understanding of child and family, is especially the field of the family doctor.

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MULTIPLE MYELOMATOSIS SIMULATING HYPERPARATHYROIDISM

BY

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It is known that hypercalcaemia may occur in multiple myelomatosis (Caylor and Nickel, 1933; Bodansky and Jaffe, 1934; Gutman *et al.*, 1936), and that this is sometimes accompanied by hypercalcuria (Caylor and Nickel, 1933; Nassim and Crawford, 1950). These findings have, on occasion, given rise to difficulty in the differential diagnosis between multiple myelomatosis and hyperparathyroidism. In almost all cases of multiple myelomatosis the serum phosphorus is normal or elevated, but, since this may also occur in cases of hyperparathyroidism in which renal impairment has developed, the serum phosphorus level may not be of help in the differentiation between the two conditions. In hyperparathyroidism there is thought to be a diminished reabsorption of phosphate by the renal tubules (Albright and Reifstein, 1948), and this is regarded as a diagnostic test for parathyroid function.

This paper reports a case of multiple myelomatosis in which, in addition to hypercalcaemia and hypercalcuria, there was a diminished reabsorption of phosphate.

Case Report

A woman aged 46 had had, for about six years, abnormal thirst with associated polyuria. Apart from tiredness for a year, her health was good until New Year's Eve, 1954. When dressing she felt a sudden sharp pain in the sternum, with a sensation of something giving. The following evening she felt sick and vomited, and from that date until her admission to hospital three weeks later she vomited three or four times daily. Her medical history and family history were negative.

On admission she was pale and moderately dehydrated; there was a protuberance about the middle of the sternum; the blood pressure was 170/100. No other abnormalities were noted. X-ray examination revealed a double fracture of the upper end of the sternum. There was a moderate degree of demineralization of the vertebral column and ribs. Films of the hands, arms, legs, pelvis, and skull did not show any definite changes. There were no renal calculi, nephrocalcinosis, or calcification of soft tissue. The x-ray appearances were thought to be consistent with the diagnosis of hyperparathyroidism.

Biochemical Data

Date	Serum Calcium (mg./100 ml.)	Serum Phosphorus (mg./100 ml.)	Urea (mg./100 ml.)	Carbon Dioxide Combining Power (ml./100 ml.)	Alkaline Phosphatase (K.A. Units)
1/2/55	16.2	—	48	—	—
4/2/55	19.1	5.9	108	70	9
7/2/55	12.9	3.2	72	62	—
9/2/55	15.7	3.5	60	—	—
15/2/55	15.2	3.3	67	65	11

The biochemical findings are shown in the Table. The original value for phosphorus was discounted because it had been determined on heparinized blood, which is unsuitable for the determination of phosphorus (McGeown *et al.*, 1955).

The glomerular filtration rate, as estimated by a continuous intravenous infusion of inulin (mean of three periods) was 18.9 ml. a minute. The urinary clearance of phosphate, expressed as a percentage of the inulin clearance, was 73% when the serum phosphorus level was 3.2 mg. per 100 ml. This represents a greatly increased tubular rejection of phosphate. The specific gravity ranged from 1008 to 1020. There was a moderate degree of albuminuria, but Bence Jones protein was not present. The patient was given a low-calcium diet (154 mg. in 24 hours) for 12 days, and during this period the daily urinary excretion of calcium varied

FIG. 1.—Biochemical data.

between 250 and 500 mg. (Fig. 1). On the diet used, the upper limit of excretion of calcium by normal subjects appears to be 150 mg. (McGeown, unpublished data).

It has been reported that cortisone lowers the hypercalcaemia of sarcoidosis (Anderson *et al.*, 1954) but has no effect on the hypercalcaemia of hyperparathyroidism. For this reason the patient was given 200 mg. of cortisone daily for six days, but no change in the serum calcium, urea, or phosphate clearance occurred (Fig. 1).

The marked degree of hypercalcaemia, the consistently high serum calcium, the fairly low serum phosphorus despite a considerable degree of renal impairment, the elevated urinary phosphate clearance, and the x-ray findings made the diagnosis of hyperparathyroidism appear almost certain, and accordingly the neck was explored by Mr. Ian Fraser and Mr. E. Morrison and three parathyroid glands were removed. These were reported to contain a large amount of fatty tissue, the chief cells were within normal limits, and there was no evidence of excess activity.

For 24 hours post-operatively the patient's condition appeared satisfactory, and there was no evidence of tetany. Then quite suddenly she became pale, with cyanosis of the cheeks and extremities. Her condition, despite vigorous resuscitative therapy, continued to deteriorate, and she died on the fourth post-operative day.

At necropsy the fourth parathyroid gland was found to be normal. The vertebral column, ribs, and sternum were demineralized and very fragile. In most areas the marrow was normal, but the bodies of the fourth and eighth thoracic vertebrae were replaced by a reddish-brown tissue. Histologically this was composed of cells which had a prominent and slightly basophilic cytoplasm and which were considered to be myeloma cells. A few liver sinusoids contained clumps of myeloma cells. In the kidneys most of the glomeruli were normal, but some contained areas of hyaline degeneration. There were fairly dense eosinophilic casts in the distal convoluted tubules, containing calcium, and they were often partly organized into the wall of the tubule by proliferation of the epithelium around them. The most severe lesions resembled little granulomas, with complete destruction of the affected segment of tubule, irregular proliferation of the epithelium around the calcified cast material, and a surrounding lymphocytic reaction (Fig. 2).

After the necropsy a stored specimen of the patient's serum was found to contain 9.6 g. of protein% (albumin 3.3 g., globulin 6.3 g.). Electrophoresis showed a sharp peak in the position of the β globulin, which made up 59.5% of the total protein.

Discussion

The interest in this case lies in the fact that the clinical and biochemical findings bore a close resemblance to hyperparathyroidism. The long history of thirst and polyuria, followed by fatigue and by a spontaneous fracture of the sternum, was consistent with the diagnosis of hyperparathyroidism, as were the x-ray appearances of demineralization of the vertebral column and ribs. The marked degree of hypercalcaemia and hypercalcuria also suggested hyperparathyroidism.

The absence of hypophosphataemia in this case was thought to be due to phosphate retention associated with the renal impairment.

We could not find any other record of the urinary phosphate clearance in multiple myelomatosis. In the present case it was greatly raised. The diminished reabsorption of phosphate was probably due to the tubular damage which was shown to be present at post-mortem examination. That the phosphate clearance is not always elevated in multiple myelomatosis is shown by studies on another case in which the phosphate clearance, as well as the glomerular filtration rate, are normal. Diminished urinary reabsorption of phosphate occurs in hyperparathyroidism, although it is not yet certain that it is invariably raised in this condition. Its importance in multiple myelomatosis lies in the fact that in this respect, too, the disease may resemble hyperparathyroidism and may appear to lend support to the latter diagnosis if the possibility of multiple myelomatosis is not kept in mind.

Although hypercalcaemia is apparently often present in multiple myelomatosis, it is difficult to discover its actual incidence, as in many of the reported cases the serum calcium has not been determined. The mechanism of the hypercalcaemia is still unknown. It is perhaps associated with widespread bone lesions and osteoporosis, but was absent in two such cases (Naylor and Chester-Williams, 1954). It has been observed in solitary myeloma of bone (Nassim and Crawford, 1950) and in the absence of demonstrable bone lesions (Wallerstein, 1951). Rawson and Sunderman (1948) thought that the hypercalcaemia might be related to the hyperproteinaemia, but others (Gutman and Gutman, 1936; Jaffe and Bodansky, 1942) did not find any such relationship. Parathyroid hyperplasia has been suggested as a cause of the hypercalcaemia by Cosgrove and La Tourette (1953), but specific study of this problem by Jaffe and Bodansky and others, and also in the present case, revealed no evidence of parathyroid hyperplasia.

The serum phosphorus is usually normal or raised in multiple myelomatosis, but a case with a low serum phosphorus was reported by Snapper (1948). When renal impairment develops in hyperparathyroidism, the serum phosphorus tends to rise, and thus may be of little help in the differential diagnosis.

The serum alkaline phosphatase is usually normal, or only slightly elevated, in multiple myelomatosis. The rise, if present, is insignificant compared with that occurring in advanced hyperparathyroidism (Gutman *et al.*, 1936; Schwartz and Cataldo, 1953). In our case the absence of a raised alkaline phosphatase in the presence of sufficient osteoporosis to cause a spontaneous fracture ought to have made us suspect that the underlying disease was not hyperparathyroidism.

If the possibility of multiple myelomatosis is kept in mind in cases of bone disease with hypercalcaemia there are other aids to diagnosis. Bence Jones protein in the urine will support the diagnosis of multiple myelomatosis. An increase in the plasma proteins, particularly affecting the globulins, is characteristically found in many cases of multiple myelomatosis. However, hyperproteinaemia may not exclude hyperparathyroidism, as it has been observed in this condition by Bull and McGeown (unpublished observations). A bone-marrow biopsy with the demonstration of an increased number of plasma cells would make the diagnosis absolute, and this appears to be an essential part of the investigation

FIG. 2.—Kidney ($\times 150$), showing tubular lesions with calcium casts and irregular tubular epithelial proliferation around a calcified cast (centre).

of all doubtful cases. A significant degree of anaemia is a usual finding in myelomatosis, but is rarely seen in uncomplicated cases of hyperparathyroidism.

Summary

A case of multiple myelomatosis presenting with a spontaneous fracture is described. Hypercalcaemia, hypercalcuria, normal serum phosphorus in the presence of severe impairment of renal function, and an elevated urinary clearance of phosphate led to the diagnosis of hyperparathyroidism. The parathyroid glands were found to be normal, and at necropsy myelomatous replacement of two vertebral bodies, invasion of liver sinusoids, and myeloma kidney were found.

This condition resembles hyperparathyroidism in that there may be an increased urinary excretion of phosphate as well as hypercalcaemia and hypercalcuria.

The possible causes of the hypercalcaemia are discussed.

The differential diagnosis between multiple myelomatosis and hyperparathyroidism is considered. The most important point would appear to be to remember how closely the two diseases may resemble each other.

Our thanks are due to Mr. Ian Fraser, who referred the patient to one of us (D.A.D.M.) and who, with Mr. E. Morrison, operated on the patient. The advice and guidance of Professor G. M. Bull are gratefully acknowledged. We are grateful to Miss Eileen Martin for the estimations of inulin and phosphorus, to Dr. G. Gibson for the post-mortem examination, to Dr. J. A. Smyth and Mr. D. Neill for some of the biochemical determinations, and Mr. George Smith for the diagram. One author (M. G. McG.) wishes to acknowledge a grant from the Medical Research Council.

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According to a leading article in the *New England Journal of Medicine* (August 11, 1955, p. 256) there has been a decline in the number of suitable applicants for admission to medical schools in the U.S.A., and some schools are already finding it difficult to fill vacancies with properly qualified students. "This phenomenon appears to be symptomatic of the declining interest of American students in mathematics and in all types of physical and biologic sciences." It is suggested that the shortage of teachers of science subjects in the secondary schools may have accelerated this trend. Half the high schools in the U.S.A. now do not offer courses in chemistry, and there are no courses in physics at an even higher proportion of schools. "The tendency in high schools is for increasing numbers of students to take 'easy' courses, such as social studies, vocational education, and 'how-to-live' subjects, while side-tracking the 'hard' subjects, such as mathematics, physics, and chemistry. This trend is carried over into the colleges and may be largely responsible for the increasing emphasis that universities and medical schools are placing on the 'behavioural' and 'social' sciences. This tendency has dangerous potentials for the future of scientific medicine."

CAT-SCRATCH FEVER

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In 1932 Lee Foshay, of Cincinnati, whilst investigating tularaemia, recognized a separate disease entity in individuals who had been scratched by cats (Daniels and MacMurray, 1951a). The condition was characterized by an initial lesion at the site of inoculation, followed by regional adenitis and fever, the adenitis progressing to a bacteriologically sterile suppuration. In 1945 F. M. Hanger and H. Rose, of New York, developed an antigen from a similar case (Hanger himself), which gave a local reaction when injected intradermally, and was successfully tried by Foshay on his own cases (Daniels and MacMurray, 1951a).

Meanwhile this condition had been well recognized in France, and in 1947 R. Debré, of Paris, following a meeting with Foshay, introduced the antigen into France. Its use in suspected cases gave results similar to those experienced by American workers (Debré *et al.*, 1950). During the past five years the condition, under various names—for example, cat-scratch disease, cat-claw disease, cat-bite fever, and benign inoculation lymphoreticulosis—has also been reported in Switzerland, in India, and on four previous occasions in Great Britain (Campbell and Wheaton, 1952; Cox, 1952; Garai, 1952; Bettley and Fairburn, 1953).

Case 1

A schoolgirl aged 7 was admitted to St. Woolos Hospital, Newport, on December 27, 1954. Eighteen days previously she had been bitten on the right thumb by the family cat, and a few days later had developed some local inflammation followed by a mild lymphangitis and axillary adenitis. This was treated by her own doctor with oral penicillin and rest, with apparent benefit, the inflammation subsiding.

He was recalled 15 days after the bite, as her temperature had risen to 102–104° F. (38.9–40° C.), the axillary glands had increased in size, and she was complaining of considerable pain in the right arm. This was accompanied by a generalized pleomorphic rash and classical erythema nodosum of both legs, with a few smaller nodes on the arms. Treatment with chlortetracycline resulted in an improvement in her general condition and a subsidence of her temperature. However, it was apparent that two of the axillary glands were becoming fluctuant, with reddening of the overlying skin, and so she was admitted to hospital.

There was nothing relevant in her past history, but she had always been subject to bouts of papular urticaria.

Examination showed her to be well nourished, with no abnormal physical signs detectable in the throat, the ears, or the cardiovascular, respiratory, and alimentary systems. There was a moderate general lymphadenopathy, but no enlargement of the epitrochlear glands, and the spleen could not be palpated. The site of the original bite showed some local indolent induration but no discharge. There was no lymphangitis in the right arm, but in the right axilla there was a tender soft bubo. Both shins and forearms showed