Summary

The previous radiological history of 100 consecutive cases of pulmonary tuberculosis in which the patient was over the age of 55 years was investigated.

Fifty had been x-rayed before: 23 (46%) of these films were clear and 27 (54%) showed no abnormality.

In films considered abnormal, inactive tuberculosis, "unresolved pneumonia," and "bronchitic changes" were the most common abnormalities found.

Only three patients were under the age of 50 when previously x-rayed, and 38 patients had been x-rayed within five years of diagnosis.

In an older person if any suspicion of pulmonary tuberculosis arises it is essential to carry out an x-ray examination of the chest even if a recent film has been reported clear.

I wish to thank Dr. A. W. Lees, consultant chest physician, Ruchill Hospital, for his constant interest in this investigation, and Dr. Agnes Macgregor for her assessment of the radiographs.

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IDIOPATHIC HYPOPARATHYROIDISM WITH NORMAL URINARY CALCIUM

BY

L. SYMON, F.R.C.S.Ed.

Neurosurgical Registrar, Aberdeen Royal Infirmary

AND

ISOBEL M. BETT, B.Sc.

Department of Clinical Chemistry, Aberdeen University

The association of symmetrical calcification of the basal ganglia with hypoparathyroidism was reported by Eaton and Haines (1939), and is now well recognized. In these cases, low levels of serum calcium accompany high levels of serum phosphate, in the absence of any evidence of renal insufficiency, generalized bone disease, or abnormality of fat absorption. Calcium is absent from the urine; indeed, its reappearance there is the yardstick of treatment recommended by Albright and Reifenstein (1948). These authors further note, however, the rare occurrence of cases in which calcium in normal quantities was present in the urine. Such a case is here recorded.

Case Report

The patient, a man aged 21, was resident in North-west Scotland and came of a family of four, with two sisters aged 25 and 8 years, and one brother aged 15 years. None save the patient gave any history of epilepsy or other neurological or endocrine disease. Radiographs of the skull of his brother and younger sister were normal. His father, aged 55, and mother, aged 48, were in good health and gave no history of neurological or endocrine disease, and

their skull radiographs showed nothing abnormal. His father's two brothers, aged 61 and 50, and his mother's three brothers, aged 58, 50, and 44, were all reported to be in good health. They and the patient's elder sister were either abroad or in inaccessible parts of Northern Scotland. Radiographs of these relatives were not obtained. The patient himself had suffered from recurrent convulsions at the age of a few weeks, attributed to birth trauma. Throughout his childhood, up to the age of 8 years, he had occasional epileptiform seizures. Thereafter he had suffered from such seizures only in response to febrile illness. There had been two such occasions in adolescence, while his first admission to another hospital and transfer to Aberdeen (December, 1957) had resulted from such a convulsion occurring in the course of influenza. For long he had been thought to be suffering from idiopathic epilepsy.

There was nothing to suggest deterioration in his general health or intellectual capacity. His memory was good, his mother had noticed no change in his personality, and he was working successfully as a stone-mason.

Examination revealed a co-operative, pleasant young man, rather slow in conversation though his speech was normal. He was easily amused, and other patients found him odd or simple without clear foundation for their opinions. Assessment of intelligence on the Wechsler adult scale gave an intelligence quotient of 90. He seemed of at least dull average intelligence, while his memory and reasoning ability appeared to be normal.

Bilateral lens opacities were detected by slit-lamp examination. The optic fundi were normal. Bilateral horizontal nystagmus was more pronounced to the right. There was no tremor of the limbs, but fine tremor of the tongue and of the eyelids on closure was constantly present. No jaw-jerk was elicited. Normal tone was present in arm and leg muscles. His performance of fine repetitive hand movements appeared to be slightly impaired.

Romberg's sign was negative. Though his gait was brisk he swung his arms considerably less than normal. He admitted no paraesthetic phenomena, nor were any abnormalities of sensation detected.

The Chvostek and Trousseau signs were initially negative, but after several days in hospital, with a much reduced milk intake as compared with his home diet, these signs became unequivocally positive, although no apparent change in the serum levels of calcium and phosphate had occurred. Trousseau's sign was elicited as recommended by Albright and Reifenstein (1948), an arm tourniquet being elevated to just above the systolic blood pressure for three minutes. Erb's test, invoked because of initially negative clinical tests, gave a cathodal opening contraction at 4.5 mA.

General examination revealed no abnormality; blood pressure was 120/70. The teeth generally were of poor development, very carious, with much gum infection. The nails and hair appeared normal, and the skin was of average texture.

Investigations

Radiographs of the skull (Figs. 1-3) showed extensive irregular calcification in the basal ganglia of both sides and calcification in both dentate nuclei. There was also some hyperostosis of the frontal and parietal bones. The long bones, hands, chest, and abdomen showed no radiological abnormality. There was no subcutaneous or renal calcinosis. Radiographs of the teeth confirmed their poor development. Many of them were mere stumps with evidence of apical infection. The lower incisors had particularly small roots (Figs. 4-6). The trabeculae of the lumbar spine were noticed to be prominent, but there was no evidence of generalized increase in bone density. On admission the serum calcium was 6.2 mg./100 ml. and the serum phosphate 6.1 mg./100 ml. Serum acid and alkaline phosphatases were found to be 1.5 and 10 King-Armstrong units respectively. Total serum protein was 8.3 g./100 ml. (albumin/globulin ratio 1.6/1). The blood urea was 37 mg./100 ml., and plasma CO₂ combining power 66 vols./100 ml.

FIG. 1

FIG. 2

FIG. 3

FIGS. 1-3.—Radiographs of the skull—antero-posterior, lateral, and Townes's view—showing calcification.

FIG. 4

FIG. 5

FIG. 6

FIGS. 4-6.—Lower incisors, upper molars, and upper incisors, showing poor development and extensive caries.

Examination of the C.S.F. revealed normal dynamics, with a protein content of 20 mg./100 ml., and one lymphocyte per c.mm. W.R. on blood and C.S.F. was negative. The complement-fixation test for toxoplasmosis was negative. The electroencephalogram showed no notable abnormality.

The urine contained no sugar or albumin and the urea clearance (standard) was 82% of normal. No excess amino-acids were present, the pattern of excretion being normal. The urinary excretion of calcium on a normal hospital diet

was found to be 300 mg. a day, the urinary phosphate excretion 1.25 g. a day.

After five days' acclimatization on a low dietary calcium intake (0.2 g. a day), the total calcium excretion was measured over three consecutive three-day periods. The total daily excretion of calcium averaged 263 mg.—160 mg. in the urine and 103 mg. in the faeces. This gave a negative calcium balance of 63 mg. a day.

The Ellsworth-Howard test was performed as described by Albright and Reifenstein (1948). 200 U.S.P. units of fresh "para-

thor-mone" was injected intravenously, with hourly urine collection by indwelling catheter for two hours before and four hours after injection. A roughly threefold increase in phosphate excretion was noted (Fig. 7).

A calcium infusion test was performed after the method of Nordin and Fraser (1954). The rise in serum phosphate associated with a rise in both urinary phosphate output and renal phosphate/creatinine clearance ratio (Fig. 8) falls into the pattern described by Nordin and Fraser (1956) in cases of hypoparathyroidism.

FIG. 7.—Ellsworth-Howard test. The effect of para-thor-mone administered intravenously on the urinary phosphate excretion.

FIG. 8.—Changes in serum calcium and phosphate, urinary phosphate excretion, and renal phosphate/creatinine clearance rates after intravenous calcium infusion (15 mg./kg. body weight).

$$C_p/C_{cr} = \frac{\text{Urinary phosphate} \times \text{serum creatinine}}{\text{Urinary creatinine} \times \text{serum phosphate}}$$

(Owing to initial difficulty in emptying the bladder, the first two results here are mean values.)

Treatment with Dihydrotachysterol and Calciferol

Dihydrotachysterol (A.T. 10) and calciferol are generally regarded as of equal efficacy in the treatment of hypoparathyroidism and pseudohypoparathyroidism (McLean, 1941). Several reports in the literature (Blohm *et al.*, 1953; MacGregor and Whitehead, 1954) indicate the occasional failure of dihydrotachysterol to elevate the serum calcium. In this case we found no response to a nine-days trial of dihydrotachysterol, although admittedly small doses were employed (Fig. 9).

As the patient lived some two days' journey from the hospital the follow-up was entirely dependent upon the good offices of the local practitioner, who kindly arranged to transmit a sample of whole blood to us weekly. Once a month a 24-hour collection of urine in "polythene" bottles, to which 10 ml. of concentrated hydrochloric acid had been added, was also sent to the laboratory. Every three months the patient himself visited hospital for a few days' check-up.

Elevation of the serum calcium required much larger doses of calciferol than we had envisaged, a daily intake of 250,000 units being reached by stages before any perceptible rise took place. On this dose, however, fairly rapid elevation of his serum calcium level occurred (Fig. 9). Reduction of the dosage to 100,000 units a day was followed by a rapid fall in serum calcium; recovery was steady with a return to a higher dosage (200,000 units a day).

The routine estimation of phosphate levels was also performed on these sera, but occasional gross haemolysis vitiated several of the results, and reliance was placed upon the calcium level in the serum as a therapeutic guide.

The effect of calciferol upon the 24-hour excretion of calcium and phosphorus is shown in Fig. 9. When his serum calcium was in the normal range on a calciferol dosage of 250,000 units a day, a 24-hour sample of his urine (volume 1,740 ml.) contained 1,455 mg. of calcium. This extremely high calcium excretion contributed to our decision to cut the calciferol dosage drastically at this point. It is clear, however, that there is little variation in the daily excretion of phosphate as the serum level fluctuates. At the time when his serum calcium reached normal levels and his urinary calcium output was very high, his phosphate output was 1.04 g. per 24 hours. We took this to indicate continuing satisfactory renal function.

Dietary Measures

Albright and Reifenstein (1948) recommend the addition of a calcium salt to the diet, and for the first few months of treatment the patient took 1 g. of calcium as calcium lactate in addition to a normal diet. He was asked to reduce his previous milk intake of about 2 pints (1,140 ml.) a day to about $\frac{1}{2}$ pint (280 ml.). This meant his complete abandonment of milk as a beverage. At the time of his second admission to hospital (May, 1958), however, his calcium lactate was discontinued. This salt contains such a small proportion of calcium that the large number of tablets necessary to provide an added gramme of calcium constitutes a real therapeutic difficulty.

From May, 1958, ammonium chloride, 30 gr. (2 g.) three times daily, was added to the diet. This has been supposed (Lachmann, 1941) to increase the ionization of serum calcium, but its use in our case was prompted mainly by the desire to ensure the production of an acid urine in view of the high level of calcium excretion with attendant dangers of stone formation.

Albright and Ellsworth's (1929) view of the mode of action of para-thor-mone would suggest that a phosphate diuresis, however produced, might aid the elevation of serum calcium levels. The use of probenecid ("benemid") was suggested to us by Nordin (1958, personal communication). This substance, besides increasing the urinary output of uric acid, has also been observed to increase the excretion of phosphate. Our data provide no confirmation of this. The withdrawal of probenecid while the patient was on high

FIG. 9.—Effect of dihydrotachysterol and calciferol on serum calcium and phosphate, and on urinary calcium and phosphate excretion.

calciferol dosage, and its recommencement at much lower serum calcium levels on a lower dose of calciferol, did not affect the trend of the serum response at all (Fig. 9). We were unable to demonstrate the disappearance of the clinical signs of tetany with the return of the serum calcium to normal in June, as the patient was not at that time in hospital; but on his admission in September, when the serum calcium level was 8.3 mg./100 ml., both the Chvostek and the Trousseau signs were negative. The calcification in his basal ganglia was at this time unchanged. His neurological signs had not advanced, nor had his lens opacities increased.

Discussion

The biochemical and radiological findings in this case of epilepsy are together sufficient to support the diagnosis of hypoparathyroidism. The absence of stigmata of the peculiar syndrome of pseudohypoparathyroidism, short metacarpal bones, stunted stature, and soft-tissue calcification, together with the clinical history, and convulsive episodes dating from early childhood, are sufficient to justify a diagnosis of idiopathic hypoparathyroidism. The response to para-thor-mone shown by the Ellsworth-Howard test may be taken as further

evidence in this differentiation, although the usefulness of this test has been disputed (Milne, 1951; Dent, 1953; MacGregor and Whitehead, 1954).

Of great interest, however, is the finding in our case of normal or high levels of calcium excretion in the urine. Reviews of published cases of idiopathic hypoparathyroidism (Lachmann, 1941; Steinberg and Waldron, 1952) are reticent on the matter of urinary calcium content. The records of most cases contain bare statements that the Sulkowitch test was either "negative" or "faintly positive"—findings which, according to Albright and Reifenstein (1948), indicate blood calcium levels of "below 7.5 mg. per 100 ml." They further admit, however, that certain individuals apparently have a low renal threshold for calcium excretion, and mention, without further details, three patients with hypoparathyroidism who excreted large amounts of calcium in the urine at low levels of serum calcium.

It would appear preferable, where possible, in further studies of cases of hypoparathyroidism to substitute for the Sulkowitch test the more precise assay of daily calcium excretion. It does not seem to us adequate to regulate the calciferol dosage by the Sulkowitch test without periodic checks upon the serum calcium level. In our own case the absence of other urinary abnormality, together with the increase in urinary calcium excretion parallel with elevation of the serum calcium, suggests an abnormality of renal threshold for calcium, an "idiopathic hypercalciuria." There is no evidence of osteoporosis, and the radiological abnormalities typical of hypoparathyroidism suggest that the hypercalciuria is no more than an incidental unassociated abnormality.

Summary

A case of idiopathic hypoparathyroidism presenting with epilepsy is described.

Restoration of normal serum levels of calcium and phosphate was achieved with calciferol in high dosage.

The unusual finding of a high normal daily calcium excretion in the urine before treatment is discussed.

Our thanks are due to Mr. W. M. Nichols for permission to publish this case and for his continued encouragement, to Dr. M. MacLeod for his advice and criticism, and to Mr. Topp for the photographs. We are particularly indebted to Dr. F. A. Macrae, Kyle of Lochalsh, for his unfailing help in the follow-up of the case.

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The Medical Directory for 1959, the 115th annual issue, is now available from Messrs. J. & A. Churchill Ltd., 104 Gloucester Place, London, W.1 (2 parts; 4 guineas). It contains 91,206 names, an increase of nearly 2,000 over the previous issue.

SERUM HAPTOGLOBINS IN HEPATOBIILIARY DISEASE

BY

J. A. OWEN,*† M.D., Ph.D., B.Sc.

IAN R. MACKAY,* M.D., M.R.C.P., M.R.A.C.P.

AND

CATHERINE GOT*

From the Department of Biochemistry, University of Melbourne, and the Clinical Research Unit of the Royal Melbourne Hospital and the Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Haptoglobins are globulins which combine with haemoglobin (Polonovski and Jayle, 1940). We have measured serum haptoglobins in 64 patients with hepatobiliary disease and have found that levels are low in parenchymatous liver disease and high in biliary obstruction. We have assessed the measurement of serum haptoglobins as an index of hepatic function in hepatitis and cirrhosis, and as an aid in the differential diagnosis of the jaundiced patient.

Material and Methods

A range of normal values was obtained by analysing sera from 50 healthy blood donors. The 64 patients with hepatobiliary disease were classified as follows: (1) Acute infective hepatitis. (2) Active chronic hepatitis: hepatitis and cirrhosis of uncertain aetiology, including cases of post-hepatic and post-necrotic cirrhosis. (3) Lupoid hepatitis: active chronic hepatitis and a positive L.E. cell test (Mackay *et al.*, 1956). (4) Nutritional cirrhosis (Laennec's cirrhosis, alcoholic cirrhosis): all patients in this group admitted to a high intake of alcohol. (5) Extrahepatic biliary obstruction due to gallstones, neoplasm of the biliary tract or pancreas, or surgical damage to the common bile duct. None of these patients had biliary cirrhosis. (6) Miscellaneous (see Table I).

Serum haptoglobins were measured by determining the amount of haemoglobin which must be added to serum to saturate the haptoglobins present. Haemoglobin solutions of different concentrations were prepared from washed human erythrocytes lysed with water. 0.1 ml. of each solution was added to 0.2 ml. of the serum to be analysed, giving serum haemoglobin concentrations varying from 0 to 400 mg. per 100 ml. The mixtures were analysed by paper electrophoresis (phosphate buffer 0.025 M, pH 6.5, temperature 3–5° C., potential gradient 10 v. per cm., duration four hours). Under these conditions the haemoglobin-haptoglobin complex migrates towards the anode while haemoglobin remains at the origin. After electrophoresis the strips were stained with a dianisidine reagent (Owen *et al.*, 1958) and the minimal amount of added haemoglobin which produced a zone of free haemoglobin was noted. Results, in mg. of bound haemoglobin per 100 ml. of serum, were expressed as the range between the amount of added haemoglobin which just failed to produce a zone of free haemoglobin on the paper strip and the amount which was just sufficient for this (Fig. 1).

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†Now at the Biochemistry Laboratory, St. Vincent's Hospital, Melbourne.