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Absorption, excretion and storage of trace elements: studies over 50 years

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Studies in the 1930s on the absorption and excretion of iron by adults with an excess of iron inside them showed conclusively that the amount of iron in the body is regulated, not by active excretion into the intestine as was believed at that time, but by controlled absorption. The same is true of manganese. One-week-old breast-fed infants excreted far more iron and manganese in their faeces than they took in the milk. Meconium also contains iron and manganese and it is suggested that the elements reach the intestine in the bile.

The urine normally contains very little zinc, but patients with albuminurea excrete larger amounts. The faeces of young infants contain more zinc than the milk; a loss of zinc from the body may continue for some months.

The kidneys control the amount of strontium in the body as they do of calcium. Young breast-fed infants did not retain strontium but formula-fed infants, with much higher intakes, retained 70%.

Silver and gold within the body were excreted only in traces. Lithium and boron were readily absorbed and excreted in the urine. The urine was the main route of excretion of vanadium, cobalt, nickel and tin.

INTRODUCTION

As life evolved 11 major elements and about 30 minor or trace elements became incorporated into animal bodies. Of the trace elements some, including copper, zinc, silicon, chromium, selenium, molybdenum, iodine, fluorine, manganese, iron and cobalt have known functions, while the others, lithium, rubidium, silver, gold, strontium, barium, beryllium, cadmium, mercury, boron, aluminium, tin, lead, vanadium, arsenic, bromine and nickel may have functions, or their presence may be merely fortuitous.

The chemical properties of elements must govern their biological behaviour to a certain extent, and elements with similar chemical properties tend to be absorbed and excreted in a similar way. However, physiological considerations also come in, and these apply particularly to transport, function and storage within the body.

Over the course of about fifty years the author has been involved in studies of the absorption and excretion by adults of 13 trace elements and, because of a general interest in infant physiology, the absorption and excretion of six trace elements by young infants have also been investigated. The results of these investigations form the main part of this paper, but mention will also be made of measurements of the storage of trace elements by the human fetus, and observations on growing animals.

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MAJOR TRACE ELEMENTS

Iron

Iron is the most plentiful trace element, it has received the most attention and it is the one with which the author began. In 1936 a patient, a Mrs H., aged 61, was admitted to King's College Hospital under Dr McCance's care. She was suffering from polycythemia rubra vera and she had a very high blood count and haemoglobin level. It was decided to treat her with acetylphenyl hydrazine, which breaks down red blood cells and was an acceptable treatment at that time. Her blood volume, and her intake and excretion of iron, before, during and after the 20 days while the treatment was in progress were measured (McCance & Widdowson, 1937*a*). We calculated that 6 g of iron

Table 1. Iron balances before, during and after treatment of polycythemia with acetylphenylhydrazine. 6000 mg iron set free in body during treatment (mg per day)

	Days	Intake	Excretion			Balance
			Urine	Faeces	Total	
Before	6	4·0	0·2	3·3	3·5	+0·5
During	14	4·0	1·7	4·2	5·9	−1·9
After	12	5·5	0·8	4·8	5·6	−0·1

were set free inside the body from the red cells, which is more than the total amount of iron in the body of an average man (Widdowson & Dickerson, 1964). To our surprise there was almost no increase in urinary or faecal iron (Table 1) and virtually the whole of the liberated iron remained within Mrs H.'s body.

This observation was followed by measuring the intake and excretion of iron before and while six normal adults (ourselves included) were receiving intravenously a ferric ammonium citrate preparation which provided 98 mg of iron in the 14 days of the experimental period (McCance & Widdowson, 1938). None of the injected iron was excreted (Table 2).

Up to that time, it was believed that the amount of iron in the body was regulated by active excretion into the intestine. Our observations led us to put forward the idea that it is controlled, not by excretion but by intestinal absorption (McCance & Widdowson, 1937*b*). If, therefore, for some reason the body has an excess of iron inside it there are no physiological means by which it can eliminate the iron. This theory has stood the test of time. We obtained further confirmation of it from a study of a patient with a haemolytic anaemia who was receiving repeated transfusions (McCance & Widdowson, 1943). She again excreted none of the superfluous iron. She was cured by the removal of her spleen. We analysed the spleen and found that it contained only a fraction of the iron that must have been stored in her body. It is well known that the liver has considerable capacity to store iron as ferritin and haemosiderin, and this was presumably where most of the unwanted iron was sequestered.

Young infants are rather different. The intake and excretion of iron by ten full-term breast-fed infants one week old were measured (Cavell & Widdowson, 1964) and it was found that they were all in negative iron

Table 2. Iron balances before and during the intravenous administration of iron (mean for six subjects—mg per day)

	Days	Intake			Excretion			Balance
		Food	By vein	Total	Urine	Faeces	Total	
Before	14	7·2	—	7·2	0·1	7·2	7·3	−0·1
During	14	9·7	7·0	16·7	0·2	9·6	9·8	+6·9

Table 3. Iron, manganese and copper balances of breast-fed infants one week old (mean for 10 infants—μg per kg per day)

	Intake	Excretion			Balance
		Urine	Faeces	Total	
Iron	100	2	1 122	1 124	−1 024
Manganese	2·02	0·07	10·86	10·93	−8·91
Copper	100	2	107	109	−9

balance. In fact the faeces contained ten times as much iron as the milk (Table 3), and the loss corresponded to 1% of the total body iron a day. This is clearly a temporary phenomenon and could not continue for long. It was suggested that the iron reached the intestine from the bile in a form which could not be reabsorbed. Adult bile normally contains very little iron (Hawkins & Hahn, 1944), and this is readily reabsorbed. Using a spectrographic method Sheldon and Ramage (1931, 1933) reported fetal bile to contain remarkably high concentrations of iron which is probably the source of the iron found in the meconium (Cavell & Widdowson, 1964). It seemed probable that this loss of iron in the bile continued for a short time after birth.

One of our interests in iron metabolism during infancy was suckling anaemia. Our first investigation was in 1947 when anaemia was a serious problem among piglets being suckled and reared in concrete pens. This could be prevented and cured by giving iron salts to the piglets but not by administering them to pregnant or lactating sows. We found that the body of a newborn piglet contained about 40 mg of iron (Venn *et al.*, 1947). It would have to retain 6 mg of iron a day to grow at a normal rate without becoming anaemic, but the milk of the sow only provides 1 mg. The administration of iron to piglets reared in a concrete pen during the first three weeks after birth made them take more milk and grow more rapidly; it also greatly increased the amount or iron in the blood, the liver and other tissues. Piglets reared outside, with free access to soil, had even more iron in their bodies at three weeks than those that had received iron salts. This was because the piglets ate soil, which contained 1·5% of iron.

This work was followed by a study of the iron intakes of other species during the suckling period (McCance & Widdowson, 1951). We found that the amount of iron in the bodies of mice, rats, rabbits and kittens rose during suckling, and that this iron came from the mother's milk. However, this was not sufficient to prevent a fall in the concentration of haemoglobin in the blood of these rapidly growing animals. The liver was unimportant as a source of iron for haemoglobin formation in all the species studied, including the human infant (Widdowson & Dickerson, 1964). In the newborn rabbit the liver was found to contain an unusually large amount of iron, but this iron was not withdrawn during suckling, and suckling rabbits also became anaemic.

It was concluded that species that are helpless at birth, and this includes the human infant, depend on their mother's milk for their iron supply. This is the time of life when growth is most rapid, and in no instance is the supply of iron sufficient for their bodies to maintain the concentration of iron that was present at birth. A fall in haemoglobin concentration is inevitable, and indeed can be considered a physiological phenomenon. Precocial newborn of species like the guinea-pig and pig, and probably also the sheep, cow and horse, that move around with their mothers, take in the iron they need from the soil and grass. It is only when they are prevented from doing so that anaemia becomes a serious problem.

Another observation made on iron in animals was on sex differences in its storage and metabolism (Widdowson & McCance, 1948). We found that with the onset of sexual development female rats accumulated iron in their livers at a much greater rate than did males. Removal of the gonads from male and female rats made the males store more and the females less iron in their livers, so that the concentrations were the same for the two sexes. Similar sex differences were found in guinea-pigs and rabbits. The livers of female rats became depleted of iron during pregnancy, and re-accumulation was rather slow.

Manganese

The absorption and excretion of manganese were found to be similar to those of iron in both adults and infants. The urine of adults contained only traces, and injected manganese was not excreted (Kent & McCance, 1941*a*). Infants one week old excreted far more manganese in their faeces than they took in in the breast milk (Table 3; Widdowson, 1969) and iron and manganese ran closely in parallel. An infant that excreted a particularly large amount of manganese also excreted a larger than average amount of iron. No evidence was found that manganese is stored in the fetal liver (Widdowson *et al.*, 1972).

Copper

More of the intake of copper is absorbed from the intestine than of iron or manganese. Some of the one-week-old breast-fed infants were in negative and some in positive copper balance. The mean faecal excretion of copper by ten infants was approximately equal to that in the milk, and the urine contained only very small amounts (Table 3; Cavell & Widdowson, 1964).

The storage of copper by the fetal liver had been of particular interest (Widdowson *et al.*, 1972). At term about half the copper in the body is in the liver (Widdowson *et al.*, 1974). Other investigators have shown that the livers of other species (rat, rabbit, guinea-pig, dog and pig) also have high concentrations of copper. Much of the copper in fetal liver is in the mitochondria as a copper-protein complex. This is peculiar to the fetus and contains much more copper than any other known protein complex. It begins to disappear soon after birth and the copper set free from it is presumably used for the needs of other tissues of the growing infant body.

Zinc

Zinc is the second most plentiful trace element in the animal body. There are three parts of the body that contain particularly high concentrations, the male reproductive organs, especially the prostate and sperm, the cells of the pancreas, and hair and wool. Our study of the absorption and excretion of zinc by normal adults (McCance & Widdowson, 1942*a*) showed that very little zinc was excreted in the urine and that the amount in the faeces was approximately equal to that in the food. After intravenous injection of a zinc salt there was no increase in urinary excretion, but some individuals increased their faecal excretion by a small amount, while others did not. In no instance was the whole of the injected zinc removed from the body over the period of observation. Since zinc salts will readily precipitate plasma proteins, most of the zinc in the plasma must be combined with protein. This explains why the urine contains so little zinc and why injecting zinc does not lead to an increase in urinary excretion. We studied some patients with albuminuria and found that they excreted about seven times the normal amount of zinc in their urine.

Studies on intake and excretion of zinc by young infants (Cavell & Widdowson, 1964) showed that, as for iron and manganese, the babies were in negative zinc balance, and the daily losses amounted to more than 1% of the total amount of zinc in the body (Table 4). This observation has been confirmed by others (Fomon, 1967), who have further shown that infants may continue to have a small negative zinc balance for some months.

Table 4. Zinc and cadmium balances of breast-fed infants one week old (mean for 10 infants—μg per kg per day)

	Intake	Excretion			Balance
		Urine	Faeces	Total	
Zinc	670	70	830	900	−230
Cadmium	3·65	1·01	1·91	2·92	+0·73

Cadmium

Although cadmium is in the same group in the Periodic Table as zinc its absorption and excretion by infants are different (Widdowson, 1969). Infants absorbed about half the cadmium in breast milk and most were in positive cadmium balance. About a third of the total amount excreted was in the urine.

Strontium

In the 1930's and 40's we were interested in the absorption and excretion of calcium and, because of its similarities in chemical properties, we decided to make some measurements of strontium (McCance & Widdowson, 1939*b*).

After a preliminary period, Professor McCance and the author injected into each other a solution of strontium lactate every day for five days. We found that the injected strontium was excreted almost completely by the kidneys. This was a similar result to that obtained previously for injected calcium (McCance & Widdowson, 1939*a*) and illustrates how elements with similar chemical properties are excreted in a similar way. However, this statement needs qualification.

In the 1960s there was concern about the presence of radioactive strontium 90 in the drinking water (Ministry of Housing and Local Government, 1965). Because ^{90}Sr will be treated by the body in the same way as stable strontium the metabolism of stable strontium acquired a more than academic interest. It was known that strontium was present in the skeleton at the time of birth (Bryant *et al.*, 1958) and that the ratio of strontium to calcium in the bones at six months was sometimes higher and sometime lower than the mean ratio at birth. The movement of calcium and strontium about the body depends on their relative rates of transmission across biological membranes. The Sr/Ca ratio is higher in the faeces than in the food which suggests that calcium is absorbed preferentially by the intestine. The renal clearance of calcium is three to five times higher than that of strontium, presumably because of preferential reabsorption of calcium by the tubules. Calcium is also preferentially secreted in milk. In the jargon of the day the body discriminates against strontium in favour of calcium. However, some strontium is absorbed and retained in the body and some is secreted in milk. Cows' milk contains six times as much strontium as breast milk and, if tap water is used to dilute a dried infant formula, this adds to the intake of strontium by formula-fed infants.

The intakes, excretions, absorptions and retentions of stable strontium by nine breast-fed and nine formula-fed infants one week old were measured (Widdowson *et al.*, 1960). Table 5 shows the results. The dried cows' milk formula, diluted with tap water as fed to the infants, contained 52·5 μg stable strontium per 100 ml compared with 6·9 μg per 100 ml for breast milk. The formula-fed infants, with their higher intakes, absorbed and retained far more strontium than the breast-fed infants, and in fact the breast-fed infants were losing the strontium that was in their bodies at the time of birth. Those breast-fed infants were in positive balance for other elements, including calcium and phosphorus. The results explain why the ratio of strontium to calcium in the bones at six months in some infants was higher and in others lower than the ratio at birth. However, a later study (Harrison *et al.*, 1965) on breast-fed infants aged six weeks showed that they were now retaining small amounts of strontium.

Table 5. Strontium balances of breast-fed and formula-fed infants (means μg per kg per day)

	No.	Intake	Excretion			Balance
			Urine	Faeces	Total	
Breast-fed						
1 week	9	8	14	14	28	−20
6 weeks	3	57	9	29	38	+19
Formula-fed						
1 week	9	72	2	19	21	+51

OTHER TRACE ELEMENTS

In the early 1940s, when we were making our prolonged metabolic balance studies to measure the absorption of calcium from different kinds of bread (McCance & Widdowson, 1942*b*) Dr N. L. Kent was one of our experimental subjects. He had access to a Hilger quartz spectrograph, and we used this opportunity to study the absorption and excretion of eight trace elements, silver, gold, lithium, boron, vanadium, cobalt, nickel and tin, about which at that time there was very little known. Some of the subjects were patients, others normal individuals, and the elements were introduced into their bodies either intravenously or by mouth (Kent & McCance, 1941*a*,*b*).

Silver

A woman who had been washing out her nose for many years with an organic silver preparation was the subject. She had absorbed silver into her body, and some of it was deposited in her skin. Her face and hands, exposed to light, reacted like a photographic plate; they became extremely pigmented and she had a grey metallic appearance. She excreted very little of the silver with which she was so saturated and it seemed likely that she would retain it for many years, if not for the rest of her life.

Gold

This used to be given therapeutically by injection for rheumatism. One woman, who had received 550 mg gold intramuscularly, excreted 16 mg over a two-week period, most of it in the urine.

Lithium

Soluble lithium salts taken by mouth by normal persons were rapidly and completely excreted in the urine, though lithium in foods seemed to be less well absorbed.

Boron

When taken by mouth as boric acid boron was rapidly absorbed and excreted in the urine. Boron in foods was much more readily absorbed than lithium.

Vanadium

This was studied because it was at one time used in the treatment of syphilis. Two normal men were given intravenous injections of sodium tetravanadate for six days. By the seventh day 81% of it was excreted in the urine and 9% in the faeces.

Cobalt

The urine was the main route of excretion of cobalt. The concentration of cobalt in fetal liver was measured (Widdowson *et al.*, 1972) and no evidence found of storage before birth.

Nickel and tin

More than half the amount of both metals in the food was absorbed and excreted in the urine. After daily intravenous injections of nickel chloride and 'Stannoxyl' for seven days the urinary excretion increased, and within seven days after the last injection 40% of the nickel and 60% of the tin had been eliminated.

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