keratoderma spread to involve all four limbs, the back, the face, and the scalp. The lesions progressed from a macular eruption to vesicular and pustular stages, finally becoming hard scaling keratotic plaques, which on the feet were painful and irritating. Fresh lesions appeared adjacent to areas of healing (Fig. 1), and in view of their severity oral prednisone 40 mg. daily and topical hydrocortisone were prescribed. The arthritis was also treated with indomethacin with partial relief, but after a few days of steroid therapy her pyrexia subsided, joint pains were further relieved, and there was a noticeable improvement in the skin lesions. After 11 weeks in hospital she was discharged, the prednisone being gradually reduced. At the time of this report no fresh skin or mucosal lesions had appeared, and repeat radiographs of the hands, the feet, and sacroiliac joints were normal.

Histological examination of involved skin (Fig. 2) showed spongiform pustules in the upper epidermis, acanthosis, infiltration with polymorphs, and hyperkeratosis. The underlying dermis showed mild perivascular chronic inflammatory cell infiltration.

FIG. 1.—Vesicular and keratotic lesions on the foot.

FIG. 2.—Skin showing thick parakeratotic horny layer infiltrated by polymorphonuclear leucocytes overlying spongiform pustule in upper stratum malpighii. ($\times 55$)

These appearances are fully consistent with the diagnosis of keratoderma blennorrhagica (Harkness, 1950), though there is a similarity to psoriasis.

COMMENT

This patient was suffering from the venereal type of Reiter's disease and gonorrhoea. In spite of the name keratoderma blennorrhagica is unrelated to gonorrhoea (King, 1964), and, as in this case, treatment of the gonorrhoea does not prevent development of keratoderma.

The literature on Reiter's disease is vast, but the aetiology is unknown. There is a very close similarity between keratoderma blennorrhagica and psoriasis, and the arthropathy of Reiter's disease is often indistinguishable from rheumatoid arthritis (Perry and Mayne, 1965; Khan and Hall, 1965). Psoriasis and Reiter's disease may share a common genetic

background, for psoriasis apparently occurs nine times as often as expected in the male relatives of patients with Reiter's disease (Lawrence, 1966). Though Reiter's disease is rare in the female we did not feel clinically that our patient was suffering from either psoriasis or rheumatoid arthritis. Psoriasis only rarely involves the mucous membranes of the mouth (Norins and Yaffee, 1957), but lesions of the tongue and buccal mucosa occur in about 10% of patients with Reiter's disease (Hancock, 1960) and are painless and superficial. The mucous membrane lesions usually precede the skin lesions and may also occur before the onset of arthritis (Nicol, 1966). It is likely that the oral lesions in this patient were present on admission but were overlooked, for when the diagnosis of Reiter's disease became obvious with the eruption of keratoderma blennorrhagica, closer inspection of the tongue showed lesions practically healed. An extremely rare feature in this case was that the keratoderma involved the face. Though lesions of the scalp may extend a little on to the forehead (King, 1964), facial involvement in Reiter's disease is practically never seen (Oates, 1970).

Treatment of Reiter's disease with steroids is not indicated unless the illness is severe. In the present case the administration of prednisone resulted in cessation of pyrexia for the first time since admission, healing of skin lesions, and a shortened stay in hospital.

I should like to thank Professor M. D. Milne, Westminster Hospital, for permission to publish this report of a patient under his care. I am grateful to Dr. J. K. Oates for his advice in the preparation of this paper, and to Dr. A. C. Branfoot for the histological examination.

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Ectopic Secretion of Parathyroid Hormone by a Renal Adenocarcinoma in a Patient with Hypercalcaemia

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Hypercalcaemia not infrequently complicates malignant disease with metastatic spread to bone. But it also occurs without bony deposits, and the accompanying hypophosphataemia suggested to Albright (*New England Journal of Medicine*, 1941) that such tumours may secrete parathyroid-hormone-like material. No hypercalcaemic factor has been isolated from these tumours (Munson *et al.*, 1965) though material has been extracted showing immunological similarity to parathyroid hormone (Tashjian *et al.*, 1964; Munson *et al.*, 1965; Sherwood *et al.*, 1967).

CASE REPORT

A housewife aged 58 had felt ill for a year and complained of muscular weakness and pains in her legs. She was anorectic and

depressed and had lost 10 kg. in weight. She had nocturia but was not constipated. There was wasting and weakness of the muscles in the arms and legs but no other neurological abnormality. Physical examination was otherwise normal, except for a temperature of 99-101°F. (37.2-38.3°C.).

Haemoglobin was 9.1 g./100 ml., the white cell count was normal, and the E.S.R. varied from 61 to 119 mm./hour. Sternal marrow showed no myeloma or malignant cells. The serum calcium was 13.0 mg./100 ml. (Clark and Collip, 1925), inorganic phosphate 2.9 mg.P/100 ml., and alkaline phosphatase 28 K.A. units/100 ml. The plasma proteins were 6.2 g./100 ml. (albumin 3.6 g., globulin 2.6 g.), with a slight excess of α_2 globulin. Liver function tests were normal. The urine showed no Bence Jones or other protein. The blood urea was 33 mg./100 ml., serum creatinine 0.72 mg./100 ml., and creatinine clearance 49 ml./minute. Serum calcium on seven occasions was 11.8-13.2 mg./100 ml. (mean 12.4 mg.), and phosphate 2.8-3.7 mg.P/100 ml. (mean 3.2 mg.). Oral cortisone 50 mg. t.i.d. for 10 days caused no appreciable alteration in serum calcium. The urinary calcium (normal diet) on seven occasions was 117-300 mg./24 hours (mean 220 mg.). The ratio of urinary calcium to creatinine was 0.3-0.5 (normal less than 0.25), and the phosphate excretion index was + 0.03 (normal - 0.1 to + 0.1). X-ray examination showed no malignant deposits in the bones or evidence of hyperparathyroidism. Chest x-ray appearances were normal. An intravenous pyelogram showed enlargement of the upper two-thirds of the right kidney, with deformity of the calices, and an arteriogram showed a rounded vascular carcinoma involving the upper pole.

At operation a circumscribed vascular yellowish tumour 5 cm. in diameter was found occupying the upper pole of the right kidney. Simultaneous blood samples were taken from the renal artery and vein before removal of the kidney. Histology showed an adenocarcinoma of the kidney, comprising clear and eosinophilic cells with pleomorphism and many mitoses. Intravascular invasion was evident.

The temperature and E.S.R. fell to normal postoperatively. Plasma calcium fell to 8.3 mg./100 ml. and the phosphate rose to 3.4 mg.P/100 ml. by the seventh postoperative day. Twelve

months after operation plasma calcium was 9.6 mg./100 ml. and phosphate 3.7 mg.P/100 ml. The urinary calcium was 34 mg./24 hours, urinary calcium/creatinine ratio 0.04, and the phosphate excretion index + 0.09. The creatinine clearance was 49 ml./minute.

MEASUREMENT OF PARATHYROID HORMONE

Parathyroid hormone was measured by radioimmunoassay (Buckle, 1969a). Two antisera to bovine parathyroid hormone were used at concentrations of 1:300,000-1:350,000 and 1:100,000 respectively. Standardization was against highly purified bovine parathyroid hormone, and all estimations are expressed in terms of their bovine equivalent. Tissue was extracted by the method of Potts *et al.* (1966) and the final pH was adjusted before assaying. Plasma was assayed without extraction. Plasma samples and tissue extracts were assayed in replicate at multiple dilutions in at least two separate assays.

Material possessing similar immunological properties to parathyroid hormone was found in extracts of the tumour but not of normal kidney (Fig. 1). The bound to free ratio of labelled hormone curve for the tumour extract was similar to that of bovine parathyroid hormone, suggesting immunological similarity, though not complete identity. Normal kidney had no such effect. The tumour extract was estimated at dilutions of 1:20-1:640, and calculations showed a mean concentration of hormone of 2.2 μ g. (S.E. $\pm$ 0.3)/g. dry weight of tumour.

The immunological behaviour of parathyroid-hormone-like material in renal venous blood draining the tumour was compared with that of the tumour. Such a comparison is shown in Fig. 2. The slopes of the two lines are closely parallel, suggesting a common identity; whereas control plasma from a parathyroidectomized patient had no such effect. The immunological behaviour of the tumour extract was compared with that of human parathyroid hormone against two different antisera (Fig. 3). Close but not complete parallelism was found with each antiserum. Extracts of normal kidney tissue and control hypoparathyroid plasma had little effect. Material from the renal adenocarcinoma appeared immunologically to be closely similar to human parathyroid hormone.

The concentrations of parathyroid hormone in the renal artery supplying the adenocarcinoma and renal vein draining the tumour are given in the Table. Mean values are shown, together with the

FIG. 1.—Effects of extracts of renal adenocarcinoma and normal kidney on the binding of 125 I-labelled bovine parathyroid hormone to specific antibody (B/F). Final concentration of antiserum 1:350,000.

●—● Extract of renal adenocarcinoma expressed as its equivalent in μ g. dry weight of tissue. X—X Extract of normal kidney expressed as its equivalent in μ g. dry weight of tissue. Also shown are the effects of purified bovine parathyroid hormone standard (O—O); concentrations of hormone are expressed in pg./ml. of incubate. Increasing aliquots of the extract of the renal adenocarcinoma caused a progressive decrease in B/F values, the slope being similar to that due to bovine parathyroid hormone; immunological similarity between the two seems likely though the slight variation in slope suggests that the tumour extract and bovine parathyroid hormone are not identical. Normal kidney tissue had no effect on the B/F values.

Concentration of Parathyroid Hormone (ng./ml.)

Right Renal Artery	Right Renal Vein	Arteriovenous Difference
0.62 ($\pm$ 0.1)	2.55 ($\pm$ 0.4)	1.93 ($\pm$ 0.3)

FIG. 2.—Comparison of the effects of an extract of adenocarcinoma of the kidney and right renal venous blood draining the tumour on the binding of 125 I-labelled bovine parathyroid hormone to specific antibody. Final concentration of antibody 1:300,000.

Extracts of adenocarcinoma (●) are expressed in terms of their equivalent dry weight of tissue. Renal vein blood (X) is expressed in μ l. plasma. Control plasma from a parathyroidectomized patient (O) is expressed in μ l.

The binding of 125 I-labelled bovine parathyroid hormone to antibody is expressed in terms of the % bound of the total tracer available. The close parallelism of the two slopes suggests a common identity of the tumour material and that present circulating in the blood.

FIG. 3.—Effects of an extract of renal adenocarcinoma and human parathyroid hormone on the binding of ^{131}I -labelled bovine parathyroid hormone with two different specific antisera. The two antisera against bovine parathyroid hormone were raised in different guinea-pigs. One antiserum was used in a final concentration of 1:300,000, the other in a concentration of 1:100,000. ●—● Adenocarcinoma extract expressed in terms of the equivalent dry weight of tissue in μg . ○—○ Human parathyroid hormone present in venous effluent blood draining a parathyroid adenoma in another patient, and expressed in μl of plasma. ▲.....▲ Extract of the normal kidney expressed in terms of equivalent dry weight of tissue in μg . X...X Control plasma from a parathyroidectomized patient, expressed in μl .

The binding of ^{131}I -labelled parathyroid hormone to the two different antisera is expressed in terms of the % bound of the total tracer available. The slopes for the extract of adenocarcinoma and human parathyroid hormone were similar to one another when tested against each of the two specific antisera.

standard error of the mean in parentheses. An arteriovenous gradient of parathyroid hormone was demonstrable across the kidney containing the adenocarcinoma. Postoperatively parathyroid hormone fell to normal ($<0.10\text{ ng./ml.}$).

COMMENT

Albright initially suggested that hypercalcaemia with hypophosphataemia occurring with non-parathyroid carcinomata without bony metastases might be due to an increase in parathyroid activity (*New England Journal of Medicine*, 1941), yet parathyroid hyperplasia has not been found (Swyer *et al.*, 1950). Serum calcium, however, may fall to normal after removal of the primary tumour (Connor *et al.*, 1956; Plimpton and Gellhorn, 1956), and this occurred in our patient. Such tumours may therefore secrete a parathyroid-hormone-like material.

The present study showed immunologically reactive parathyroid-hormone-like activity in the tumour, but not in normal kidney tissue, and confirms previous studies (Tashjian *et al.*, 1964; Munson *et al.*, 1965; Sherwood *et al.*, 1967). The immunological behaviour of the tumour material was similar to that of both bovine and human parathyroid hormone, and this was found by using two different antisera, further supporting the specificity of the immunological reactions.

The concentration of hormone was $2.2\text{ }\mu\text{g./g. dry weight of}$

tumour and falls within the range $0.75\text{--}8.9\text{ }\mu\text{g./g. dry weight}$ reported by Sherwood *et al.* (1967). The total quantity present in the tumour would therefore be less than the minimum detectable by bioassay.

The concentration of parathyroid hormone in the peripheral venous blood was likely to be similar to that in the renal artery. Its preoperative concentration would therefore have been approximately 0.60 ng./ml. , and was higher than in normal subjects (normal $<0.10\text{--}0.25\text{ ng./ml.}$; Buckle, 1969b). After removal of the tumour parathyroid hormone became normal and the serum calcium fell.

A tumour could theoretically take up and concentrate from the blood parathyroid hormone that is produced elsewhere. Nevertheless, the demonstration of an arteriovenous gradient across the tumour of hormone-like material, immunologically identical with that in the tumour, strongly suggests that the tumour was synthesizing parathyroid hormone and secreting it into the circulation. Removal of the tumour removed the site of its synthesis and led to a fall to normal of both serum calcium and parathyroid hormone.

These results further support the belief that parathyroid-hormone-like material may be synthesized and secreted by malignant non-parathyroid tumours.

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