic) origin.

In the present case, however, the affected area was not visible to the naked eye, and histological examination showed it to be poorly demarcated and to consist mainly of coarse fibroelastic tissue and inflamed, proliferating lymph vessels. Dilatation and new formation of vessels and epithelial-like proliferation of endothelium are to some extent common features of both lymphangio-endothelioma and chronic proliferative lymphangitis. However, the predominance of the fibrous over the angioblastic component in this case, and in particular the presence of perilymphangitis, are suggestive of an inflammatory process.

It is easy to conceive a sequence of events leading from long-standing lymphangitis with impairment of lymphatic drainage to sclerosis and atrophy following the pattern outlined by Drinker and Yoffey (1941) and described in human endomyocardial fibroelastosis by Kline *et al.* (1964). It is possible that congenital dysplasia of lymphatic vessels predisposes to lymphangitis; but this is unlikely to have been the case here, since lymphangiectatic malformations usually present at a much earlier age (Kline *et al.*, 1964). It is therefore postulated that the cause of the damage to the conducting system and of the heart-block in this case was a chronic proliferative lymphangitis.

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Imipramine in Treatment of Parkinsonism : a Double-blind Placebo Study

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A review of the literature discloses such fundamental differences of opinion regarding the efficacy and mode of action of imipramine that further clinical studies are more than justified.

Though a number of reports confirm the specific anti-depressive effect first described by Kuhn in 1957, a recent comprehensive survey of American and British journals revealed ten placebo-controlled trials in which the effect of imipramine on depression was better than that produced by the placebo in four, no better in five, and equivocal in one (Hare *et al.*, 1964). The slight improvement obtained by these authors was ascribed entirely to sedative effects. Rees *et al.* (1961) stated that imipramine influenced anxiety more favourably than depression.

Sigwald *et al.* (1959), who first used the drug in Parkinsonism, were particularly impressed with the improvement of akinesia. In spite of the chemical similarity of imipramine to the phenothiazines, subsequent reports tended to confirm its value in Parkinsonism, though its mode of action was disputed. Strauss (1959) and Blomberg and Eriksson (1961) stated that the neurological effects were entirely secondary, while, on the other hand, Di Cristo and Di Cristo-Tedeschi (1961), Denmark *et al.* (1961), Mandell *et al.* (1961), and Gillhespy and Mustard (1963) claimed that the neurological improvement resulted from the specific action of the drug.

In view of its anticholinergic, antihistaminic, and anti-serotonin properties (Domenjoz and Theobald, 1959) it would be surprising indeed if imipramine did not possess a measurable specific action in ameliorating the symptoms of Parkinsonism.

CLINICAL MATERIAL AND METHODS

Seventy unselected patients were given, alternatively, either imipramine or placebo tablets, the exact sequence differing with

each group examined. The code was kept by an independent observer who, when necessary, advised the patients during the four months' observation period.

There were 18 women and 11 men over the age of 59 years, nine women and 19 men between 50 and 59, and four women and nine men between 40 and 49. Five patients had a history of encephalitis, and in 10 the presence of arteriosclerotic cerebrovascular disease was noted at the time of onset of Parkinsonism.

All examinations were carried out by the author, and the signs and symptoms were graded clinically and/or mechanically in units of 10, from 0 (normal) to 100 (maximum severity). An improvement of 10 to 25% was considered "fair," 26 to 50% "moderate," 51 to 75% "good," and 76 to 100% "excellent." A number of timed performance tests were used as a partial measure of the patients' functional capacity.

Results of Imipramine Therapy in the Treatment of 30 Patients with Parkinsonism Observed for a Period of Four Months

Symptom or Sign Evaluated	Total No.	Improved				No Change	Worse
		10-49%	50-100%	No.	%		
Depression	20	8	4	12	60	8	—
Rigidity	24	9	1	10	42	14	—
Tremor	25	7	—	7	28	16	2
Akinesia	13	5	2	7	54	5	1
Hypersalivation ..	14	5	3	8	57	5	1
Functional capacity (performance tests)	30	13	3	16	53	12	2

Patients over 55 received daily increments of 10 mg. imipramine until (1) an optimal effect was produced, or (2) the dose had to be adjusted because of side-effects, or (3) a total daily dose of 150 mg. was attained. Those between the ages of 40 and 55 were given a dose of 25 mg. daily for three days, followed by daily increases of 25 mg., as above, or until the total daily dose was 200 mg.

No patient had received any medication for at least one week before the trial was instituted, and laboratory examinations were performed in 12 cases.

RESULTS

During the first week of the trial five patients discontinued imipramine because of adverse reactions which are described below. Thirteen patients stopped placebo medication because of clinical deterioration, and 14 because of a failure to respond. Of the eight taking placebo tablets at the end of four months, two were subjectively better, two worse, and four unchanged.

Of the patients who took imipramine 16 (53%) were improved as measured by performance tests, and the results are analysed in the Table. In addition, insomnia was improved in 60% of patients, anxiety and tension in 38%, and oculogyric crises in 50% (three out of six patients). There was very little improvement of memory, of the inability to concentrate, of speech, or dysphagia.

Fourteen patients were unimproved, but of these, seven did in fact show a favourable and significant response for periods of one to three months. Increasing the dose in these cases, however, failed to re-establish the initial effect. The drug had no effect in five patients and two showed very slight clinical deterioration.

At the conclusion of the trial almost all patients over the age of 55 were taking between 30 and 75 mg. daily (maximum 100 mg. in two), while in those between 40 and 55 years the average daily dose was 50 to 100 mg. (maximum 150 mg. in three).

Side-effects were rarely a problem and usually disappeared when the dose was reduced for three to five days. Dryness of the mouth and throat of sufficient severity to necessitate altering the dosage occurred in four instances, nausea and attacks of sweating in two each, and lethargy, constipation, paraesthesiae, and an unpleasant taste in the mouth in one each.

Three of the five patients who discontinued imipramine did so because of dizziness and severe gastro-intestinal disturbances, and two because of an exacerbation of symptoms, particularly tremor, together with confusion, ataxia, and slurred speech. No significant cardiac or blood-pressure changes were noted.

In one case there was a mild leucopenia, and in one a mild eosinophilia which disappeared within a week of stopping the drug.

DISCUSSION

A most satisfactory degree of improvement in 16 patients (53%) confirms the value of imipramine in Parkinsonism. There was no significant difference in the response of the arteriosclerotic, idiopathic, or post-encephalitic groups.

The best clinical results were seen in patients under the age of 50, who usually had the shortest histories and the less incapacitating forms of the disease. The least satisfactory results occurred in patients over 59.

Relief of a reactive depression was clearly apparent to patient, relatives, and examiner in 12 patients (60%). The degree of relief was considered to be "moderate" in eight, "good" in two, and "excellent" in two. This effect was felt to be the primary reason for the improvement of tremor, with which it was associated in seven cases. Direct measurement of tremor for an hour after a dose of 50 mg. failed to show any significant alteration.

Since three of ten patients with rigidity showed moderate to good improvement, without any significant relief of an associated, moderately severe depression, and since four of the twelve patients with a reactive depression who improved showed no significant, concomitant physical improvement, it may be concluded that the drug exerted both a specific anti-depressive action and a specific effect against the majority of the symptoms and signs of Parkinsonism.

The increased functional performance was primarily the result of the improved physical status.

The dosages used produced an optimal response, and side-effects were few and readily controlled in most patients by reducing the dose for three to five days, with subsequent careful increases if further improvement was desirable. Once the drug began to lose its effect further increases failed to establish any worth-while clinical response. The dosage schemes for the two age groups were developed from an earlier hospital trial when it was observed that doses of 150 mg. daily in older patients and of 200 mg. daily in younger patients were optimal.

A sedative effect was unequivocally observed in only two of seven patients, five of whom had no associated depression.

Clinical improvement began within two to three days of starting treatment, and not after a delay of two to three weeks as commonly stated (Hare *et al.*, 1964).

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