CALCIUM METABOLISM AND BONE CHANGES IN SARCOIDOSIS

BY

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Although hypercalcaemia is uncommon in sarcoidosis it is important for two reasons. It may cause difficulties in reaching a correct diagnosis, and when persistent leads to complications such as renal failure or nephrocalcinosis. Unless this renal damage is recognized and treated it may be fatal. There is, moreover, evidence that the use of calciferol for the treatment of sarcoidosis in the last decade has increased the risk of hypercalcaemia and of its attendant dangers. The purpose of this paper is to record the frequency of disturbed calcium metabolism in a series of patients with sarcoidosis and to relate it to other features. As this involves a study of the bone lesions in the disease an account of their incidence and forms is also included, from which it is possible to estimate the value of bone radiographs as a diagnostic aid in sarcoidosis.

Clinical Material and Methods

The patients studied belonged to a group of over 160 seen personally during the last few years. The age range was 12 to 65 years, and females preponderated in a ratio of 3:2. About two-thirds of them had widespread pulmonary disease and most of the others had bilateral hilar lymph-node enlargement. Many were referred for investigation after a mass miniature radiograph had shown these abnormalities, and were free from symptoms at the time. About one-quarter of them had a uveitis, one-fifth superficial lymph-node or splenic enlargement, and one-tenth skin lesions. The diagnosis of sarcoidosis was based on a typical chest radiograph and clinical features, supported by negative cultures of sputum and urine for *Mycobacterium tuberculosis*. Confirmation by biopsy was obtained from liver, lymph nodes, skin, or conjunctiva in more than two-thirds of the series.

Radiographs of the hands and feet of 120 of these patients were examined and reported upon by a radiologist. In addition they were reviewed personally at the time of this survey and any doubtful abnormalities were scrutinized together. A control series of radiographs of 101 hands and 14 feet were taken from patients of the same age groups as those with sarcoidosis who attended the casualty department.

Estimations of serum calcium by the method of Trevan and Bainbridge (1926) were made in 86 patients with sarcoidosis (normal range 8.5–11 mg./100 ml.). The serum proteins were estimated by the micro-Kjeldahl method, albumin and globulin being separated by precipitation with sodium sulphate. All patients were examined by the slit-lamp for signs of corneal or conjunctival calcification. Radiographs of the renal tract and function tests were done when there was any reason for thinking that the kidneys were affected.

Bone Radiographs

Bone changes were seen in only 9 of the 120 patients with sarcoidosis (Table I). They were revealed by a coarse reticular pattern in two, typical cystic appearance in two, and intermediate states of medullary and cortical bone replacement in five (Figs. 1 and 2). Confirmation of the diagnosis by liver, skin, or lymph-node biopsy was possible in eight of the nine patients. Estimations of serum calcium in six gave normal results. Local bone pain occurred in three and soft-tissue swelling in two. Five of the nine patients with bone lesions had cutaneous sarcoids, but only eight of the other 111 patients—confirming the relationship between these two forms of sarcoidosis which has long been suspected. The skin lesions did not occur over the areas of bone disease, nor were they of any particular type: all were confirmed by biopsy. Bone disease was not associated with any particular type of pulmonary disease or with other features such as uveitis.

Lesions resembling those of sarcoidosis were not seen in any of the control group of radiographs.

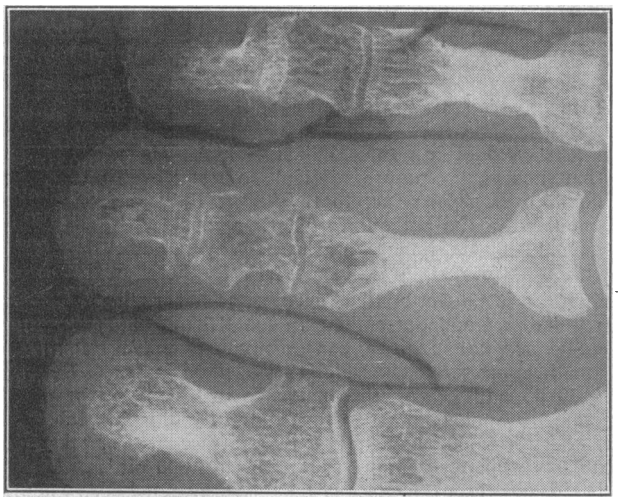

FIG. 1.—Radiograph of right foot of Case A, Table I. Destruction of cortical and medullary bone is seen most obviously in the middle phalanx of the second toe. (By courtesy of Drs. R. J. Cairns and J. D. Craig.)

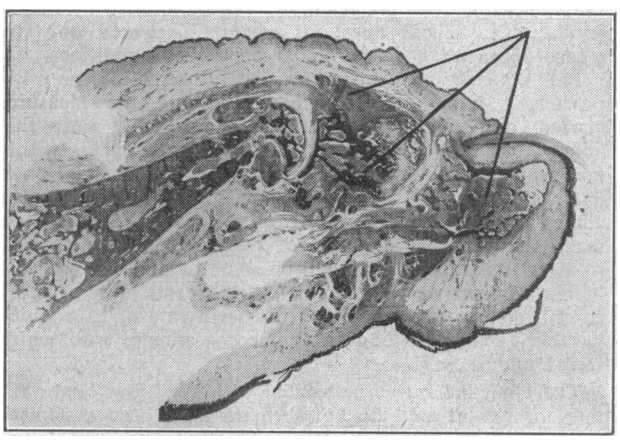

FIG. 2.—Longitudinal section of the second toe of Case A, removed because of pain. Lines point to extensive replacement of bone and surrounding structures by sarcoid tissue. (Haematoxylin and eosin stain. ×2.)

Serum Calcium in Untreated Sarcoidosis

A serum calcium over 11 mg./100 ml. was found in four of 86 patients tested and below 8.5 mg./100 ml. in four others (Table II). No patient had been treated with vitamin D. None of these eight patients had digital bone lesions. There was no relationship between the serum calcium and the serum albumin, but two patients were found to have a parallel change in the level of total globulins. In Case 4 hypercalcaemia was found together with serum globulin of 3.4 g./100 ml. and in Case 5 hypocalcaemia with serum globulin of 0.29 g./100 ml.

One patient only in the series had any symptoms or signs referable to a disturbed calcium metabolism. His case history is given in detail because of the many interesting features.

Case 1

A fit Service man aged 20, with no previous serious illness, was found by a mass radiograph in August, 1952, to have bilateral hilar-node enlargement and basal infiltration. Examination revealed a transient pleural friction rub and crepitations in the base of the left lung. The Mantoux reaction was positive to 100 T.U. *M. tuberculosis* was not isolated from repeated sputum cultures. A liver biopsy confirmed the diagnosis of sarcoidosis.

Two months later he developed enlarged superficial lymph nodes, iritis, and retinal periphlebitis. This responded to a two-months course of systemic cortisone, 100 mg. daily. His general condition remained good and he gained weight while resting in hospital. In August, 1953, proteinuria was noticed and a chest radiograph showed increased pulmonary infiltration. On account of this he was admitted to King's College Hospital in November. Examination then revealed vascularization of the right cornea and circumscribed retinal scars in the left eye. There was generalized lymph-node enlargement, and fine crepitations were heard at the base of the lungs.

Investigations.—Chest *x*-ray examination: bilateral hilar-node enlargement with infiltration at both bases. *X*-ray films of hands and feet: normal. Intravenous pyelography: horseshoe kidney with two stones in right renal pelvis, also calcified mesenteric node in right iliac fossa. Blood count: normal. E.S.R., 44 mm./hour (Westergren). *M. tuberculosis* not found on repeated sputum and urine culture. Lymph-node biopsy: typical sarcoid follicles. Urine: albumin +, hyaline casts +, white cells +, red cells +, sterile on culture. Urine concentration and dilution test: range of S.G., 1014–1010. Blood urea, 37 mg./100 ml.; standard urea clearance, 40% of normal; serum calcium. 11.6 mg./100 ml.; alkaline phosphatase, 8 K.A. units/100 ml.; plasma phosphorus, 3.3 mg./100 ml.; serum proteins, 7.2 g./100 ml. (albumin 4.2 g., globulin 3 g.).

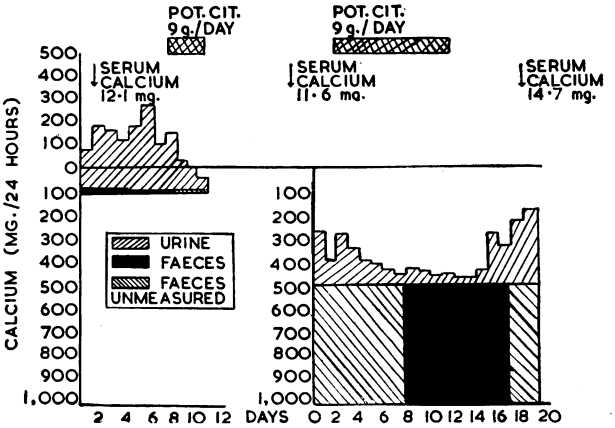

FIG. 3.—Calcium balance in Case 1 on a low and normal calcium intake from December 9–20, 1953, and January 2–21, 1954, respectively. Daily intake is measured downwards from and output upwards towards the zero line. The effect of potassium citrate is seen.

Calcium Balance (Fig. 3).—On an intake of 100 mg. of calcium and 90 I.U. of vitamin D per 24 hours there was a very low calcium excretion in the faeces, but an excretion in the urine which exceeded the intake by about 150 mg. per 24 hours; this was reduced by taking 9 g. potassium

TABLE I.—*Bone Changes in Sarcoidosis* (120 *Patients*)

Case	Age Sex	Clinical Features	Biopsy Positive	*X*-ray Examination		Serum Calcium (mg./100 ml.)
				Chest	Bone	
A	41 F	Skin lesions, pain in toes	Skin, toe	Normal	Erosions of medulla and cortex of right second toe, proximal and middle phalanges. Erosion of nasal bones (Figs. 1 and 2)	10·8
B	47 F	Skin lesions, aching and swelling of hands and feet, myxoedema	Skin	Hilar nodes +. Diffuse fine infiltration	Cysts of several digits of hands and feet	—
C	40 M	Skin lesions, aching in hands and feet	Skin, liver	Normal	Cortical erosion right second metatarsal head	—
D	43 M	Lupus pernio	Skin, palate	,,	Coarse reticulation with early erosion of heads of several proximal phalanges	8·9
E	40 M	Lymph-node enlargement	Lymph node	Hilar nodes +	Early cystic erosion base middle phalanx right ring-finger	—
F	35 F	Tiredness, dyspnoea, painless swellings of fingers	Subcutaneous tissue	Diffuse coarse mottling	Coarse reticular pattern of several phalanges	9·3
G	47 M	Skin lesions	Skin, liver	Bilateral infiltration, mainly upper zones	Coarse trabeculation and early erosion middle phalanx right ring-finger	9·4
H	42 F	No symptoms or signs	—	Symmetrical coarse reticulation	Typical cyst base of distal phalanx right ring-finger	9·2
I	12 M	Loss of weight and energy. Inguinal nodes	Lymph node	Hilar nodes +	Coarse trabeculation and cortical erosions in proximal phalanges of both third toes	8·8 9·7

TABLE II.—*Abnormal Serum Calcium in Sarcoidosis* (86 *Patients*)

Case	Age, Sex	Clinical Features	Biopsy	*X*-ray Examination		Serum Calcium (mg./100 ml.)	Serum Proteins (g./100 ml.)		
				Chest	Bone		Total	Alb.	Glob.
				High					
1	20 M	Generalized lymph-node enlargement, uveitis, renal stone	Lymph node, liver	Hilar nodes +. Slight lung infilt.	Normal	11·6	7·2	4·2	3·0
2	24 M	Delayed puberty	—	,, ,, ,,	,,	12·3 8·7*	5·92	4·50	1·42
3	23 M	Bilateral iridocyclitis	Liver	Hilar nodes +. Bilateral lung infilt.	,,	11·4	6·54	4·41	2·13
4	22 M	Lymph-node enlargement	Lymph node, liver	,, ,, ,,	,,	11·5	7·7	4·3	3·4
				Low					
5	18 F	Skin lesions, splenic enlargement	Skin	Hilar nodes +. Bilateral lung infilt.	,,	7·8 7·9	4·66 4·7	4·37 3·6	0·29 1·1
6	56	Bilateral iridocyclitis	—	Hilar nodes +	,,	8·4	6·42	4·46	1·96
7	25	Slight chest pain	Liver	Hilar nodes +. Bilateral lung infilt.	,,	8·1	6·84	4·45	2·39
8	36	Skin lesions, uveoparotitis	Skin	Hilar nodes +. Coarse infilt.	,,	8·0	—	—	—

* One month later.

citrate daily. The citrate was given in order to see the effect of alkalizing the urine, as the low calcium diet has an acid ash. On an intake of 983 mg. of calcium and 1,200 I.U. of vitamin D an average of 300 mg. of calcium was retained per 24 hours, with a normal proportion of urinary and faecal excretion; the urinary component was greatly reduced when potassium citrate was given. During this period the serum calcium rose from 11.6 to 14.7 mg./100 ml. The effect of calciferol (10,000 units daily) and cortisone on the calcium balance when on a calcium intake of 718 mg. is shown in Fig. 4. The serum calcium rose from

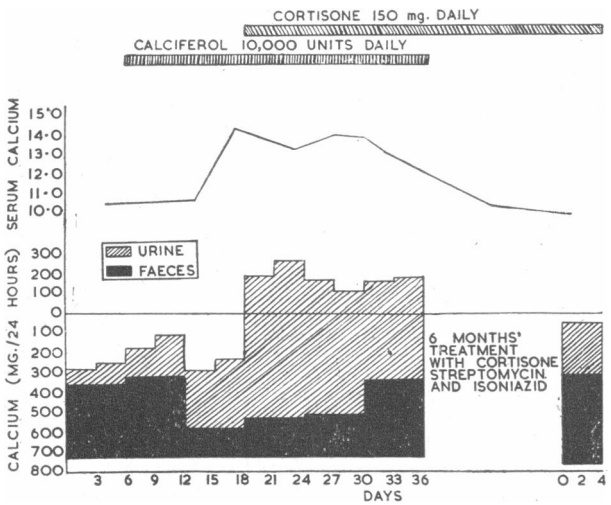

FIG. 4.—Calcium balance in Case 1 during treatment with cortisone from February 20 to March 28, 1954.

10.5 to 14.3 mg. during the 12 days with calciferol alone and there was a fall in the faecal excretion and a steady rise in the urinary excretion. The addition of cortisone, 150 mg. daily, coincided with a still greater urinary loss of calcium due to the calciferol, but this then diminished and there was a steady fall in the level of serum calcium to 10.4 mg. A short balance experiment after treatment with cortisone for six months, calciferol having been discontinued, showed a normal calcium balance and a normal level of serum calcium (10 mg.).

Progress.—During observation in hospital and investigation of the calcium metabolism the patient developed marked photophobia with aching in the eyes. On the exposed area of the bulbar conjunctiva follicles were found containing minute chalky granules, together with an early band-shaped opacity in each cornea. This appearance was thought to be associated with the hypercalcaemia, as the serum calcium at this time was 14.7 mg./100 ml. The follicles and band-shaped opacities resolved rapidly when the calcium intake was reduced, and had disappeared within six weeks, leaving only small amorphous deposits in the position of the follicles.

Treatment.—He was given a course of streptomycin sulphate, 1 g. intramuscularly daily, together with isoniazid, 100 mg. b.d., for three months. There was little response in either the clinical or the radiographic features. Cortisone, 150 mg. daily by mouth, was then added and produced a rapid reduction in the size of the superficial lymph nodes, a clearing of the pulmonary infiltration, and a shrinkage of the hilar nodes. The effect on calcium metabolism is shown in Fig. 4. This treatment was continued for three months, during which he returned to work. The dose of cortisone was then reduced to 100 mg. daily, and the streptomycin to 1 g. twice weekly. The chest radiograph and superficial lymph nodes remained normal, there were no signs of active uveitis, and the serum calcium was within normal limits. All treatment was stopped after one year. The patient remained well, and one year later there had been no relapse. The serum calcium was still normal, and kidney function had improved; there was no albuminuria, and the standard urea clearance was 76% of normal.

Disturbed Calcium Metabolism Due to Treatment with Calciferol

No patients were treated with calciferol, but four were seen who showed signs of poisoning after having this drug elsewhere. They are not included in Table II. The case histories of three of them are given.

Case 9

A 51-year-old woman had complained of tiredness and lack of energy for three years. For two years she had noticed a skin lesion on the side of the neck and enlarged cervical lymph nodes which had increased in size six months previously. For 18 months she had had slight dyspnoea on exertion, with a cough productive of a few blobs of white sputum daily. In November, 1954, biopsy of a cervical lymph node had revealed sarcoid follicles. A chest radiograph showed extensive disease, thought to be tuberculous, although the sputum was negative for *M. tuberculosis*. She was treated by rest at home and given 2 pints (1,140 ml.) of milk a day, but there was no real change. Between February 7 and March 8, 1955, she was given 5 ampoules by mouth, each containing 600,000 units of calciferol. On March 11 headache and vomiting began, and the possibility of cerebral tumour was entertained until the serum calcium was found to be 15.4 mg./100 ml. and the blood urea 128 mg./100 ml. There was no frequency of micturition, and no pain or haematuria. The headaches and vomiting were temporarily relieved by chlorpromazine and compound codeine tablets.

When examined at King's College Hospital she displayed a slow mentality, perhaps due to the chlorpromazine. She was anaemic, but the skin was bronzed. In the eyes a few chalky fragments were visible on the exposed area of bulbar conjunctiva. The retinal vessels showed early hypertensive change. There were discretely enlarged cervical, right axillary, and epitrochlear lymph nodes and the spleen was just palpable. Bronchial breathing was heard over the right dorsal lobe, but there were no adventitious sounds. The cardiovascular system was normal apart from a blood pressure of 170/110.

Investigations.—Chest *x*-ray examination: bilateral coarse nodulation, becoming confluent in the upper lobes with upward retraction of the hila by fibrosis. Hands and feet: mild arthritic changes only. Kidneys: no calcification seen. Blood count: haemoglobin, 66%; white cells, 4,300, with normal differential count. E.S.R. (Westergren): 60 mm. hour. Sputum (×6) and E.M.U.: no *M. tuberculosis* on culture. Urine: sterile, albumin 1+, pus cells +++, occasional hyaline and granular casts. Blood urea 55 mg./100 ml.; standard urea clearance, 32% normal. Range of specific gravity, 1006–1012. Serum proteins, 7.27 g./100 ml. (albumin 3.69 g., globulin 3.58 g.). Serum calcium, 12.7 mg./100 ml. Phosphorus 4 mg./100 ml. Alkaline phosphatase, 8 K.A. units/100 ml. E.C.G.: normal. Mantoux: positive to 100 T.U.

A calcium balance was undertaken three months after the last dose of calciferol. On a fixed intake of 615 mg. of calcium per 24 hours there was an excessive excretion of calcium in the urine: an average of 597 mg. in the urine and 336 mg./24 hours in the faeces during six days. The effect of 100 mg. of cortisone daily was to lower the blood calcium to normal, with little change in the proportion of calcium excreted in the urine and faeces during the 12 days in which these were measured.

Progress.—She improved steadily while taking cortisone. The nausea and headache ceased; she became more alert and energetic and resumed an active life. By November, 1955, she looked and felt very fit except for some dyspnoea on exertion due to her old pulmonary lesions, which were unaltered. Her serum calcium has remained within normal limits since June, 1955.

Case 10

A 53-year-old woman in 1940 noticed blurred vision due to uveitis. She developed parotitis and pulmonary sarcoidosis and later multiple skin lesions, and enlarged spleen and lymph nodes. During the next 10 years she became breathless from increasing pulmonary fibrosis. In 1950 she was treated with calciferol, 50,000 units, by mouth daily for nine days, without benefit, but this had to be discontinued on account of vomiting and weakness due to hypercalcaemia. The serum calcium rose to 12 mg./100 ml. In 1954 she had renal colic due to stones, which were later removed. Her blood pressure was 150/95 before treatment with calciferol, but steadily rose afterwards, and reached 235/135, with persistent albumin in the urine. It seems probable that all these complications were caused by the temporary hypercalcaemia. She took her own life in 1955; necropsy confirmed fibrosing sarcoidosis. There was extensive scarring of the kidneys from arteriolar disease, scattered calcification of the renal tubules and interstitial tissue but no sarcoid follicles, and a calculus in the right renal pelvis.

Case 11

A 45-year-old woman noticed enlarged lymph nodes in the neck and axilla in 1946 which were subsequently shown at biopsy to be due to sarcoidosis. Since 1949, during the summer months, she had developed lassitude, vomiting, and constipation of such severity as to make her cease work. In June, 1950, there was an episode of misty vision associated with a painful right eye. In November, 1955, she was given 50,000 units of calciferol daily by mouth for four weeks; but this caused severe lassitude, vomiting, and constipation. She was then referred to King's College Hospital for further investigation. Enlarged cervical, epitrochlear, axillary, and inguinal nodes were found, and an early corneal band-shaped opacity. The blood pressure was 180/90, but there were no abnormalities in the chest, heart, or abdomen.

Investigations.—Radiographs of the chest, skeleton, and kidneys were normal. A barium meal showed only delayed gastric emptying. The Mantoux test was positive to 100 T.U. E.S.R. (Westergren) 45 mm./hour. Cultures of gastric washings and urines were sterile. Serum calcium, 15.2 mg./100 ml. (repeated); phosphorus, 3.2 mg.; urea 65 mg. Total serum proteins, 8 g./100 ml. with increase of globulin on electrophoresis.

Progress.—She was treated with a low-calcium diet and cortisone, 150 mg. daily. Within a month the serum calcium had returned to normal limits (10.8 mg.) and her symptoms had disappeared. Her treatment was interrupted by an attack of acute appendicitis, which, however, gave the opportunity to confirm the diagnosis of sarcoidosis by biopsy of a mesenteric node. Treatment with cortisone has continued on a maintenance dose of 150 mg. daily; her lymph nodes have returned to normal size and gastro-intestinal symptoms have disappeared.

Corneal Band-shaped Opacities

Although examination for these opacities was undertaken as a routine, they were found in only three patients. Case 1 was the most obvious. In another patient with uveitis and hilar-node enlargement, corneal calcification was seen, but unfortunately there was no histological proof of sarcoidosis and the serum calcium was not estimated. In the third patient (Case 12) there was circumstantial evidence of transient hypercalcaemia, but the serum calcium was not estimated at the time.

Case 12.—A 65-year-old diabetic woman developed uveitis in 1949 followed by parotitis and skin lesions, which on biopsy were shown to be sarcoids. One year later she developed neuritis, nausea, and vomiting; there was a trace of albumin in the urine, and the blood urea was 140 mg./100 ml. Band-shaped opacities developed, but the serum calcium was not estimated until two years later, when the nausea and vomiting had stopped and the blood urea had returned to 65 mg./100 ml. There was persistent albuminuria. It is probable that both the kidney damage and the corneal opacities were caused by a transient hypercalcaemia.

Discussion

Bone Lesions

The earliest descriptions of the radiographic appearance of bone sarcoid were by Kienböck (1902) and Kreibich (1904), although Jüngling (1919) first described the histological changes. The frequency of bone involvement was found to be 9 in 55 cases by Holt and Owens (1949) and 19 in 100 cases by Longcope and Freiman (1952). Bone disease was found less often in the present series—only nine times in 120 patients. The true frequency of bone involvement may be much higher than any of these reports suggest, as the epithelioid cell follicles of sarcoidosis have been seen at biopsy or necropsy even when the radiograph has been normal (Schaumann, 1926). Also the earliest radiographic changes—a stippled medullary pattern from diffuse lacunar absorption—may be so indefinite that a firm diagnosis cannot be made, especially when the process affects many phalanges.

The explanation for the lower frequency in this series compared with others may be that most of the patients had predominantly intrathoracic sarcoidosis, and that there were only 13 examples of skin sarcoids, of which five showed digital bone disease. The relation between skin and bone sarcoidosis is well known (Holt and Owens, 1949), and it is because so many of the early reports of sarcoidosis were of skin lesions that bone changes were thought to be so frequent. In the last two decades pulmonary forms of the disease have been recognized to be the most common, so that bone sarcoid is seen relatively less frequently.

In the nine patients of this series the diagnosis of sarcoidosis had already been made from the clinical and radiographic features, supported by biopsy in eight. The finding of bone lesions in Cases F and H (Table I) was valuable support for the diagnosis, but their absence would not have changed this. Hence it is thought that radiographs of the hands and feet give little help in the diagnosis of sarcoidosis, and are wasteful as a routine procedure.

The most common type of radiographic change is a coarse reticulation of the shaft of the bone due to follicle formation along the cortical blood vessels, as seen in six of the nine cases. This and a stippled medullary pattern from diffuse lacunar absorption are the earliest changes. The classical punched-out areas in the medulla occurred in two cases, with less definite areas of bone replacement in four others. Thinning and expansion of the cortex, sometimes even with pathological fractures, have been reported due to the enlarging granuloma, but no examples were seen in this series. When the disease remits spontaneously there is seldom complete resolution of the bone lesions; a "cyst" of fibrous tissue may remain indefinitely. Bone sarcoid has been described in practically every bone in the body, but it has an overwhelming predilection for the middle and distal phalanges of the hands and feet. The reason is unknown.

In the differential diagnosis of bone sarcoid many diseases have to be considered. Both rheumatoid arthritis and gout have quite distinct clinical features. Here pain and swelling of the joints predominate, and the radiographic changes of osteoporosis or bony erosions are usually most pronounced at the articular ends of the bones, although in the arthropathy of psoriasis these may spread to involve the shaft as well. Enchondromata usually expand the cortex and are homogeneously translucent. Resembling these are the small degenerative cysts which occasionally occur as an incidental finding in the carpals and digits. Tuberculous dactylitis, a very rare condition in adults, causes the bone to appear distended and provokes a periosteal reaction; later destructive changes may occur accompanied by sinuses. Hyperparathyroidism should seldom be mistaken for sarcoidosis, as here there is decalcification affecting the whole skeleton,

with fibrous cysts in a few bones. Sometimes it may not be possible to separate xanthofibroma and tuberous sclerosis of the digits except by features of these diseases elsewhere, The most common error is to diagnose digital sarcoidosis too frequently through failure to appreciate the range of normal bone architecture. Areas of radiolucency in the metacarpal heads are especially apt to be interpreted falsely, as are the coarsening of the bone structure with increasing age and with osteoarthritis. Features which help in the diagnosis of sarcoidosis are the lack of joint involvement and periosteal reaction, and the usual absence of pain.

No relationship has been found between demonstrable bone disease and hypercalcaemia either in the past (Holt and Owens, 1949) or in the present series (Table I). This is not surprising, as other localized diseases of bone, such as osteomyelitis or tumours, likewise do not upset calcium metabolism. Bone sarcoid must be regarded as an oddity which seldom causes symptoms or demands treatment.

Hypercalcaemia

The first recognition of hypercalcaemia in sarcoidosis was by Harrell and Fisher (1939). Isolated reports of nephrocalcinosis and renal calculi had appeared (Salvesen, 1935), but their relationship to hypercalcaemia was not appreciated until 1941 (van Creveld). Estimates of the frequency of hypercalcaemia have varied from 11 in 44 patients (Longcope and Freiman, 1952) to 4 in 86 of the present series. Harrell and Fisher (1939) reported hypercalcaemia in 6 of their 11 patients, but in one patient the serum calcium was only 10.6 mg./100 ml., and, in another, hypercalcaemia developed only after intensive treatment with cod-liver oil. The explanation for the lower frequency in the present series compared with those of previous workers may be that many of the patients had disease affecting the hilar nodes or lungs alone and none was given vitamin D. Many of the reported cases had widespread disease, and no mention was made of whether vitamin D had been given as treatment. Hypercalcaemia in patients not receiving vitamin D occurs so infrequently in sarcoidosis that estimation of the serum calcium routinely is unnecessary. It should be done if there are symptoms of hypercalcaemia such as thirst, polyuria, tiredness, muscular weakness, and vomiting, if ectopic calcification is found, or if renal colic or albuminuria occurs, pointing to nephrolithiasis or calcinosis.

The explanation for the hypocalcaemia in four patients (Table II) is obscure, but merits further investigation. Case 5 was of particular interest in that there was an associated hypoglobulinaemia despite extensive sarcoidosis.

The cause of hypercalcaemia remains obscure. It bears no relation to a high serum protein (Harrell and Fisher, 1939; and Table II); in any case, protein disturbances affect only the serum globulin, which has little calcium-binding power (Schmidt and Greenberg, 1935; Gutman and Gutman, 1937). Also the hypercalciuria is evidence that increased calcium in the blood is largely of the ionizable fraction. Hypercalcaemia is not due to parathyroid stimulation, as there is no hypophosphataemia or generalized osteoporosis. In several cases normal parathyroid glands have been removed (Albright and Reifenstein, 1948; Klatskin and Gordon, 1953; Davidson *et al.*, 1954; Anderson *et al.*, 1954). One case has been recorded where hyperparathyroidism simulated sarcoidosis by showing diffuse pulmonary reticulation (Salmon and Meynell, 1951).

Hypercalcaemia is not due to widespread bone sarcoid, as there is seldom radiographic evidence of this, and in the nine cases (Table I) with known bone lesions there was no upset of calcium metabolism. Furthermore, balance studies do not support this hypothesis. It is not due to renal sarcoidosis, as there are many examples of hypercalcaemia where biopsy or necropsy has failed to show epithelioid cell follicles (Dent *et al.*, 1953; Davidson *et al.*, 1954; Correa, 1954; Case 10), and in those cases where renal sarcoidosis has occurred it is not extensive enough to cause impaired function (Longcope and Freiman, 1952). It may be due to a primary metabolic disorder, such as excessive sensitivity to vitamin D as suggested by Anderson *et al.* (1954). Case 1 showed on the calcium balance an excessive absorption of calcium similar to that seen in their cases. This patient's metabolism also reverted to normal during cortisone treatment, a feature observed by Shulman *et al.* (1952), Lovelock and Stone (1953), Phillips (1953), Dent *et al.* (1953), Lane (1954), Citron (1954, 1955), and Anderson *et al.* (1954).

Further support for the hypothesis of vitamin-D sensitivity comes from the observations on Case 1 and of others that treatment with this drug even in small doses or with ultra-violet light may cause hypercalcaemia (Scadding, 1950; Cantwell, 1954; Letman, 1954; Anderson *et al.*, 1954). The recurrent symptoms of hypercalcaemia in Case 11 before calciferol was given all occurred during the summer months and were especially severe during the sunny summer of 1955. This suggests that the hypercalcaemia was provoked by ultra-violet light. Moreover, the clinical as well as the biochemical features of hypercalcaemia in sarcoidosis are in every way typical of hypervitaminosis D. Sensitivity to vitamin D is also thought to be the cause of infantile hypercalcaemia (Bonham Carter *et al.*, 1955; Schlesinger *et al.*, 1956), and there is some evidence that cortisone helps to reverse this abnormality (Creery and Neill, 1954).

The dangerous effects of hypercalcaemia, whether spontaneous or provoked by vitamin D, are primarily on the kidney, where irreversible damage may be done by nephrocalcinosis and renal stones (Cases 9 and 10). Impairment of function may be so severe that a fatal uraemia ensues (Cantwell, 1954; Correa, 1954; Davidson *et al.*, 1954). Hypercalcaemia may also cause band-shaped corneal opacities (Walsh and Howard, 1947; Cogan *et al.*, 1948; Cases 1, 9, and 11), and calcification in tissues, such as the blood vessels, lungs, subcutaneous tissue, and joint capsules. In addition to these potential dangers, there is considerable doubt about the efficiency of calciferol in the treatment of sarcoidosis. In the only recorded controlled trial of calciferol (Nelson, 1949) the frequency of remissions was the same in the treated and untreated groups. For these reasons the use of calciferol for the treatment of sarcoidosis should be discontinued.

When hypercalcaemia is encountered, a diet low in calcium and vitamin D may be effective. Cortisone has been shown to have some antagonistic action to vitamin D and is effective in reducing hypercalcaemia in sarcoidosis. It should be used when there is evidence of renal damage and when dietary measures prove ineffective.

Summary

Radiographs of the hands and feet have been examined from 120 patients with sarcoidosis: bone lesions were found in only nine. Such radiographs are thus of little value in diagnosis. The common association of cutaneous sarcoids with bone disease was confirmed (five out of the nine patients). No examples of disturbed calcium metabolism were seen in those with bone disease.

Estimations of serum calcium in 86 untreated patients showed hypercalcaemia in only four. Hypocalcaemia occurred in four. The effects of hypercalcaemia are described, with special reference to kidney damage. Examples of hypercalcaemia following the treatment of sarcoidosis with calciferol are given and its dangers emphasized.

Clinical and biochemical studies support the hypothesis that hypercalcaemia in sarcoidosis is due to excessive sensitivity to vitamin D. Control of this complication may be achieved by a diet low in calcium and vitamin D, although cortisone is sometimes necessary.

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ANAESTHESIA FOR AORTIC RECONSTRUCTION*

BY

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Reconstruction of the thoracic and abdominal aorta calls for an anaesthetic technique appropriate to other operations in the region of these structures. There are, however, certain features peculiar to this branch of surgery which demand some special thought from the anaesthetist. Apart from the technical problems involved in maintaining (often for many hours) an even state of anaesthesia, combined with the profound degree of muscular relaxation necessitated by the surgical approach, there are other, and vital, matters concerning blood and respiratory chemistry, fluid and blood replacement, and the control of the haemodynamic disturbances of the surgical procedure. The nature of the operation may necessitate interruption of the circulation to vital organs for long periods, and in such cases the operation can be conducted safely only with the aid of induced hypothermia; this technique will itself impose some problems of anaesthetic management.

The anaesthetic techniques described below have been followed in 71 of the cases of aortic occlusion or aneurysm undergoing operation by members of the surgical unit of St. Mary's Hospital, London, under the direction of Professor Charles Rob. The anaesthetic procedure was conducted by three members of the hospital consultant staff, and their assistants. The 71 cases concerned are briefly summarized in Table I.

*Abstracted from a paper read before the Section of Anaesthetics at the Annual Meeting of the British Medical Association, Brighton, 1956.

TABLE I

	Requiring Hypothermia	Not Requiring Hypothermia
Aneurysm	5	37
Thrombosis	6	22
Coarctation	1	0
Total	12	59

TABLE II.—*Fatal Cases*

Requiring Hypothermia		Not Requiring Hypothermia	
Aneurysm:		Aneurysm:	
Haemorrhage	1	Haemorrhage	3
Suprarenal failure	1	Myocardial infarction ..	2
Myocardial infarction ..	1	Paralytic ileus and pulmonary sepsis	1
		Undecided	1
Thrombosis	0	Haemorrhage	1
Coarctation	0	Coronary thrombosis ..	1
Total	3		9

The operative mortality (deaths occurring in the first 24 hours of the operative period) was 12 out of 71 (16.9%) (Table II).

Anaesthesia as a contributory cause of death could be implicated for certain in one case (pulmonary sepsis following aspiration of vomitus during induction of anaesthesia for reopening abdomen 12 hours after operation for aortic aneurysm. Ileus not diagnosed preoperatively). One other case (listed as "undecided") was a possible "anaesthetic death." In the light of later experience it was thought that respiratory acidosis might have been a contributory factor (see last two cases in second column).

Type of Patient

Although, in the main, the patients likely to be encountered in surgery of the aorta may be described as being "in the prime of life," they are by no means in the prime of physical condition. With some few exceptions (such as the rare traumatic case, and some cases of aortic coarctation) they have reached middle or late middle age, and are suffering from severe arterial disease. Atherosclerosis is not likely to be confined to the portion of the aorta requiring surgery; coronary, cerebral, and renal vessels are likely to share in the general disease. Often there is hypertension, which may be of severe degree. There may have been past episodes of cardiac infarction or cerebral thrombosis. Such patients tend to be "old beyond their years," physically flabby, and often obese.

This is our somewhat unpromising material, and to subject such patients to major surgery, with the attendant hazards of blood loss and traumatic shock, under general anaesthesia (possibly maintained for as long as 12 hours), without the most careful pre-operative assessment and preparation, would be to court almost certain disaster. Only in the case of true emergency (such as leading aneurysm or haemorrhage from other causes) is it justifiable to omit the full pre-operative routine which is described below. The period of assessment and preparation may precede the operation by 7 to 10 days.

Pre-operative Investigations

Aortography.—In all cases the site of the lesion is determined by an aortogram, usually performed under local analgesia, assisted by intravenous pethidine. Only in exceptionally difficult cases, or with unusually apprehensive patients, will a general anaesthetic be necessary; since complete apnoea at the time of the exposure and the prone position are demanded, this will require tracheal intubation