HYPERCALCAEMIA AND IMPAIRMENT OF RENAL FUNCTION IN GENERALIZED SARCOIDOSIS

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Patients with generalized sarcoidosis occasionally show evidence of impaired renal function. In most of the cases reported in the literature this has been associated with marked hypercalcaemia (van Creveld, 1941; Schüpbach and Wernly, 1943; Klinefelter and Salley, 1946; Westra and Visser, 1949; Longcope and Freiman, 1952). The pathological mechanisms underlying these disturbances remain obscure, and we have recently had an opportunity of studying a case with these two complications and of observing the effect on them of cortisone therapy.

Case Report

A married man aged 23 was first seen in July, 1950. He complained of vague dyspepsia, which he had had for three months, and also admitted to the loss of 16 lb. (7.3 kg.) in weight and to nocturia up to four times a night. The only abnormality noted on physical examination was a moderately enlarged gland in the right axilla. The chest x-ray film showed bilateral hilar gland enlargement and milary mottling in the lung fields. He was admitted to hospital and various investigations were carried out. No tubercle bacilli were found in the sputum, urine, or gastric contents. The Mantoux test was negative at 1/100. The urine contained a few pus cells and hyaline casts, the concentration-dilution range was 1010 to 1006, and the maximum urea concentration was 1.49 g. per 100 ml. The blood urea was 60 mg. per 100 ml. and the urea clearance (C_m) 65% of average normal. An intravenous pyelogram showed no abnormality. The plasma albumin was 3.8 g. per 100 ml., globulin 2.5 g. per 100 ml.; the serum flocculation tests were positive; and the E.S.R. was 58 mm. in one hour (200 mm.). A diagnosis of pulmonary sarcoidosis was made and the patient was discharged to out-patient supervision.

In June, 1951, he started to get attacks of pain in his right loin; these became increasingly severe, and from April, 1952, were accompanied by haematuria. He was readmitted to hospital for further study. Physical examination revealed a few enlarged glands in the right axilla, and there was early calcification of the corneal limbus of both eyes. The chest x-ray film still showed enlarged hilar glands and further mottling of the lung fields. A straight x-ray film of the abdomen showed a "mulberry calculus" in the right renal area; x-ray films of the skeleton were normal. The urine contained numerous pus and red blood cells, and was sterile on culture; the concentration-dilution range was 1010 to 1008, and the maximum urea concentration 1.4 g. per 100 ml. The blood urea was 60 mg. per 100 ml. and the urea clearance (C_m) 47%. The E.S.R. was 46 mm. in one hour (100 mm.). The plasma albumin was 3.5 g. and the globulin 4.6 g. per 100 ml.; the electrophoretic pattern showed an increase of γ -globulin. The serum calcium was 14.3 mg. per 100 ml., plasma inorganic phosphorus 4.2 mg. per 100 ml., and serum alkaline phosphatase 11.1 (K.-A.) units per 100 ml. The urinary calcium output was 350 mg. in 24 hours on an ordinary ward diet containing about 1 g. of calcium. Estimations of serum and C.S.F. calcium were performed on specimens obtained nearly simultaneously; the

serum contained 13.8 mg. and the C.S.F. 5.1 mg. per 100 ml. The Mantoux test was negative at 1/100. Biopsy of a gland in the right axilla showed the typical appearance of sarcoidosis.

It was decided to study the effect of cortisone on the radiological appearance of the lung fields and on the calcium metabolism and serum proteins. In view of the relationship between sarcoidosis and tuberculosis and of the danger of activating tuberculous lesions with cortisone, it was also decided to give streptomycin during this period. Preliminary determinations of the blood streptomycin levels after various doses were made in view of the impaired renal function. The dose chosen was 1 g. of streptomycin a day. This was started on May 10 and continued until July 13, periodic blood-level determinations being made during this time. After a preliminary nine-day period on a low-calcium diet (170 mg. a day) cortisone, 150 mg. daily in six-hourly doses by mouth, was started on May 11. During the preliminary period on the low-calcium diet the serum and

Chart of the case, showing effect of cortisone therapy and variation of dietary calcium on serum and urinary calcium, serum globulin, and renal function.

urinary calcium fell. Reduction of the serum level continued while the patient was on cortisone, despite an increase of the dietary calcium after 10 days. The lowest figure obtained was 10.1 mg. per 100 ml. The urine calcium also fell further when the patient was first given cortisone with a low-calcium diet, but there was a slight temporary increase when the calcium intake was raised. The plasma inorganic phosphorus fell to 2.2 mg. per 100 ml. The alkaline phosphatase was unchanged. There was some reduction of the serum globulin, an improvement in renal function, and the Mantoux test became positive (Pyke and Scadding, 1952). (These changes are shown in the Chart.) The sedimentation rate showed no significant change. The course of cortisone was continued for 23 days and all diets given during this period had a low-sodium content.

X-ray examinations of the chest during the treatment showed steady improvement, and by the end of the course there had been marked clearing, which has persisted (August, 1952).

Surgical opinion advised exploration of the kidney and removal of the stone, and this was done on June 26 by Mr. D. R. Davies. The stone was found to be almost pure calcium oxalate. A renal biopsy performed during the operation showed evidence of very mild chronic pyelonephritis but no characteristic sarcoid lesions or evidence of calcification.

The patient's recovery from operation was uneventful, but subsequently he started to get pain in the left side; the serum calcium level had risen to 12.6 mg. per 100 ml. before

his discharge from hospital and his urinary calcium output remained over 300 mg. per 24 hours despite moderate restriction of the calcium intake.

Discussion

This patient had "band keratitis" and a renal calculus, clinical manifestations of hypercalcaemia and of hypercalciuria respectively. Calculi, almost always of calcium oxalate, have occasionally been reported in patients with generalized sarcoidosis (van Creveld, 1951; Albright and Reifstein, 1948; Longcope and Freiman, 1952), and corneal calcification is apparently equally rare (Haldimann, 1941; Cogan *et al.*, 1948). The origin of hypercalcaemia has not been satisfactorily explained, although three suggestions have been put forward: that it is due to the disturbance of plasma protein; that it is a manifestation of parathyroid overactivity; or that it results from bone destruction by sarcoid deposits. It is unlikely that the extra calcium is bound to the additional globulin, because the serum calcium and globulin levels (as determined by the present crude methods) do not vary in parallel (Harrell and Fisher, 1939; van Creveld, 1941; Albright and Reifstein, 1948). Under normal circumstances albumin and not globulin is the protein chiefly concerned in calcium binding (Gutman and Gutman, 1937), and if the extra calcium were all bound to protein hypercalciuria should not occur. Parathyroid hyperplasia has been found in some cases of sarcoidosis with hypercalcaemia (Westra and Visser, 1949; Longcope and Freiman, 1952), but in others exploration has shown the glands to be normal (Albright and Reifstein, 1948; C. E. Dent (unpublished observation). No case has been reported with a low plasma inorganic phosphorus level, and this also makes it unlikely that there is primary parathyroid overactivity.

The most probable explanation of the hypercalcaemia is that it is due to active destruction of bone from widespread involvement by sarcoid deposits. This would be comparable to that found in some cases of myelomatosis. Radiological changes in the bones in sarcoidosis are usually confined to the hands, and generalized bone rarefaction is rare, although van Creveld (1941) and Schüpbach and Wernly (1943) have reported cases in which it was present. Radiological evidence of generalized rarefaction is found only when there has been a negative calcium balance for many years, and sarcoidosis is a self-limited process in which hypercalcaemia has seldom persisted for any considerable time (Longcope and Freiman, 1952). The absence of x-ray evidence of rarefaction in most cases does not therefore exclude active bone destruction as the cause of the hypercalcaemia. More direct evidence is provided by the histological studies of Schaumann (1926), who demonstrated widespread osseous lesions and thinning of the bony trabeculae without any radiological changes.

The effect of variation of calcium intake on the serum calcium concentration and urinary output has seldom been reported. Albright and Reifstein (1948) found little change in the urinary calcium with intakes varying from 360 to 2,967 mg. a day. In our patient the serum level and urinary output of calcium fell slightly when he was placed on a diet containing much less calcium (170 mg. a day), although the urinary output remained abnormally large. Klinefelter and Salley (1946) also reported a slight fall in serum and urinary calcium on a low-calcium diet. The fact that the urine calcium remained fairly high when the intake was only 170 mg., together with the histological evidence of Schaumann, suggests that the hypercalcaemia results from osseous sarcoidosis and rapid bone destruction. The further reduction of serum and urinary calcium following cortisone therapy would be consistent with this hypothesis. There was radiological evidence of improvement in the lung condition while cortisone was being given, and it is probable that the bone lesions, if any, were similarly affected.

Impairment of renal function is a rare finding in cases of sarcoidosis; in only two has a post-mortem examination been reported, and little is known about its causation. It

cannot be correlated with the severity of the sarcoid process in the kidney, but seems to have some association with hypercalcaemia. Longcope and Freiman (1952) reported a case in which the patient died of renal failure and the kidneys showed chronic pyelonephritis and tubular calcification. In another patient, dying of miliary tuberculosis, sarcoid lesions, miliary tubercles, and calcified tubules were found in the kidneys (Horton *et al.*, 1939). Our studies clearly indicate the reversibility of the renal function impairment and its lack of association with any permanent structural damage to the kidney. Reversible impairment of renal function is known to result from a number of biochemical disturbances, of which hypercalcaemia is one. Long-continued elevation of the serum calcium leads to permanent renal damage with tubular calcification and hyalinization of the glomeruli; transient hypercalcaemia, on the other hand, leads to a temporary impairment. The improvement in renal function in the patient reported here was more rapid than is usual, for example, after vitamin-D overdosage. The renal biopsy performed a few weeks after the serum calcium fell to normal showed no evidence of calcification, but, in view of the report by Bjørnboe and others (1952) of the disappearance of tubular calcification within three weeks of discontinuing treatment in a case of vitamin-D intoxication, this does not exclude the presence of tubular calcification before the cortisone administration, and there is always the possibility that the renal biopsy may not have been typical of the whole kidney.

Hypercalcaemia in sarcoidosis is of importance for three reasons. First, it may lead to impairment of renal function, which, however, rarely progresses to uraemia; secondly, calcium oxalate stones may form in the renal pelvis; and, thirdly, if it occurs in the absence of x-ray changes in the lungs or of hyperglobulinaemia it may be attributed to hyperparathyroidism and lead to an unnecessary neck exploration. Renal calculi and band keratitis with hypercalcaemia, hypercalciuria even on a low calcium intake, normal bone x-ray films, and a normal serum phosphatase may be found in "hyperparathyroidism without bone disease." In this condition the plasma inorganic phosphorus is usually reduced, but it may be normal if there is impairment of renal function—that is, in Albright and Reifstein's (1948) "hyperparathyroidism - without bone disease - with renal failure." The differential diagnosis can therefore be very difficult. Howard *et al.* (1949) have reported that in sarcoid with hypercalcaemia the C.S.F. calcium is elevated, whereas in hyperparathyroidism it is normal. The C.S.F. calcium estimations in our patient were performed in duplicate in two laboratories and do not support this claim, but our studies do suggest the possible value of cortisone in differentiating between the two conditions, though we have not yet had an opportunity of investigating the effect of this hormone on the serum calcium level in a case of hyperparathyroidism. A similar reduction in serum calcium concentration in a case of sarcoidosis treated with cortisone has been observed by Professor G. M. Bull (personal communication).

Summary

Hypercalcaemia and impairment of renal function may occur in generalized sarcoidosis. A case is described in which the effects of variation of dietary calcium and cortisone therapy were studied. Clinical, radiological, and biochemical improvement followed the administration of cortisone. There was reduction of serum calcium and serum globulin, and renal function was much improved.

It is suggested that hypercalcaemia and hypercalciuria result from active bone destruction due to generalized sarcoidosis, and that in some cases the impairment of renal function is a consequence of the continuing disturbance of calcium metabolism.

A renal biopsy performed after cortisone therapy showed no sarcoid deposits or tubular calcification.

The differentiation of sarcoidosis with hypercalcaemia from hyperparathyroidism is discussed.

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ADDENDUM.—Since this report was prepared we have had another opportunity of studying the patient under constant normal dietary intake of calcium with and without cortisone. This time no change in serum proteins was observed, but again the cortisone reduced the serum calcium level to normal, improved renal function, and greatly improved the patient's well-being. This has now been repeated on three other patients with similar results. It appears that the improvement can be maintained for some months at least on a reduced dose of cortisone. It is hoped to publish these results later when a longer follow-up has been obtained. A recent paper by Shulman, Schoenrich, and Harvey (*Bull. Johns Hopk. Hosp.*, 1952, **91**, 371) on the general effects of cortisone on patients with sarcoidosis briefly mentions changes in calcium levels and in renal function which are very similar to those we have described above.

SPLenic VENOGRAPHY

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Great interest has lately been taken in the surgical treatment of cirrhosis of the liver (Berman *et al.*, 1951; Reinhoff, 1951; Leger *et al.*, 1952; Hunt, 1952) and portal hypertension (Whipple, 1945; Blakemore and Lord, 1945; Blakemore, 1951; Walker, 1952; Hunt, 1952). Valuable information may be obtained by needle biopsy of the liver in cases of hepatic cirrhosis. The procedure is sometimes difficult owing to the hardness and smallness of the liver and to the presence of ascites. Portal hypertension is usually determined by noting the pressure in one of the tributaries of the portal vein. Cavernomatous changes in the portal vein and obstruction in its prehepatic part or in the splenic vein may be made out by injecting a radio-opaque dye in the tributaries. In all these cases the abdomen has to be opened to carry out the investigation. Moreover, a surgeon must be sure that the splenic vein is patent and that the veins are large enough before attempting spleno-renal anastomosis. If useful information could be obtained

without laparotomy by a procedure which is safe it would be welcome. Splenic venography was done by Dreyer and Budtz-Olsen (1952) in 11 cases without any untoward incident. They suggested, among other things, that the method might be useful in finding out the site of block in cases of portal hypertension.

We carried out splenic venography in two control cases, in two with portal hypertension, in three cases with cirrhosis of the liver, and in seven cases of splenomegaly of unknown aetiology.

Method

The patients fasted overnight. Half an hour before the procedure 50 mg. of pethidine hydrochloride was injected. The patients lay supine on the x-ray table. The left ninth intercostal space in the mid-axillary line was chosen as the

FIG. 1.—Splenic venogram showing iodoxyl in spleen, splenic vein, upper part of a superior mesenteric vein, portal vein, and intrahepatic branches of portal vein.

FIG. 2.—Most of the dye has left the spleen and accumulated in the right lobe of the liver.

site for injection of the radio-opaque dye. The part was sterilized and the space up to the splenic capsule was anaesthetized with 2% procaine hydrochloride solution. About 5 ml. was needed. Then 20 ml. of a solution of "iodoxyl" (N-methyl-3:5-di-iodo-4-pyridone-2:6-dicarboxylic acid) was taken into a 20-ml. Record syringe to which a lumbar puncture needle was attached. It was pushed in medially and slightly downwards. The engagement of the needle in the spleen could be felt. The patients were asked to hold their breath at the end of inspiration until the whole amount was injected. An assistant held the lower pole of the spleen in cases in which it was enlarged.

The dye was injected as quickly as possible and a picture was taken when 15 ml. of dye had been injected (Fig. 1). That amount took about five seconds to inject. The next picture was taken five seconds later, when the full amount of the dye had been injected (Fig. 2). The needle was taken out and the site was sealed. At first we used a fine lumbar-puncture needle (children's size) attached to a 20-ml. all-glass syringe. It required great force to inject the dye into the splenic pulp. Later on, an adult lumbar-puncture needle attached to a Record syringe was used, when it became easy to inject the dye in five seconds. If the spleen was enlarged the needle was pushed for about 5 cm. from the skin surface. In cases without splenic enlargement this