1.5%, after having been steadily around 8% during the previous 12 years. The evidence that at least a part of this recent improvement in results is directly due to local corticosteroid treatment is discussed.

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THE RESEMBLANCE BETWEEN SARCROIDOSIS WITH HYPERCALCAEMIA AND HYPERPARATHYROIDISM

BY

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AND

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Hypercalcaemia was first observed in sarcoidosis by Harrell and Fisher (1939); since then it has been recognized with increasing frequency, and probably occurs in at least 5% of cases (Longcope and Freiman, 1952). If left untreated it may lead to nephrocalcinosis, which is the commonest cause of renal failure in sarcoidosis (Citron, 1955). The metabolic abnormality in this condition closely resembles vitamin-D intoxication, with an increased absorption of calcium from the gut which is reversible by cortisone (Anderson *et al.*, 1954; Henneman *et al.*, 1956).

In this paper we report a case of sarcoidosis with hypercalcaemia in which there was an unusually close biochemical resemblance to hyperparathyroidism and discuss the differential diagnosis between the two conditions. This differentiation is important because excellent treatment is available for both; that it may also be difficult is shown by reports of at least 10 patients with sarcoidosis who have been subjected to operation because they were suspected of having a parathyroid adenoma (Albright and Reifstein, 1948; Westra and Visser, 1949; Howard *et al.*, 1949; Klatskin and Gordon, 1953; Anderson *et al.*, 1954; Davidson *et al.*, 1954; Scholz and Keating, 1956; Hauch and Fisher, 1957).

Case Report

A married man aged 48 was referred to one of us (P.E.) for investigation of splenomegaly and admitted to St. Stephen's Hospital on September 3, 1956. He complained

of tiredness and shortness of breath on exertion for one year and loss of appetite, loss of weight, constipation, lower abdominal pain, and increasing thirst and nocturnal frequency and polyuria for two months. At the age of 2 he had tuberculous cervical glands removed. In 1939 he first noticed pain and swelling in the ankles, and over a period of many years he developed slight outward bowing of the tibiae. He was given calciferol for three months for these symptoms in 1946, but he had not received vitamin D in any form after that time.

His wife had quiescent pulmonary tuberculosis. He had been an engineer for most of his life, but recently he had worked in the open air as a builder's labourer. His diet was adequate and had not recently altered, and he had never taken excessive amounts of milk or alkali.

On examination he had a ruddy complexion and did not look ill. There were numerous firm, moderately enlarged axillary, inguinal, and femoral lymph nodes, and the firm edges of both liver and spleen were palpable 2 in. (5 cm.) below the costal margins. The blood-pressure was 160/100, and the fundi were normal. There were bands of calcification in both corneae. The tibiae were bowed outwards and the knees separated by 1½ in. (3.8 cm.). The patient's weight was 130 lb. (59 kg.), height 63 in. (160 cm.) (crown to pubis 31½ in. (80 cm.), pubis to heels 31½ in.), and span 67 in. (170 cm.).

The urine contained a trace of protein and a few pus cells and granular casts; it was sterile, and culture for tubercle bacilli was negative. No Bence Jones protein was detected. The specific gravity range was 1006–1010. An intravenous pyelogram showed impaired concentration only. The haemoglobin was 10.5 g./100 ml. and E.S.R. 68 mm. in one hour (Westergren). Results of biochemical determinations on blood were: urea, 55 mg./100 ml.; calcium, 12.9 mg./100 ml.; inorganic phosphorus, 2.6 mg./100 ml.; alkaline phosphatase, 3.9 units (King-Armstrong); bilirubin, 0.5 mg./100 ml.; zinc sulphate turbidity, 16 units; albumin, 3.5 g./100 ml.; globulin 4.4 g./100 ml. Electrophoresis showed a slight increase in gamma-globulin. The Mantoux test was positive to 1/100. A skeletal survey was normal. X-ray examination of the chest showed increased striations in both lower zones. Biopsy of a right axillary gland showed histological appearances typical of sarcoidosis.

After four weeks in hospital with no treatment except bed rest the patient felt much better and had gained 4½ lb. (2 kg.) in weight; the serum calcium had fallen to 10.9 mg./100 ml. and the serum inorganic phosphorus to 2.2 mg./100 ml. However, the E.S.R. was still raised (67 mm. in one hour), the blood urea was 56 mg./100 ml., and maximum urine specific gravity 1012; a 24-hour specimen of urine contained 465 mg. of calcium in 960 ml. Because of the hypercalciuria and renal insufficiency he was started on cortisone 100 mg. daily despite the absence of symptoms and the normal serum calcium. The E.S.R. fell progressively, the haemoglobin increased to 13.5 g./100 ml., and he continued to gain weight. The serum calcium remained at the upper limit of normal (see Fig. 1).

After two weeks the 24-hour urine calcium was still 420 mg., and after one week on a low-calcium diet (less than 200 mg. daily) it was 326 mg. Despite the persistence of hypercalciuria there was a gradual improvement in renal function; after a month's treatment the maximum urine specific gravity had risen to 1018, the urine no longer contained any protein casts or pus cells, and there had been a gradual fall in blood urea. After three months' treatment the corneal calcification had almost disappeared. The dose of cortisone was reduced progressively to 37.5 mg. daily, but later had to be increased to 50 mg. daily. One year after treatment was started the 24-hour urine calcium excretion was 294 mg. and the patient was symptom-free; however, the serum calcium remained between 10.5 and 11.5 mg./100 ml. The affected lymph nodes gradually became smaller, but there was no significant change in the spleen or liver for two years. However, when the patient was last seen (October, 1959) his spleen was only just palpable.

*Died May 10.

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FIG. 1.—Chart showing progress of case.

	Serum P mg./100 ml.	Urine P mg./24 hr.	Urine P mg./min.	Clearance ml./min.
1. Before treatment ...	2.5	930	0.65	25.8
2. After cortisone 100 mg. daily $\times 14$...	1.6	460	0.32	20.0
3. After a low-calcium diet $\times 7$	1.5	440	0.31	20.4
4. After treatment for 21 months ...	2.9	—	0.81	27.9

FIG. 2.—Rates of phosphate excretion plotted against serum level; with normal limits taken from Herbert, 1951.

Studies in Phosphate Excretion

The phosphate excretion data are tabulated (Fig. 2). On the first three occasions urine was collected for 24 hours and blood taken at 9.30 a.m. On the last occasion urine was collected for one hour with the patient fasting and blood was taken midway.

In Fig. 2 the rates of phosphate excretion are plotted against serum level, with the normal limits established by Herbert (1951). All the points fall in the "hyperparathyroid" range, indicating reduced tubular reabsorption.

Discussion

The usual biochemical criteria for the diagnosis of primary hyperparathyroidism are a high serum calcium, a low serum phosphate, and increased loss of calcium in the urine (Albright and Reifstein, 1948). In addition, it is usually possible to demonstrate reduced tubular reabsorption of phosphate (Nordin and Fraser, 1956). All these criteria were fulfilled in our patient, and it is fortunate that the diagnosis of sarcoidosis was clearly established on other grounds.

In the differential diagnosis between the two conditions much stress has been laid on the level of serum phosphate, which is usually normal in sarcoidosis and low in hyperparathyroidism, in the absence of renal failure (Albright and Reifstein, 1948). However, in at least five cases of sarcoidosis the serum phosphate has been below 3 mg./100 ml. before treatment (Longcope and Freiman, 1952; Klatskin and Gordon, 1953; Davidson *et al.*, 1954; Scholz and Keating, 1956), and a normal level is quite common in hyperparathyroidism (Chambers *et al.*, 1956).

Parathyroid hormone reduces the tubular reabsorption of phosphate (Jacobs and Verbanck, 1953), and this effect has been used as the basis of various diagnostic tests (Nordin and Fraser, 1956; Chambers *et al.*, 1956). However, if renal failure is present, tubular reabsorption of phosphate is progressively reduced (Goldman and Bassett, 1954), and, under these circumstances, tests of phosphate excretion are of little diagnostic help (Dent, 1956). Furthermore, reduced phosphate reabsorption is also found in other diseases associated with hypercalcaemia, including sarcoidosis (Chambers *et al.*, 1956), malignant disease (Schatten *et al.*, 1959), and myelomatosis (Thomas *et al.*, 1958). In the present case it was tempting to link the impaired phosphate reabsorption with the short stature (height 4 in. (10 cm.) less than span) and the development of pain and slight deformity of the legs, and to postulate that the patient had in a mild form the defect characteristic of resistant rickets.

The most reliable means of distinguishing the two conditions is by observing the effect of cortisone, which regularly corrects the hypercalcaemia of sarcoidosis, but has no significant effect on the hypercalcaemia of hyperparathyroidism (Dent, 1956). Neither result is specific, since cortisone may correct the hypercalcaemia in some, but not all, cases of myelomatosis (Thomas *et al.*, 1958), Hodgkin's disease (Kabakow *et al.*, 1957), and metastatic

malignancy (Myers, 1958). However, a fall in serum calcium with cortisone is very good evidence against a diagnosis of hyperparathyroidism. Correspondingly, if a raised serum calcium does not fall with cortisone it should not be attributed to sarcoidosis even if that disease is known to be present (Snapper *et al.*, 1958).

In our patient the initial change in serum calcium on bed rest alone precluded the diagnostic use of cortisone but was of great diagnostic value in itself. The patient's symptoms of anorexia, loss of weight, and constipation, which were probably due to hypercalcaemia, started while he was working in the open air, exposed to the sun. The fall in serum calcium, which was accompanied by symptomatic improvement, occurred after removal from this exposure. This relationship to sunlight has been observed before (Mather, 1957), and Dent (1958) has shown that ultra-violet irradiation may exacerbate both hypercalcaemia and hypercalciuria in sarcoidosis.

Summary

The case is presented of a patient with sarcoidosis and hypercalcaemia in whom decreased tubular reabsorption of phosphate was demonstrated, producing a biochemical resemblance to primary hyperparathyroidism.

The differential diagnosis between the two conditions is discussed, and it is concluded that tests of phosphate excretion may be misleading, but that the response to cortisone gives valuable information.

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POTASSIUM DEFICIENCY IN ANOREXIA NERVOSA, WITH REFERENCE TO RENAL TUBULAR VACUOLATION*

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Electrolyte deficiency in anorexia nervosa may create a therapeutic problem, not mentioned in several recent papers, in the treatment of this disorder (Williams, 1958; Wall, 1959). Diagnostic difficulties may arise, especially when secondary renal involvement occurs, leading to serious consideration of the alternative diagnoses listed in Table I. Investigation of a case presenting typical features of anorexia nervosa together with hypokalaemic alkalosis, and evidence of renal failure with chronic pyelonephritis, led to a search of the relevant literature. Sunderman and Rose (1948)

TABLE I.—*Differential Diagnosis*

1. Hypopituitarism and Addison's disease
2. Malabsorption syndrome
3. Habitual purgation
4. Potassium- and sodium-losing nephritis
5. Primary aldosteronism
6. Chronic nephritis and chronic pyelonephritis
7. Pineal tumours and hypothalamic lesions
8. Familial periodic paralysis

TABLE II.—*Summary of Cases Reported to Date (Serum Levels in mEq/l.)*

Authors	Age	Na	K	Cl	HCO ₃	Evidence of Renal Involvement	Notes	
Sunderman and Rose (1948)	26	—	3.0	58	62	—	Enemas and vomiting	
Elkinton <i>et al.</i> (1951)		127	2.8	74	44.5	Yes	No vomiting; laxatives	
Beck and Bröchner-Mortensen (1954; Case 26)	28	137	2.6	96	—	„	Vomiting. Blood urea 51 mg.; 26 mg. after treatment	
Luft and Sjögren (1954)	1	26	139	2.2	45	49	„	Vomiting and tetany.
	2	34	139	1.5	98	21	„	Albuminuria
Klotz and Lumbroso (1955)	29	141	2.0	—	55	—	„	No vomiting. No albuminuria
							—	Vomiting
							—	—
Rossier <i>et al.</i> (1955)	28	140	2.0	74	45	—	Yes	Pyelonephritis
	24	—	2.9	—	29	—	—	Diarrhoea and vomiting
	24	146	2.6	97.4	28	—	—	Vomiting
	23	142	3.1	78	37	—	—	—
	17	148	3.6	105	29	—	—	—
	28	143	3.4	—	24	—	—	—
Siebenmann (1955)	27	133	1.8	109	20	Yes	—	Took laxatives
Forssman (1955)	17	143	3.0	50	—	„	—	Said to have nephritis
Ljunggren <i>et al.</i> (1957)		128	2.9	85	40	—	—	—
Elkinton and Huth (1959)	29	120	1.7	53	52	Yes	—	Magnesia
	43	126	2.4	69	44	—	—	Vomiting and magnesia

described the first case with hypokalaemic alkalosis. Seventeen cases have now been reported (Table II). Elkinton and Huth (1959) have reviewed the electrolyte disorders that may occur. Most of the cases showed alkalosis, some hyponatraemia, and eight showed evidence of renal dysfunction.

*Based on a paper read at a meeting of the Royal Australasian College of Physicians at Auckland on September 17, 1959.