source of faecal iodine is endogenous thyroid hormone, a fraction of which is excreted into the bile (Myant, 1956).

Further evidence for an endogenous origin of faecal iodine is obtained from balance studies in patients with abnormal thyroid function (Harrison *et al.*, 1965a). Patients with thyrotoxicosis excrete significantly more iodine in the faeces than normal, ranging from 21 to 72 μg /day on a low iodine intake. Patients with untreated hypothyroidism, on the other hand, excrete less iodine in the faeces than normal, 1–16 μg /day on the same intake. In patients with non-toxic goitre due to iodine deficiency, the faecal excretion of iodine is normal, so that losses of iodine by this route are important in producing iodine deficiency when the intake is very low. In severe iodine deficiency the urinary excretion of iodide by contrast falls to very low levels.

It may be inferred from the studies described here that the levels of faecal and urinary iodine reflect the size of the two pools of iodine which circulate in the body outside the thyroid gland. Faecal iodine is derived from circulating organic iodine, a pool about 500 μg in size which is replenished by thyroid hormone secreted from the gland, while the source of urinary iodine is the smaller inorganic iodine pool of about 50 μg which is supplied by dietary iodine and by deiodination of thyroid hormone. Abnormalities of iodine metabolism affect each of these pools in different ways, which produce characteristic alterations in the pattern of balance studies. The

intestine plays an important role in the body's economy of iodine in health and disease, and ability to measure iodine balance has enhanced our understanding of the complicated metabolism of this element.

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John McMichael's multisystem interests

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For this Festschrift salute to Sir John McMichael we have chosen to span his many interests by discussing them in relation to sarcoidosis, a versatile multisystem disease. From it we can both recollect and redefine Sir John's far-ranging impact in many different fields.

The multisystem pattern

In a series of 537 personally-studied patients with both clinical and histological evidence of sarcoidosis (Fig. 1), it becomes clear that most

organs of the body are invaded; this multi-system involvement is so predictable that it is possible to construct a table of the relative frequencies of involvement (Tables 1a and 1b). These data emphasize the fact that sarcoidosis transcends boundaries demarcating various disciplines and makes specialists realize that the grass is even greener in the next field.

Paediatrics

Soon after qualification John McMichael was

FIG. 1. Sarcoidosis clinic, 1954-64.

a house-physician at Paddington Green Children's Hospital where he became absorbed in the problem of an 18-month-old child with unique post-mortem findings suggestive of visceral endarteritis obliterans (McMichael, 1929). Evidence of tuberculous infection was present in the form of a positive Pirquet reaction and slightly enlarged caseous glands. It is almost certain that he did not deal with sarcoidosis during this 6 months' apprenticeship for sarcoidosis rarely affects children. In our series, it was only seen once in the first decade and in only twenty-

four instances in the second decade (Table 2). Sarcoidosis is peculiarly a disease of the child-bearing years of life, so it is not surprising that it is not listed among the fifteen disorders of the thirty children whose diurnal variation in pulse rates constituted his second full-length publication (Sutherland & McMichael, 1929).

Spleen

He undoubtedly confronted sarcoidosis as Goodsir Memorial Fellow of the University of Edinburgh in the early 1930s for he was then actively correlating the pathology and physiology of splenic anaemia (McMichael, 1931). His unique series of cases of hepato-lienal fibrosis undoubtedly included one or two patients with sarcoidosis of the spleen, and also deservedly earned him a gold medal Edinburgh M.D. (McMichael, 1934).

Splenic involvement occurred in sixty-two of 537 (12%) of our series of patients with sarcoidosis. It may be silent; or it may cause hypersplenism; or lead to pre-sinusoidal portal hypertension (Sherlock, 1968a). It would be un-

TABLE 1(a)
Frequency of involvement of various tissues in sarcoidosis: (a) absolute numbers

No. of patients	All	Lungs	Erythema nodosum	Lymph nodes	Eyes	Skin	Spleen	CNS	Parotid	Bone cysts
All	537	452	167	153	147	135	62	38	33	19
Lungs	452	452	147	140	111	101	51	31	29	17
Erythema nodosum	167	147	167	38	38	32	10	6	4	1
Lymph nodes	153	140	38	153	44	48	38	10	18	7
Eyes	147	111	38	44	147	53	21	22	18	12
Skin	135	101	32	48	53	135	22	11	14	16
Spleen	62	51	10	38	21	22	62	4	12	3
CNS	38	31	6	10	22	11	4	38	6	1
Parotid	33	29	4	18	18	14	12	6	33	5
Bone cysts	19	17	1	7	12	16	3	1	5	19

TABLE 1(b)
Frequency of involvement of various tissues in sarcoidosis: (b) percentages

No. of patients	All	Lungs	Erythema nodosum	Lymph nodes	Eyes	Skin	Spleen	CNS	Parotid	Bone cysts
All	100	84	31	29	27	25	12	7	6	4
Lungs	84	100	33	31	25	22	11	7	6	4
Erythema nodosum	31	88	100	23	23	19	6	4	2	6
Lymph nodes	29	91	25	100	29	31	25	7	12	5
Eyes	27	75	26	30	100	36	14	15	12	8
Skin	25	75	24	36	39	100	16	8	10	12
Spleen	12	82	16	61	34	35	100	6	19	5
CNS	7	82	16	26	58	29	11	100	16	3
Parotids	6	88	12	55	55	42	36	18	100	15
Bone cysts	4	90	5	37	63	84	16	5	26	100

charitable to leave the spleen without paying tribute to it as the only useful source of Siltzbach-Kveim antigen (Siltzbach, 1961; Anderson *et al.*, 1963). This test has simplified the recognition and diagnosis of sarcoidosis (James, 1966).

TABLE 2
Age incidence of apparent onset of sarcoidosis in 537 patients

Age (decades)	No.	%
0-10	1	—
11-20	24	5
21-30	207	39
31-40	126	23
41-50	98	18
51-60	64	12
61 and over	17	3
Total	537	100

Liver

Sir John's diversion from the spleen to the liver via the splanchnic circulation benefited British gastroenterology and also brought to light the fact that the liver is a rich source of sarcoid tissue. Aspiration liver biopsy can be expected to reveal miliary granulomata in two-thirds of patients with sarcoidosis, and this technique has materially assisted in its diagnosis (Sherlock, 1968b). In this respect, we are indebted to Sir John who pioneered aspiration liver biopsy in this country. Nowadays the technique provides hepatic miliary granulomata so readily that we are forced to differentiate their many causes (Fig. 2). In a series of 100 sarcoid granulomas revealed by liver biopsy in our series, the final diagnosis was sarcoidosis in seventy-six patients, cholestasis in ten, and a miscellany of condi-

tions in the remainder (Fig. 3). Because of the confusing similarity of hepatic granulomas irrespective of the cause, the following practical plan of management is suggested:

(a) Chest radiography, slit-lamp examination of the eyes, the Siltzbach-Kveim test, and urinary calcium output provide the most helpful routine for segregating those due to sarcoidosis.

(b) A strongly positive tuberculin reaction and fever point towards tuberculosis, and specific anti-tuberculous chemotherapy should be contemplated.

(c) If the patient has pruritus or any other features of cholestasis, serum should be examined for non-organ specific anti-mitochondrial antibodies by the immunofluorescent technique.

(d) Neoplasia should not be overlooked in the older age group. The malignant disorders associated with this series of 100 hepatic granulomata comprised one instance each of carcinoma of the uterus, and of the oesophagus, Hodgkin's disease and chronic myeloid leukaemia. The fact that all four had received radiotherapy may be significant. It is conceivable that some biochemical breakdown product of radiotherapy is granulomagenic.

FIG. 3. Miliary hepatic granulomas in 100 patients.

FIG. 2. Causes of sarcoid granuloma.

Lung

When Sir John turned his attention from the liver to the lungs, he confronted sarcoidosis, for 84% of all cases have intrathoracic involvement (Table 1b), some of which progress to the stage of irreversible pulmonary fibrosis and cor pulmonale. He evolved the technique of cardiac catheterization in order to help these unfortunate sufferers, for this is the commonest mode of death in an otherwise benign disorder (James & Thomson, 1959). Resolution of the chest radiograph can be expected in two-thirds of patients with pulmonary sarcoidosis within 2 years (Table 3). Clearing is more likely to occur in the younger person or in those with erythema nodosum. Resolution of pulmonary sarcoidosis is less likely to occur if there are extrathoracic lesions

(Fig. 4). Bone cysts, chronic uveitis and skin lesions (other than erythema nodosum) constitute the hallmark of chronicity of pulmonary sarcoidosis. These are the patients most likely to develop cor pulmonale (James, 1961).

TABLE 3
Resolution of chest radiograph in sarcoidosis

Stage*	Total no. of patients	Patients with changes followed for more than 2 years	Resolution within 2 years	
			No.	%
0	85	—	—	—
1	243	185	139	75
2	129	108	58	54
3	80	74	29	26
Total	537	367	226	62

* Stage 0 = Clear chest radiograph.

Stage 1 = Bilateral hilar lymphadenopathy (B.H.L.).

Stage 2 = B.H.L. $\pm$ pulmonary infiltration.

Stage 3 = Diffuse pulmonary infiltration $\pm$ fibrosis.

Pulmonary function

In a Festschrift for the person who introduced lung function tests to the Postgraduate Medical School of London and to British medicine this article would be without inner meaning if it did not include discussion of pulmonary function. Even in the absence of symptoms or radiological abnormality, sarcoidosis can affect the lung and is only detectable by delicate tests of respiratory function. The discrepancy between normal radiographic appearances and abnormalities of lung function is best explained by the presence of granulomas surrounding small vessels

FIG. 4. Resolution of chest X-ray changes.

in the lung, causing impairment of gas transfer. Only patients with severe impairment of diffusing capacity improve with corticosteroids. There is no consistent benefit in patients with mild impairment (Sharma, Colp & Williams, 1966a, b).

Heart

Myocardial involvement must clearly be included in this discussion for infiltrating sarcoid tissue may cause sudden death, arrhythmias, conduction block, acute myocarditis or cardiac hypertrophy. Unfortunately it is difficult to confirm the diagnosis of myocardial sarcoidosis in life and it needs a Sir John to urge us to undertake cardiac muscle biopsy more often if we are to recognize treatable cases earlier.

Epilogue

Sarcoidosis was strewn across Sir John's path once he progressed from paediatrics to the spleen, the portal circulation, the liver, the lung and the heart. May it never be far from his mind for we still need the clues which will help prepare clinicians of many different disciplines for a final assault against the remaining outstanding problem, namely its aetiology.

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