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Iodine balance in man

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THE information provided by metabolic balance studies enables us to determine the minimal requirements of foodstuffs, their availability to the body after ingestion, their routes of excretion, and the modifications of all of these which may arise as a result of disease or administration of other substances. For some nutrients such as fat and nitrogen, balance studies may be readily carried out in man as the quantities involved are easily measured and intake easily controlled. In the case of iodine, however, one must deal with minute quantities which are mixed with large amounts of interfering substances, for example in the faeces where about 1 part of iodine per 10 million by weight is present, together with relatively vast amounts of organic material that must be removed before iodine can be measured. To the technical difficulties of measuring such small amounts are added the risks of contamination of specimens from extraneous sources and unintentional administration of iodine to the individuals during the balance period. These difficulties have prevented large-scale investigation of iodine balance in man, and most of our knowledge of iodine metabolism has been derived from studies with radioactive isotopes of iodine, particularly ^{131}I. These studies have added enormously to our knowledge of thyroid function, but due to the transient radioactivity of these isotopes they are of greatest value in short-term studies, and their use is limited in balance studies and others in which a longer period of observation is desired.

We have attempted to study stable iodine metabolism in men and women with normal thyroid function under different conditions and in others with thyroid disorders. Balance studies have been carried out in a metabolic ward under conditions of controlled intake of iodine with precautions to prevent access of unwanted iodine either to the individuals being studied or their excreta. Urine and faeces were collected over periods of several weeks, the urine daily and faeces in pooled collections averaging 6 days. Details of the collection methods and measurements of iodine have been reported previously (Harrison *et al.*, 1965a).

The effects of varying the intake of iodine in normal people were first studied. Iodine balances were carried out during two levels of iodine intake, a low level of approximately 100 μg/day, which is near the minimal level at which equilibrium can be maintained (Wayne, Koutras & Alexander, 1964), and a level of approximately

600 μg/day, which is above the normal intake of dietary iodine, but may readily be achieved by supplements of seafood or potassium iodide.

TABLE 1
Iodine balance in normal individuals on low and high iodine intakes

	No. of balances	No. of individuals	Mean urinary iodine (μg/day)	Mean ± SEM faecal iodine (μg/day)
Low iodine intake (approximately 100 μg/day)	38	13	71	16·4 ± 1·93
High iodine intake (approximately 600 μg/day)	36	5	304	23·2 ± 2·43 $P < 0·025$

SEM = Standard error of mean.

The results are summarized in Table 1. On the lower intake the combined average urinary and faecal excretion of iodine is close to the intake, and eleven of the thirteen individuals were in equilibrium or slightly positive balance. With the higher intake of iodine there is a positive balance in every case, which persists for at least 2 months while the intake is maintained. The urinary excretion of iodine rises markedly, but the increase of faecal iodine, although significant, is of a lower order of magnitude than both the intake and urinary increases. This suggests that the small increase in faecal iodine may be derived not from the ingested iodine, but may represent a change in excretion of endogenous organic iodine in the form of thyroid hormone, in response to the increase of inorganic iodine intake.

Evidence that the iodine present in the edible part of fish is all available to the body, since intestinal absorption is complete, was obtained by labelling plaice with radioactive iodine and then feeding them to volunteers (Harrison *et al.*, 1965b). This iodine moreover is entirely in inorganic form; although in other iodine-containing foods part of the iodine may be present in other forms, it is probable that this iodine also is completely absorbed. Important losses of iodine may occur during cooking, however.

Under normal conditions absorption of dietary iodine is virtually complete, but impairment of absorption has been noted in some circumstances. In one patient with a total gastrectomy faecal iodine rose markedly after a fish meal, and in other patients after the same operation the level of inorganic iodine in the plasma was below normal despite an adequate intake (Harden & Adams, 1964) suggesting impaired absorption of iodine. In pancreatic steatorrhoea excessive losses of thyroxine in the faeces occur, which are corrected by treatment (Hiss & Dowling, 1962). A substance which interferes with the intestinal absorption of iodine is soya flour, used in artificial feeding mixtures for infants. Goitre and hypothyroidism have been described in babies fed on these formulae, which disappeared when the soya flour was withdrawn (Shepard *et al.*, 1960). If iodine is added to the soya flour goitre does not occur. Soya flour prevents the intestinal reabsorption of endogenous thyroxine and the absorption of ingested thyroid hormone, leading to high faecal iodine levels and iodine deficiency (Pinchera *et al.*, 1965).

Calcium has also been suggested as a factor interfering with the absorption of iodine, and Selwyn Taylor (1954) demonstrated its goitrogenic effect in rats receiving an iodine-deficient diet. To determine whether calcium affects the absorption of iodine in man we studied the effects of large doses of calcium, 3 g/day, on iodine balance in three volunteers, and found no evidence of impairment of intestinal absorption (Harrison, Harden & Alexander, 1967). Other studies in osteoporotic patients who had received therapy with calcium supplements for 1–2 years showed no evidence of a goitrogenic effect of calcium.

There is good evidence that the fate of organic compounds of iodine in the intestine is different from that of iodide. When *l*-thyroxine or *d*-thyroxine are administered orally a considerable fraction of the iodine, averaging 40%, appears in the faeces, as shown in Table 2. Similar

TABLE 2
Effect of orally-administered thyroxine on faecal iodine levels

	No. of balances	No. of individuals	Mean faecal iodine μg/day	Mean faecal iodine % intake
l-Thyroxine, 0·15 mg/day	5	1 (hypothyroid)	48	49
d-Thyroxine, 2·0 mg/day	13	2	555	40

results have been obtained when radioactive thyroxine was administered (van Middlesworth, 1960). It follows that only slightly more than half of the amount of thyroxine given to patients with hypothyroidism is available to them. This finding also suggests that the normal

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 multisystem 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