of the disease phases of increased and decreased pain occur. For this reason caution must be exercised in pressing the claims of a new preparation before extended trials have been made. We believe, however, in view of our results, that such trials of cavodil are fully justified and should be undertaken.

Summary

A controlled "double-blind" trial of cavodil has been made in 28 patients with angina pectoris.

Improvement occurred in almost twice as many patients with cavodil as with the control tablet, and in some patients this improvement was remarkable.

It is suggested that an extended trial of this drug is fully justified and should be undertaken.

Side-effects were minimal and unimportant.

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EPIDEMIC OF CHRONIC NEPHRITIS OF UNKNOWN AETIOLOGY

BY

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Since 1957 a remarkable increase in the number of persons suffering from chronic nephritis has been observed in some regions of Yugoslavia. In certain villages this outbreak has shown all the main signs of an epidemic. As a similar occurrence has not been described before and therefore no experience has been obtained concerning this condition, extensive investigations have been undertaken in the affected area. It was found in the neighbourhood of Lazarevac, a city of Serbia, that cases of chronic nephritis have occurred in great numbers in three of the villages situated in the inundated area of the river Kolubara (Milojčić *et al.*, 1958). Epidemiological inquiry established that most of the persons attacked were adults over 30 years of age; only 10–14% were children under 14 years old. Incidence in women was 10–30% greater than in men. The illness is confined to certain families and is restricted to those parts of the villages which are situated in the inundated area. In these families the morbidity rate is from 38 to 44%. Of the whole population of these

villages 1–6% became ill with characteristic symptoms, as 30–36% suffered only from albuminuria, the first sign of renal disease.

The patients are agricultural workers, employed under average economic conditions. Their diet is mixed, contains milk products and meat, and does not differ from that of the healthy villagers. The water-supply is unhygienic, the wells being shallow and liable to pollution. However, no intestinal infection has been registered during the past 25 years, nor has there been any epidemic among domestic animals or trouble with rodents. Mosquitoes are present in great numbers, but malaria has not been unusually prevalent. No effect of seasonal influence has been observed on the spread of illness; nor has a diffusion of illness by contact been noticed, since uninundated areas of villages have been spared though continual contact existed with affected families. No other epidemics of infectious diseases in this region are remembered, and no trace of scarlet fever, sore throat, or other streptococcal infection has been reported among the patients.

Onset

It is significant that about 90% of the patients have not been aware of the onset of the illness. The starting-point is imperceptible, and subjective symptoms are so infrequent, even in the final stage, that the patients pay no great attention to them. For that reason many are not conscious of their illness until the physician tells them. The most common symptoms are lassitude, fatigue, anorexia, headache, and gastric pains. The only objective symptom is albuminuria, and that is the first sign of renal disease (Danilović *et al.*, 1957). The remaining urinary findings are uncharacteristic, red cells and casts mainly being absent. Oedema and hypertension are seldom present. Urea is usually within normal limits until the final stage, when uraemia begins, death following shortly. Patients are apyrexial, thin, and anaemic, and have a characteristic dark-coloured skin. Inspection of the fundus oculi has not indicated any change.

Clinical Picture

The illness is characterized by a gradual development from the beginning of albuminuria to the final uraemic stage. The renal lesion develops throughout the years; it may be detected in children as albuminuria, reaching the final stage of renal failure only at the age of 40 or over. Acute cases, with a rapid and definite beginning of the disease, do not occur. The mortality rate is 3–5%. At necropsy the kidneys show interstitial chronic inflammation, localized mainly to the tubules.

Because of the uncharacteristic clinical picture, the possibility of some form of chronic poisoning has been under consideration. This theory was discarded as soon as it was established that the illness lasts for several decades in some families, and that sometimes all members of a family died of chronic nephritis. Though the illness was known long ago, only the obvious increase in the number of cases has drawn the attention of specialists to it. Water and food have been analysed for various toxic elements, such as mercury, arsenic, phenols, aniline, cresols, insecticides, and radioactive substances, but without positive results. In the flour used by some families lead was found in the proportion of 0.3 mg./kg. As this flour comes from the little village mills it was decided to investigate the millstones concerned. Some of these had a high proportion of lead

(Danilović *et al.*, 1957); but these findings applied only to individual cases, and most of the patients had no trace of lead in their food. As the clinical picture does not correspond to that of chronic lead-poisoning, there is not enough evidence that this is the cause.

Bacteriological and virological investigations for known infections were not successful, and exhaustive tests showed that leptospirosis could be excluded. Acute infections with renal symptoms, epidemic haemorrhagic fever, and viral "nephroso-nephritis" are not commonly found in these patients.

Though a large number of cases of serous nephritis were reported during the second world war, especially among prisoners-of-war, no relation has been established between these and the present epidemic. Pellagra, which is prevalent in some regions of the country, is unknown in these villages.

Possibility of Streptococcal Infection

Recent communications have stressed the important part played by streptococcal infection in promoting acute nephritis (Rammelkamp, 1956; Kodama *et al.*, 1959), and attention has been concentrated on the possibility that it may have some relation to the present outbreak. This possibility cannot be excluded, even though all patients deny having had manifest streptococcal infection in the past. Also, no case has been reported of epidemic chronic nephritis as a consequence of streptococcal infection. Bearing in mind that all the patients have a common history—that they live in humid conditions and are exposed to constant cold—it is possible that this factor, together with streptococcal infection, unapparent or latent, may provoke renal disease. Bacteriological and epidemiological investigations having been negative, an investigation was carried out in the neighbourhood of Belgrade on persons who had had scarlet fever 10 years previously. Only 0.5% of these had chronic nephritis. In other control groups of inhabitants who were exposed to streptococcal infections the percentage with albuminuria did not exceed 3%, and with nephritis 0.8%. It has not been proved, therefore, that streptococcal infection has a part in the causation of these renal lesions.

It is significant that similar phenomena have been observed in recent years in Bulgaria and Rumania (personal communication). In those countries, also, the condition is connected with villages in inundated areas, and the aetiology remains unknown in spite of numerous investigations. Owing to the number of patients and the gravity of the illness a serious problem faces medical science in countries where this form of chronic nephritis occurs.

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The Chairman of the Education Committee, London County Council, was asked at a recent meeting what percentage of secondary schoolchildren in the council's schools were drinking milk provided free by direct Government grant, and how did that percentage compare with the corresponding figures for 1957 and 1958? The reply was 69.23% in 1959, 76.81% in 1957, and 71.45% in 1958.

RENAL EXCRETION OF PHOSPHORUS AND HYPOPHOSPHATAEMIA AFTER PARATHYROIDECTOMY

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In primary hyperparathyroidism two characteristic biochemical changes occur in the blood—hypercalcaemia and hypophosphataemia—which, when combined with a raised alkaline phosphatase, are almost pathognomonic of the disease. The hypercalcaemia probably results from a direct action of the parathyroid hormone on bone (Barnicot, 1948; Howard, 1956). The hypophosphataemia, on the other hand, results from a different action of the hormone on the renal tubules, diminishing the proportion of glomerular filtered phosphorus which is reabsorbed, so that there is excessive phosphorus loss in the urine (Crawford *et al.*, 1950). When the disease is cured by parathyroidectomy it is usual for the hypercalcaemia to disappear rapidly, often within a few hours. However, the hypophosphataemia sometimes persists for up to several weeks after operation, and it has been suggested that this is particularly likely to occur when severe bone disease is present (Albright and Reifenstein, 1948). One reason for this might be that phosphorus is rapidly removed from the blood and deposited in new bone, preventing the plasma level from rising to normal. This cannot be the complete explanation, however, as hypophosphataemia is often prolonged post-operatively in the absence of hypocalcaemia, or in patients with hypocalcaemia it may persist after restoration of the serum calcium level to normal. It was noted (Nordin, 1958) that this persistent hypophosphataemia may be associated with an abnormally high renal phosphate excretion, and so may be due to secondary hyperparathyroidism, for reasons discussed below. In this paper we are reporting serial observations after parathyroidectomy in seven patients that tend to support this hypothesis.

Methods

Patients Studied.—Seven patients (five females and two males) with hyperparathyroidism due to parathyroid adenoma were studied. The clinical features are set out in Table I. It will be seen that five patients had obvious bone disease, in one the bones were normal both radiologically and on biopsy, and in one the x-ray films were normal and biopsy showed only a slight increase of osteoclasts. The patients were, however, unselected. Two patients had impaired renal glomerular filtration as shown by a raised blood urea, and six of the seven patients had a low fasting plasma phosphate pre-operatively (Figs. 1–7).

Assessment of Parathyroid Function.—The fraction of glomerular filtered phosphorus appearing in the urine is influenced both by the plasma phosphate level and by the activity of the parathyroid glands, the latter tending to reduce the tubular reabsorption of phosphate