Introduction

Although impaired renal function is uncommon in sarcoidosis the recognition of this complication is of importance since it may cause death and because prompt treatment may result in recovery of renal function.

The kidney is a common site for sarcoid lesions. Thus, in a combined series of 45 autopsies the kidneys showed macroscopic or microscopic involvement in 20 per cent. (Ricker and Clark, 1949; Longcope and Freiman, 1952). In view of the known tendency of sarcoid lesions to infiltrate organs extensively and impair function, it was assumed by earlier authors that renal impairment was due to massive invasion of the kidneys (Klinefelter and Salley, 1940). However, sarcoid lesions in the kidney are in fact usually small and relatively few in number and would be unlikely to produce renal insufficiency (Longcope and Freiman, 1952).

Evidence has accumulated pointing to another mechanism of renal damage. In 1939 Horton, Lincoln and Pinner recorded a case of sarcoidosis associated with renal impairment in which the kidneys at autopsy were contracted and showed marked calcification and degeneration of the tubules. The serum calcium was not estimated in this case, but in the same year Harrell and Fisher (1939) noted the occurrence of hypercalcaemia in some cases of sarcoidosis. Van Creveld in 1941 recorded the case of a child with sarcoidosis associated with hypercalcaemia, renal stone and impaired kidney function and in 1948 Albright and Reifenstein pointed out that nephrocalcinosis and nephrolithiasis might occur in sarcoidosis in association with hypercalcaemia. Finally this concept was confirmed by Longcope and Freiman (1952) who described a case of sarcoidosis where death was due to uraemia; hypercalcaemia was present and at post-mortem there was extensive calcification in and around the renal tubules.

The case of sarcoidosis to be described offered the opportunity of studying this condition and also of following the response to cortisone therapy.

Case Record*

Miss I.E., aged 23, had in 1948 commenced work in a factory where she was engaged in coating the inside of fluorescent tubes with a mixture containing beryllium phosphor. This exposure to beryllium lasted one year. A chest radiograph at the end of this time was stated to be normal. However, ten months later, in April 1953, she attended the Brompton Hospital complaining of dry cough and dyspnoea on exertion. Physical examination at this time showed no abnormality but the chest radiograph showed miliary mottling in both lungs and enlarged hilar shadows (Fig. 1). The Mantoux reaction was negative 1:100 O.T. and the E.S.R. was 75 mm. in one hour (Westergren).

The following month she developed erythema nodosum on both legs. Soon after this raised nodules appeared on the skin of the hands and some of these were situated over old scars. Biopsy of one of these nodules revealed the histological features of sarcoidosis (Fig. 2). Histochemical tests using Denz's naphthochrome technique (Denz, 1949) failed to demonstrate the presence of beryllium in the lesions. By September 1950 the liver had become palpable and she had lost one stone in weight.

In 1952 a painless bulbous swelling gradually appeared on the right fourth toe (Fig. 3). Radiography of this showed a calcified excrescence on the terminal phalanx (Fig. 4). This swelling occasioned discomfort during walking and the toe was therefore amputated. The specimen revealed a granulomatous reaction around deposits of calcium in the soft tissues (Fig. 5).

In 1953 frequency of micturition and nocturia developed. In July 1953 she noted discomfort in the eyes and conjunctival abnormalities were found. She was admitted to hospital in October 1953.

*This case was shown at the Clinical Section of the Royal Society of Medicine and is briefly described in Proc. Roy. Soc. Med. (1954), 47, 507.
FIG. 1.—Chest radiograph, October 1950, showing miliary shadowing in lungs.

FIG. 2.—Biopsy of skin nodule showing sarcoid infiltration (magnification × 110).

FIG. 3.—Photograph of right foot showing bulbous swelling of fourth toe.

FIG. 4.—Radiograph of right foot showing calcification in soft tissues of fourth toe.
On examination she was thin. No abnormal physical signs were found in the respiratory or cardiovascular systems and the blood pressure was 120/80. No rash was present. No lymph nodes were palpable, but the liver was palpable three fingers breadth below the costal margin.

In the conjunctivae of both eyes there were many small raised nodules, ocular appearances similar to those described by Walsh and Howard (1947) in hypercalcaemic states and attributed to deposits of calcium phosphate in the conjunctiva. (Fig. 6.) Both tympanic membranes showed white calcareous areas. There was no previous history of ear disease and the audiogram was normal.

Investigations. Review of the chest films showed no change in the miliary mottling over three and a half years. Tomography confirmed hilar node enlargement. Mantoux negative, 1/1000 T.U. P.P.D. E.S.R., 28 mm. in one hour (Wester-gren). No tubercle bacilli found on culture of gastric lavage.

Radiograph of the hands in 1952 showed translucencies in the tips of the terminal phalanges and opaque deposits in the soft tissues of the fingers, especially the left fifth and the right middle (Fig. 7). The film in 1953 was similar except that the deposits in the soft tissues were absent.

A radiograph showed two calcified areas in the left kidney (Fig. 8). Urine contained a trace of albumen, casts and calcium oxalate crystals. Culture was sterile.

The biochemical findings are demonstrated in Fig. 9. The serum calcium was remarkably high (19 mg. per 100 ml.) and serum phosphorus was also raised (5.6 mg. per 100 ml.). Alkaline phosphatase, 6.5 King-Armstrong units. Serum protein; total 8.5 g., albumen 4.3 g., globulin 4.2 g. per 100 ml. Blood urea 50 mg. per 100 ml. The urea clearance was 50 per cent. of normal. Marked hypercalcuria was present (0.8 g. calcium per 24 hours).

Treatment. She was given isoniazid and streptomycin. The dose of the latter had to be reduced to only ½ g. on alternate days on account of high blood streptomycin levels due to renal impairment. No significant change in biochemistry or renal function occurred during one month of this treatment.

Cortisone was then given in dosage of 150 mg. daily for ten days and thereafter 100 mg. daily. Fig. 9 shows the rapid fall in serum calcium and phosphorus which took place as a result of this treatment. Urinary calcium excretion also diminished. Eleven weeks later the urea clearance was 96 per cent. of normal and the blood urea 25 mg. per 100 ml. Cortisone dosage was scaled down to a maintenance dose of 25 mg. daily. Therapy was terminated after eight months at which time serum calcium and phosphorus were normal. She felt much better in herself and had gained one stone in weight. Frequency of micturition was absent. Dyspnoea on exertion she claimed was less, though lung function tests showed no significant change nor was the chest radiograph altered. The conjunctival deposits were no longer evident and deposits on the tympanic membranes were less extensive.

In summary, investigations of this case of sarcoidosis revealed hypercalcaemia with metastatic calcification in the conjunctivae, tympanic membranes, the soft tissues of the fingers and toes and kidney, and renal impairment thought to be due to nephrocalcinosis. Treatment with cortisone resulted in correction of the hypercalcaemia and renal impairment. The relationship of the sarcoidosis to exposure to beryllium is not established since beryllium was not demonstrated in the skin lesions and erythema nodosum is not recorded as a feature of beryllium sarcoidosis. It seems likely that the case is one of non-industrial sarcoidosis with an incidental history of possible beryllium hazard.

Review of the Literature

Many hundreds of cases of sarcoidosis are recorded in the voluminous literature on the subject yet only 37 with renal impairment have been found. However, it is likely that more frequent investigation of renal function and serum calcium would reveal more cases.

Analysis of these 37 cases indicates clearly that
Fig. 6.—Drawing of ocular appearances showing deposits of calcium in conjunctiva.

Fig. 7.—Radiograph of hands showing translucencies in tips of terminal phalanges and calcium deposits in soft tissues of left fifth terminal phalanx.
nephrocalcinosis is the cause of renal insufficiency in the great majority of cases.

Table 1 lists 28 cases of sarcoidosis with renal insufficiency in which serum calcium levels are recorded. Hypercalcaemia was present in 25. Of three cases with normal serum calcium one (Holt and Owens, 1949) showed nephrocalcinosis radiologically and another (Markoff, 1951) showed nephrocalcinosis on renal biopsy. In both only one estimation of calcium is recorded and it is almost certain that the level was high at some time in the course of the disease. It is recognized that serum calcium like the plasma globulin tends to parallel the activity of the sarcoid process and is normal in quiescent phases (Freiman, 1948). The third case (Parker, 1950) at autopsy had a congenital single fused kidney unrelated to sarcoidosis and is therefore excluded from further discussion. Thus in 27 cases hypercalcaemia was present or can reasonably be presumed to have been present at some time during the course of the disease.

In hyperparathyroidism, hypervitaminosis D and other conditions causing hypercalcaemia and hypercalcuria renal impairment is well recognized.
### Renal Impairment in Sarcoïdosis with Special Reference to Nephrocalcinosis

**Table 1.** Sarcoïdosis with Renal Impairment. Serum Calcium Known.

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>Renal Radiographs</th>
<th>Blood urea (or N.P.N.)</th>
<th>Serum calcium mg.%</th>
<th>Serum phosphorus mg.%</th>
<th>Alkaline Phosphatase</th>
<th>B.P.</th>
<th>Histological Abnormality of Renal Pelvis or Ureter</th>
<th>Renal histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Creveld (1941)</td>
<td>F. 12</td>
<td></td>
<td>+</td>
<td>49 (N.P.N.)</td>
<td>15.6</td>
<td>3.7</td>
<td>2.9</td>
<td>Raised</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Schupbach and Wernly (1943)</td>
<td>M. 20</td>
<td></td>
<td>+</td>
<td>138</td>
<td>16.3</td>
<td>5.8</td>
<td>4.0</td>
<td>2.7 (B.)</td>
<td>N.</td>
<td>N.</td>
</tr>
<tr>
<td>Esperson (1944)</td>
<td>F. 29</td>
<td></td>
<td></td>
<td>49</td>
<td>18</td>
<td>N.</td>
<td>-</td>
<td>200?</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Klinefelter and Salley (1946)</td>
<td>M. 23</td>
<td></td>
<td></td>
<td>70</td>
<td>17.4</td>
<td>4.3</td>
<td>N.</td>
<td>N.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Westra and Vissa (1949)</td>
<td>M. 20</td>
<td></td>
<td>+</td>
<td>77 (N.P.N.)</td>
<td>14.0</td>
<td>5.0</td>
<td>5.6</td>
<td>3.0 (K.A.)</td>
<td>N.</td>
<td>N.</td>
</tr>
<tr>
<td>Holt and Owens (1949)</td>
<td>M. 42</td>
<td></td>
<td></td>
<td>50</td>
<td>15.3</td>
<td>4.8</td>
<td>3.0 (B.)</td>
<td>+</td>
<td>Autopsy nephrocalcinosis</td>
<td></td>
</tr>
<tr>
<td>Keech (1951)</td>
<td>F. 28</td>
<td></td>
<td></td>
<td>105</td>
<td>9.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Markoff (1951)</td>
<td>M. 23</td>
<td></td>
<td></td>
<td>48 (N.P.N.)</td>
<td>9.8</td>
<td>-</td>
<td>-</td>
<td>130/140+</td>
<td>Biopsy nephrocalcinosis</td>
<td></td>
</tr>
<tr>
<td>Longcope and Freiman (1952)</td>
<td>F. 36</td>
<td></td>
<td>+</td>
<td>75 (N.P.N.)</td>
<td>15.5</td>
<td>4.7</td>
<td>5.2</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M. 34</td>
<td></td>
<td>+</td>
<td>108</td>
<td>16.5</td>
<td>6.1</td>
<td>-</td>
<td>-</td>
<td>Autopsy nephrocalcinosis</td>
<td></td>
</tr>
<tr>
<td>Schulman <em>et al.</em> (1952)</td>
<td>M. 33</td>
<td></td>
<td></td>
<td>60 (N.P.N.)</td>
<td>15.8</td>
<td>5.0</td>
<td>9.0</td>
<td>3.7 (B.)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M. 33</td>
<td></td>
<td></td>
<td>102</td>
<td>12.5</td>
<td>N.</td>
<td>N.</td>
<td>-</td>
<td>Autopsy nephrocalcinosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M. 37</td>
<td></td>
<td></td>
<td>66 (N.P.N.)</td>
<td>16.9</td>
<td>N.</td>
<td>N.</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Dent <em>et al.</em> (1953)</td>
<td>M. 23</td>
<td></td>
<td>+</td>
<td>56</td>
<td>14.3</td>
<td>4.2</td>
<td>11.1 (K.A.)</td>
<td>N.</td>
<td>Biopsy pyelonephritis</td>
<td></td>
</tr>
<tr>
<td>Klatskin and Gordon (1953)</td>
<td>M. 68</td>
<td></td>
<td></td>
<td>90 (N.P.N.)</td>
<td>15.0</td>
<td>5.2</td>
<td>5.3</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M. 51</td>
<td></td>
<td>+</td>
<td>114</td>
<td>12.8</td>
<td>4.2</td>
<td>6.8</td>
<td>5.1 (B.)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Phillips (1953)</td>
<td>M. 29</td>
<td></td>
<td></td>
<td>11 (N.P.N.)</td>
<td>14.6</td>
<td>3.4</td>
<td>4.3</td>
<td>(B.)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Davidson <em>et al.</em> (1954)</td>
<td>F. 42</td>
<td></td>
<td>+</td>
<td>42</td>
<td>16.8</td>
<td>4.0</td>
<td>2.6</td>
<td>(B.)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F. 32</td>
<td></td>
<td>+</td>
<td>122</td>
<td>12.8</td>
<td>2.6</td>
<td>7.0</td>
<td>220/110+</td>
<td>+</td>
<td>Autopsy nephrocalcinosis</td>
</tr>
<tr>
<td>Dent <em>et al.</em> (1954)</td>
<td>M. 36</td>
<td></td>
<td></td>
<td>129</td>
<td>16.3</td>
<td>3.8</td>
<td>8.1 (K.A.)</td>
<td>N.</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M. 14</td>
<td></td>
<td></td>
<td>58</td>
<td>14.0</td>
<td>-</td>
<td>-</td>
<td>N.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F. 56</td>
<td></td>
<td></td>
<td>192</td>
<td>15.0</td>
<td>-</td>
<td>-</td>
<td>N.</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Citron (1954)</td>
<td>F. 23</td>
<td></td>
<td>+</td>
<td>52</td>
<td>19.0</td>
<td>5.6</td>
<td>6.4</td>
<td>N.</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Zeldenrust (cited by Van Creveld, 1941). Renal impairment with hypercalcaemia. No other data.

Longcope and Freiman (1951). Two cases with renal impairment and hypercalcaemia. No other data.


*Bodanski or King-Armstrong units.
and is due to deposits of calcium in the kidney, renal pelvis or both (nephrocalcinosis or nephrolithiasis). Hence one would expect to find similar changes in hypercalcaemia with sarcoidosis. Analysis of Table 1 shows this to be the case. Thus all four autopsies in this series showed nephrocalcinosis and of two renal biopsies one also showed nephrocalcinosis and the other, taken during pyelolithotomy, showed pyelonephritis secondary to calculous obstruction. Of the 27 cases radiography showed nephrocalcinosis in seven and nephrolithiasis in six. Histological or radiological evidence of calcium in the kidneys was obtained in 13 cases out of a total of 24 for whom full clinical details are available.

Renal insufficiency when due to hypercalcaemia is known to be often reversible if the hypercalcaemia is corrected (Adams, 1951). In six cases in Table 1 serum calcium levels fell spontaneously or in response to low calcium diet and in all renal function improved. In seven renal function improved as a result of control of the hypercalcaemia with cortisone or ACTH.

TABLE 2

<table>
<thead>
<tr>
<th>Author</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvarsen (1935)</td>
<td>Clinically compatible with nephrocalcinosis.</td>
</tr>
<tr>
<td>Horton et al. (1939)</td>
<td>Autopsy. Nephrocalcinosis</td>
</tr>
<tr>
<td>Ustvedt (1939) two cases</td>
<td>Clinically compatible with nephrocalcinosis.</td>
</tr>
<tr>
<td>Longcope and Freiman (1952)</td>
<td>No data.</td>
</tr>
</tbody>
</table>

Table 2 lists nine cases for which serum calcium is not known. Post-mortem examination was made in five of which two showed nephrocalcinosis. Renal insufficiency was attributed to extensive sarcoid invasion of the kidney in another. The fourth showed hyalinization of the glomeruli and periglomerular capillaries. In the fifth the lesion was an arterial and periarterial lesion unrelated to sarcoidosis. Of the remaining four cases three are clinically compatible with nephrocalcinosis and no clinical information is available for the other.

Analysis of these cases therefore shows that nephrocalcinosis or nephrolithiasis is the principal cause of renal impairment in sarcoidosis. In only one case (Chanials, 1943) can impairment reason-ably be attributed to massive invasion of the kidney by sarcoid granulomata.

The case of Rutishauser and Rywlin (1950) in which the main lesion was hyalinization of glomeruli and preglomerular capillaries demonstrates a third possible mechanism of renal impairment in sarcoidosis. The changes in this case were similar to those described by Teilum (1951) in sarcoidosis and also in diffuse lupus erythematosus and in other collagen diseases associated with hyperglobulinæmia. Teilum ascribed these to a common type of mesenchymal reaction, probably allergic in nature.

The Clinical Pattern of Renal Impairment in Sarcoidosis

Review of the published cases suggests that renal impairment in sarcoidosis presents a recognizable clinical picture.

Renal symptoms comprise frequency, polyuria, nocturia, sometimes renal colic, but there may be no symptoms referable to the urinary tract.

Symptoms resulting from hypercalcaemia are frequent and include lassitude, weakness, loss of weight, anorexia and nausea suggesting gastritis. Davidson et al. (1954) mention finding prominence of gastric rugæ on plain X-ray of the abdomen in some cases.

Blood pressure is usually but not invariably within normal limits and retinopathy and oedema are usually absent, thus distinguishing the condition from Ellis types I and II nephritis.

The eyes may show punctate calcium deposits in the conjunctiva or in the cornea showing as a semilunar opacity near the limbus which has been described as band keratopathy (Walsh and Howard, 1949; Cogan et al., 1948).

Urine shows small amounts of albumen with a few casts and red cells. The daily excretion of calcium is usually excessive.

Blood chemistry is characteristic (Table 1). Serum calcium is raised and may be very high. Probably calcium like globulin is raised only when the sarcoid process is active, so that in quiescent phases its level may be normal though some renal impairment remains. Serum phosphorus is normal or high, but not low, an important distinction from hyperparathyroidism. Alkaline phosphatase is usually normal. Globulin is usually increased.

Radiologically the kidneys often show scattered areas of calcification or calculi (calcium oxalate) in the renal pelvis. Radiographs of the soft tissues or blood vessels may show metastatic calcinosis. Bones may reveal localized destruction but extensive translucency to X-rays is rare.

The course of the disease untreated is prolonged. Death from renal failure may occur though more often there is a gradual spontaneous
correction of the hypercalcaemia and sufficient functioning uncalcified kidney may remain to maintain life.

The Aetiology of Hypercalcaemia in Sarcoidosis

Hypercalcaemia, which is not uncommon in sarcoidosis (i.e. 25 per cent. in 44 cases, Longcope and Freiman, 1952), might result from the following factors:
1. Disturbed plasma proteins.
2. Hyperparathyroidism.
3. Bone destruction by sarcoid granulomata.
4. Increased absorption of calcium from the gut.

The extra calcium in the blood is unlikely to be due to its being bound to protein, for there is no constant relationship between hyperglobulinaemia and hypercalcaemia (Longcope and Freiman, 1952; Harrell and Fisher, 1939), and albumen rather than globulin is mainly concerned in binding calcium. Further, hypercalcuria would not occur if protein were calcium bound.

Hyperparathyroidism is also unlikely. Records of the parathyroids on exploration or autopsy in eight cases (Albright and Reifenstein, 1948; Westra and Vissa, 1949; Longcope and Freiman, 1952; Klatskin and Gordon, 1953; Davidson et al., 1954 (two cases); Dent et al., 1954b) shows some hyperplasia in two and normality in six. Further, the characteristic low phosphorus of hyperparathyroidism is not found (Table 1).

Liberation of calcium from bone invaded by sarcoid granulomata is unlikely, for radiological changes are usually minimal and, moreover, the fall of serum calcium which occurs in response to low calcium diet in these cases is against this hypothesis (Dent, et al., 1954b).

Dent (1954a, b) has recently shown convincingly by means of calcium balance studies that hypercalcaemia in sarcoidosis is due to excessive absorption of calcium from the gastrointestinal tract. Increased absorption of calcium may result from giving large doses of vitamin D. It might also result from increased sensitivity to normal amounts of vitamin D, and this is the probable explanation for the increased absorption of calcium in sarcoidosis, for there is abundant evidence that many patients with sarcoidosis are abnormally sensitive and rapidly develop hypercalcaemia when given vitamin D therapeutically (Scadding, 1950; Curtis, Taylor and Grekin, 1947). This is in contrast with experience with patients suffering from other conditions. For instance Steck et al. (1937) found toxicity in only 8 per cent. of 773 patients given more than 100,000 units of vitamin D for up to five years. The patient described in this paper had taken doses of cod liver oil equivalent to 800 units of vitamin D daily, occasionally replacing this by halibut liver oil capsules equivalent to 2,500 units daily over a period of about two years. The cause of the abnormal sensitivity to vitamin D in sarcoidosis remains obscure.

Treatment

Since hypercalcaemia is liable to cause renal damage it is advisable to estimate the serum calcium in all cases of established sarcoidosis. If the level is elevated, renal function should be investigated. Persistent hypercalcaemia above 12 mg. per 100 ml., with or without renal damage, merits treatment with cortisone. The case described here demonstrates the correction of renal insufficiency and hypercalcaemia by cortisone, and other equally satisfactory therapeutic results have been reported. Dent (1954b) has shown that cortisone acts by diminishing the abnormally high absorption of calcium from the gut, thus correcting hypercalcaemia. Other evidence which he quotes to show that cortisone has an action antagonistic to vitamin D is the low absorption of calcium to be found in Cushing’s disease (Freyberg et al., 1936) and the fact that cortisone increases the requirement of vitamin D (Moehlig and Steinbach, 1954).

Initially doses of 150 to 100 mg. of cortisone daily by mouth causes rapid control of the hypercalcaemia (Fig. 9). Thereafter the dosage is gradually reduced according to serum calcium levels, but usually small doses are found to be required for prolonged periods to control the metabolic defect. The patient should be warned against supplementing the normal diet with preparations containing vitamin D.

Summary

1. A case of sarcoidosis with renal impairment due to nephrocalcinosis secondary to hypercalcaemia is described.
2. The literature on renal insufficiency in sarcoidosis is reviewed and it is found that nephrocalcinosis is the principal cause.
3. The aetiology of hypercalcaemia in sarcoidosis is discussed.
4. Cortisone treatment is discussed.

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K. M. Citron

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