(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

BY

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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

(Crawford *et al.*, 1950 ; Sirota, 1953 ; Schaaf and Kyle, 1954 ; Nordin and Fraser, 1954 ; Chambers *et al.*, 1956). This fraction can be estimated approximately from the concentrations of phosphate and creatinine in samples of blood and urine collected at the same time. The phosphate/creatinine clearance ratio (Cp/Ccr) is derived from the formula:

$$\text{Cp/Ccr} = \frac{\text{Urine phosphate} \times \text{plasma creatinine}}{\text{Plasma phosphate} \times \text{urine creatinine}}$$

It is measured in the fasting state, from a two-hour specimen of urine, and from plasma obtained near the midpoint of the collection (Nordin and Fraser, 1954, 1956). As the Cp/Ccr normally varies with the plasma phosphate (Milne *et al.*, 1952), a correction must be made for the plasma level. We have found that the following relationship holds:

$$\text{Theoretical Cp/Ccr} = \frac{\text{Plasma phosphate}}{20} - 0.07$$

The deviation of the observed Cp/Ccr from the theoretical is called the phosphate excretion index (P.E.I.) and is influenced by parathyroid function (Nordin and Fraser, 1956). In normal subjects the 95% confidence limits of P.E.I. are ± 0.09 .* At least two estimations of P.E.I. were made on each patient before operation, and over the early post-operative period observations were made at least daily while there was evidence of a rapid change. Subsequently P.E.I. was determined less frequently until normal values had been attained.

Estimations.—Phosphate in plasma and urine was measured by the method of King and Wootton (1956), using ascorbic acid. Plasma was used in preference to serum for phosphate estimation because haemolysis is less likely to occur. Urine and plasma creatinine were determined by the method of Roscoe (1953). Calcium in serum was estimated by flame spectrophotometry (MacIntyre, 1957).

Results

The serial data of the seven patients are shown in Figs. 1-7. Preoperatively, all patients had hypercalcaemia, which disappeared rapidly after operation. In all patients hypophosphataemia persisted after operation for a variable time, the shortest being 10 days (Case 5), the longest over three weeks (Case 1). Before operation the Cp/Ccr was abnormally high, as shown by a raised P.E.I., and in every case operation was followed by an immediate fall (less rapid in Case 4)

*This formula and the 95% limits of P.E.I. differ very slightly from those given in a previous preliminary publication (Nordin and Fraser, 1956).

of P.E.I. to normal or subnormal levels. Thereafter the P.E.I. rose again to abnormally high levels in five of the patients, and the same trend is seen in Case 6. This rise occurred on the third day in three patients, slightly later in the others, and persisted for from one day to several weeks (Table II). The P.E.I. then fell to normal again, and has remained so in the four

TABLE II.—Post-operative Rise of P.E.I.

Case No.	Day of Onset	Duration in Days
1	3	Over 22
2	5	10
3	3	2
4	15-16	Over 12
5	3	2
6	7-8 (not above normal limits)	—
7	—	—

TABLE III.—Subsequent Plasma Phosphate and Phosphate Clearances

Time after Operation	Case No.	Plasma PO ₄ (mg./100 ml.)	Cp/Ccr	P.E.I.
5 months	1	3.09	0.11	+0.01
3 "	2	2.94	0.10	0.00
9 "	2	3.64	0.19	+0.06
4 "	3	3.78	—	—
4 "	7	3.10	0.06	-0.05

FIG. 1.—Case 1.

TABLE I

Case No.	Age	Sex	Presenting Feature	Duration of Symptoms	Alkaline Phosphatase (K.A. Units) Pre-operative	Blood Urea (mg./100 ml.) Pre-operative	X-ray Films	Bone Biopsy
1	51	F	Backache	1 year	37	24	Thin bones and erosions	Osteitis fibrosa
2	47	F	Polyuria and nausea	1-2 years	27	42	Cysts and erosions	Normal
3	61	F	Bone pains	3 "	96	75	Thin bones and erosions	Osteitis fibrosa
4	48	M	Sciatica	9 months	37	153	" "	" "
5	67	M	Stiffness and limb pain	Uncertain—"Cervical spondylosis" 10 years before	9	37	Normal	Slight excess osteoclasts only
6	32	F	Nephrocalcinosis	None	6	24	" "	Normal
7	43	F	Cysts in jaw	Over 3 years	45	40	Cysts and erosions	Osteitis fibrosa and wide osteoid seams

patients in whom it was measured several months later (Table III). In Case 1 the P.E.I. was still elevated at the 25th post-operative day, when observations were discontinued, but five months later the value was normal.

In Case 7 the secondary rise of P.E.I. did not occur, and the urinary phosphorus remained very low for several weeks after operation. When a high phosphorus

diet was given, the plasma phosphate concentration rose, but the P.E.I. remained unchanged. This phenomenon is seen in hypoparathyroidism, whereas normal subjects on a high phosphorus intake have a high phosphate clearance (Goldman and Bassett, 1954; Fraser and Harrison, 1960). However, this patient has since shown normal parathyroid function with normal serum calcium and a normal P.E.I. (Table III). In Case 4

FIG. 2.—Case 2.

FIG. 4.—Case 4.

FIG. 3.—Case 3.

FIG. 5.—Case 5.

both the initial fall and the subsequent rise of P.E.I. occurred later than in the other patients. This patient had exceptionally high serum calcium levels before operation (up to 20 mg./100 ml.), and also had the most severe degree of renal failure pre-operatively with a blood urea of 153 mg./100 ml.

Discussion

In this series seven patients with primary hyperparathyroidism had abnormally high levels of phosphate

FIG. 6.—Case 6.

FIG. 7.—Case 7.

clearance, indicated by a raised P.E.I. Immediately after operation the P.E.I. returned to normal, together with the serum calcium level, but plasma phosphate remained low. This fall in P.E.I. probably reflects a change in parathyroid activity; it is very unlikely that impairment of renal function could account for changes of such extent and rapidity.

Several days after operation a rise of P.E.I. occurred in six of the seven patients without further alteration in calcium or phosphate levels at the time of the rise. This rise may indicate a phase of secondary hyperparathyroidism, possibly due to stimulation of the remaining parathyroid glands by the rapid fall in serum calcium. Recent studies have shown that in hyperparathyroidism the rate of new bone formation is more rapid than normal, and this feature may persist for a long time after removal of the tumour, especially if bone disease is severe (Fraser *et al.*, 1960). Before operation the parathyroid tumour causes increased bone resorption, and thus supplies adequate calcium for deposition in new bone. But after operation the increased bone resorption suddenly ceases, and it is probable that the persisting rapid deposition leads to a rapid fall of the serum calcium, often to subnormal levels. Compensatory parathyroid hyperfunction then ensues and the serum calcium levels is restored to normal.

It seems possible that two factors determine the extent of this secondary phase of hyperparathyroidism—namely, the severity of the bone disease and the duration of the primary hyperparathyroidism. The two patients without evidence of more than minimal bone disease showed less striking post-operative rises in P.E.I. (Figs. 5 and 6); in fact, phosphorus excretion remained within normal limits post-operatively in Case 6, whose bones were normal. Cases 1, 2, and 4, with obvious bone disease, showed a more striking rise in P.E.I. after operation (Table II). However, the patients with the most severe and prolonged primary hyperparathyroidism (Cases 3 and 7) did not show this phenomenon: in Case 3 there is only a transient secondary rise, and in Case 7 no rise. These two patients had suffered from hyperparathyroidism in its most severe form for several years, and it is possible that the remaining parathyroid glands were depressed to such an extent that they were unable to respond normally after operation. In Case 4 the delay in the onset of the initial fall and subsequent rise of P.E.I. may be related to renal damage consequent on the exceptionally high level of serum calcium before operation.

The data presented in this paper suggest that after removal of a parathyroid tumour there is frequently a phase of secondary hyperfunction of the remaining parathyroid glands, and that this is one factor responsible for the persistent hypophosphataemia which may occur post-operatively.

Summary

In seven patients with primary hyperparathyroidism serial assessments of renal phosphate excretion by measuring the phosphate excretion index were made after removal of the parathyroid tumour. In all patients the phosphate excretion was abnormally high before operation, and it fell to normal values immediately after operation. However, in five patients there was a secondary rise to abnormally high levels, and a sixth patient showed the same trend. Plasma phosphate

levels remained low in these patients during the secondary rise in excretion.

We believe these findings indicate a phase of post-operative hyperparathyroidism arising in the remaining parathyroid glands, which is due to the rapid fall of serum calcium following removal of the tumour.

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hypoproteinaemia, and two of Laennec's cirrhosis (Pappenheimer and Victor, 1946; Ansanelli and Lane, 1957; Schwartz and Jarnum, 1959). In experimental animals, similar pigmentation of intestinal muscle has been recorded in dogs with bile fistulae (Whipple and Hooper, 1917; Hooper and Whipple, 1917), and also in dogs that had been fed large amounts of whole liver or cod-liver oil (Nachtnebel, 1933).

The commonest opinion is that this pigment is a lipofuscin (Paulley, 1954; Schwartz and Jarnum, 1959; Gresham *et al.*, 1958) similar to the common "wear and tear" pigment or *Abnutzungspigment* that is found in heart muscle and liver with increasing age. Lipofuscin is thought to be derived from many unsaturated lipoids and lipoproteins by a process partly involving oxidation. The pigment is a heterogeneous collection of substances resulting from this breakdown.

Case Reports

Summary of Cases

Case No.	Diagnosis	Sex	Age	Bowel Habits	Weight
1	Jejunal diverticulosis	F	82	Steatorrhoea 31 g. fat/24 hrs	4 st. 4 lb. (27.2 kg.). Weight loss ++
2	Chronic pancreatitis	M	44	Steatorrhoea 74 g. fat/24 hrs	10 st. 5 lb. (65.8 kg.). History of some weight loss
3	Jejunal diverticulosis	M	71	Steatorrhoea 45 g. fat/24 hrs	9 st. 3 lb. (58.5 kg.). Gained 20 lb. (9 kg.) in one year post-op.
4	" "	F	88	Normal	—
5	Ulceration of small intestine	F	54	Severe diarrhoea	4 st. 7 lb. (28.6 kg.). Weight loss ++
6	Portal cirrhosis	F	87	Normal	—
7	" "	F	70	"	—
8	Chronic peptic ulcer	M	75	"	—

PIGMENTATION OF JEJUNAL MUSCLE

BY

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Recently pigmentation of intestinal muscle fibres has been increasingly recognized in steatorrhoea and other gastro-intestinal conditions. Fifty cases from the literature have been collected and eight new cases are described. Three of the new cases had secondary steatorrhoea, and among the eight are three cases of jejunal diverticulosis.

Of the 50 cases previously described, 25 definitely had steatorrhoea: 18 had idiopathic steatorrhoea or coeliac disease, 2 had Whipple's disease, 4 had jejunal diverticulosis, and 1 had chronic jejunitis (Pappenheimer and Victor, 1946; Adlersberg and Schein, 1947; Tverdy *et al.*, 1949; Paulley, 1954; Ansanelli and Lane, 1957; Himes and Adlersberg, 1957; Gresham *et al.*, 1958; Richards, 1959). Six cases recorded by Richards (1959) had local gastro-intestinal disease but no steatorrhoea. Two of these had hiatus herniae with oesophageal ulceration, two had duodenal ulcers with pyloric stenosis, one had had a partial gastrectomy, and one a duodenal lesion of uncertain aetiology. The presence or absence of steatorrhoea is not recorded in the other 19 cases. These comprise nine cases of fibrocystic disease of the pancreas, one of duodenal ulcer with gastro-colic fistula, three of malnutrition or malabsorption, aetiology not stated, four of idiopathic

Case 1.—A woman aged 82 was admitted to hospital with hypertensive congestive cardiac failure. She was grossly emaciated, weighing 4 st. 4 lb. (27.2 kg.). She had a history of steatorrhoea for several months and was passing 31 g. of fat in 24-hour faeces. She died from recurrent chest infections. At necropsy gross diverticulosis of the small intestine was found. This was maximal in the jejunum but extended to the terminal ileum. The diverticula were of classical mesenteric distribution and up to 3 cm. in size. Pigmentation of the jejunum was noted macroscopically. Histologically, the muscle of the small intestine showed well-developed brownish granular pigmentation within the myofibrils. There was no pigment in the muscularis mucosae.

Case 2.—A man aged 44 had a partial gastrectomy for a duodenal ulcer, which had caused symptoms for 20 years. An abnormal pancreas was noted at this time. Five months later he had an attack of acute pancreatitis and then developed steatorrhoea, passing up to 74 g. of fat in 24-hour faeces. At further laparotomy the small intestine was seen to be yellowish brown and the pancreas hard and irregular, containing many small retention cysts. His steatorrhoea improved on pancreatin. A surgical biopsy of the jejunum showed numerous pigment granules in the cells of the muscularis propria. The villi of the intestinal mucosa were normal, supporting the pancreatic origin of his steatorrhoea (Shiner, 1959).

Case 3.—A 71-year-old man had dyspepsia for 17 years and steatorrhoea for six years, and was passing 45 g. fat in 24-hour faeces. He weighed 9 st. 3 lb. (58.5 kg.). At laparotomy diverticulosis was found, limited to the first 8 ft. (2.4 m.) of jejunum. This was resected. Since the resection his steatorrhoea has stopped, and he gained 20 lb. (9 kg.) in the first year. Microscopy of the jejunum showed widespread pigment in the fibres of the muscularis propria.