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THE ABSORPTION AND EXCRETION OF IRON FOLLOWING ORAL AND INTRAVENOUS ADMINISTRATION

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FROM a study of the literature and from experimental work on patients and on normal persons McCance & Widdowson [1937] have suggested that the capacity of the body to excrete iron may be very much less than has generally been supposed. It may, in fact, be negligible. There is no dispute over urinary iron, which is agreed by all to be very small and almost constant in amount. The "new" theory differs from those currently accepted in that it postulates no regulatory excretion of iron by the intestine. Admittedly, traces must be derived from abraded cells and glandular secretions, but essentially the iron found in the faeces represents unabsorbed iron. The present paper records the results of further experiments planned to study whether or not the human intestine can excrete iron and by so doing regulate the amount of iron in the body. The investigation has been carried out on normal human adults and has consisted of three stages. In all a mixed diet with a fairly low iron content has been taken. In stage 1 the food constituted the sole source of iron. The subjects, as expected, were found to be in balance, and this was an essential preliminary finding. Current theories of iron metabolism would explain this by stating that measurable quantities of iron were being absorbed every day and that the subjects were maintained in iron equilibrium by a process of regulated or controlled excretion. If this were true, the fact that they were in balance showed that they were saturated with iron up to normal capacity. Consequently any increase in the quantity of iron in the body should have been followed by the excretion of a corresponding amount. The new theory would explain the facts by postulating that practically no iron was being absorbed or excreted as the metal passed through the intestinal tract. In stage 2 balance experiments were carried out with the intakes of iron raised 50–100 % by medicinal supplements. The object of this stage was to test the response of the subjects to a "physiological" increase of iron taken by mouth. Should they continue in balance, it was clear beforehand that either theory would be able to cover the results. Positive balances would be difficult to explain on current theories but easy to explain on the new theory (*vide infra*). In stage 3 balance experiments were carried out as before and iron was injected intravenously in amounts similar to those administered as medicinal supplements in stage 2. According to current theories iron so given to subjects in iron equilibrium should certainly have led to the excretion of the administered iron in the faeces. According to the new theory, however, the injected iron should have been retained.

Experimental organization

The subjects consisted of three women and three men. E. M. W., M. M. and M. H. L. were women aged respectively 30, 22 and 24. All were research workers in the department. They menstruated regularly and the experimental stages were arranged to fall into three successive intermenstrual periods. R. M. L., R. H. E. and R. A. M. were men aged 23, 23 and 39 respectively. The first two were medical students, the last a physician. All the subjects were in good health when the experiment began and remained so throughout.

Each stage consisted of 14 experimental days, of 2 or 3 preliminary days and of 1 or 2 concluding days. During the preliminary and concluding days the experimental diet was eaten but the food was not weighed. The experimental days were divided into two periods each of 7 days. The technique was almost exactly the same as that given by Widdowson & McCance [1937] for stages 1 and 3 of the investigation then being described. In this experiment, however, (1) the aliquot of wet faeces taken to be ashed was not always 30 g. but varied between 30 and 50 g., (2) after the ashed faeces had been treated with concentrated HCl the solution was merely taken to dryness on the sand bath and not heated for some hours. The iron administered by mouth during stage 2 was a ferric ammonium citrate preparation and was made up in solution with salts of magnesium, potassium and zinc, since a study of the way in which the body dealt with these metals was being carried out at the same time. The solution was measured out daily with a marked pipette and aliquots taken with the same pipette for analysis. The iron administered intravenously during stage 3 was also an ammonium citrate preparation obtained as a solution in ampoules from British Drug Houses, Ltd., and labelled "Injection of iron, B.P." It was administered in combination with calcium, magnesium and zinc in the following way. A sterile 20 c.c. syringe, fitted with a two-way attachment, was connected (*a*) to a reservoir of sterile saline, (*b*) to a piece of rubber tubing about 40 cm. in length. To the distal end of this the needle was connected by a piece of stout rubber tubing about 5 cm. long and a short piece of glass tubing. The whole system was filled with saline before the needle was inserted. When the needle was in the vein, the rubber tubing between the needle and the glass tubing was clamped off with a pair of Spencer Wells forceps about 4 cm. from the needle, and through this piece of rubber tubing four fine needles were inserted each connected directly to a syringe. Two of these syringes contained respectively calcium and magnesium gluconates, the third contained a solution of zinc chloride and the fourth the iron preparation of which 2 c.c. (=7 mg. of Fe) were administered daily. The contents of the four syringes were slowly injected, the whole process taking 30–45 min. With a little practice the subjects managed to do this for themselves. The plungers of the syringes were pressed gently and slowly in rotation, the pace being so regulated that all four syringes were emptied at about the same time. After the syringes had been emptied the clip on the tubing was removed and the injection material still in the tubing swept into the vein by a stream of saline. The investigations which have been made upon potassium, calcium, magnesium and zinc will form the basis of a separate paper.

Results and discussion

The balances of all six subjects during stage 1 are shown in Table I. In the 14 experimental days the iron intakes of the six subjects varied from

TABLE I. Iron balances on low iron intakes by mouth

Subject	Intake mg./14 days	Excretion (mg./14 days)			Balance
		Urine	Faeces	Total	
E. M. W.	93·3	1·6	86·9	88·5	+ 4·8
M. M.	87·0	1·1	94·0	95·1	− 8·1
M. H. L.	82·2	1·0	79·0	80·0	+ 2·2
R. M. L.	102·0	1·1	97·6	98·7	+ 3·3
R. H. E.	118·5	1·6	132·0	133·6	−15·1
R. A. M.	120·3	1·4	117·5	118·9	+ 1·4
Totals	603·3	7·8	607·0	614·8	−11·5

82·2 to 120·3 mg. (5·9–8·6 mg./day). These variations were due to appetite and individual food selection. The distribution of iron between the urine and faeces is characteristic of the way in which iron is excreted and requires no comment. On these intakes four subjects were in positive balance and two in negative balance. R.H.E., who showed the largest negative balance, was in iron equilibrium during the second 7 day period, and it is possible that his negative balance was due to an iron contamination or to an error in marking the faeces during the first 7 days. On the whole, however, the balances are close and the group results of −11·5 mg. on a total intake of 603·3 mg. is as near a balance as the experimental difficulties of this sort of work are likely to allow. These six persons therefore were concluded to be "in balance" on these intakes of iron and to be suitable for the investigation.

The balances of all the subjects during stage 2 are shown in Table II. It will be recalled that the object of this stage was to test the response of

TABLE II. Iron balances on higher iron intakes

Subject	Intake mg./14 days		Total intake mg./14 days	Excretion mg./14 days		Total excretion mg./14 days	Balance
	Food	Medicine		Urine	Faeces		
E. M. W.	94·4	82·8	177·2	2·3	167·2	169·5	+ 7·7
M. M.	99·2	82·8	182·0	0·9	185·0	185·9	− 3·9
M. H. L.	84·6	82·8	167·4	1·2	158·5	159·7	+ 7·7
R. M. L.	112·5	82·8	195·3	1·7	205·1	206·8	−11·5
R. H. E.	130·6	82·8	213·4	1·1	205·5	206·6	+ 6·8
R. A. M.	142·2	82·8	225·0	1·7	202·5	204·2	+20·8
Totals	663·5	496·8	1160·3	8·9	1123·8	1132·7	+27·6

persons in iron equilibrium to a moderate increase of iron taken by mouth. Accordingly, each person's intake was raised by 82·8 mg. in the 14 days. The food intakes were also slightly larger so that the total intakes ranged from 167·4 to 225 mg. in the fortnight (12–16 mg./day). On these intakes the output in the urine was not significantly changed. The output in the faeces rose with the intake by mouth and four subjects were found to be in positive and two in negative balance. One of the positive balances was relatively large and weighted the final result, but a group balance of +27·6 mg. on a total intake of 1160 mg. is probably within experimental error. It is evident therefore that these persons were sensitive to physiological variations of intake and responded by raising their rates of excretion to approximately the same extent. Current theories would explain this by laying the burden of the regulation on the mucosa of the intestinal tract, but the new theory by stating that only minute amounts of iron were absorbed either on the low or the raised intake.

It is known that if the intake of iron by mouth is sufficiently high, people tend to go into positive balance [Brock & Hunter, 1937; Fowler & Barer, 1937; Hutchison, 1937]. This would hitherto have been explained by supposing that excretion was not able to keep pace with absorption, but Widdowson & McCance [1937] have shown that the absorbed iron is not excreted after the intake is restored to normal. The new theory supposes that the amount of iron in the body is regulated by the amount absorbed and this in turn is regulated among other things by the amount taken by mouth. Hence positive balances on high intakes are simply explained. The small positive balance of the group of six subjects in stage 2 may be an indication of positive balances due to raising the intake, but it is impossible to say whether this is so or not.

The results of administering the supplementary iron by intravenous injection are shown in Table III. The amount of iron in the food was again

TABLE III. Iron balances during the intravenous administration of iron

	Intake (mg./14 days)		Excretion (mg./14 days)			Balance including injected iron	Balance neglecting injected iron
Subject	Food	Intra-venous	Urine	Faeces	Total		
E. M. W.	115·6	98	3·0	111·0	114·0	+ 99·6	+1·6
M. M.	106·2	98	2·3	104·3	106·6	+ 97·6	−0·4
M. H. L.	107·2	98	2·8	107·5	110·3	+ 94·9	−3·1
R. M. L.	160·5	98	3·1	166·0	169·1	+ 89·4	−8·6
R. H. E.	164·5	98	2·0	160·0	162·0	+100·5	+2·5
R. A. M.	151·6	98	3·4	153·8	157·2	+ 92·4	−5·6
Totals	805·6	588	16·6	802·6	819·2	+574·4	−13·6
Correcting for the extra excretion in the urine						+583·2	−4·8

a little higher and ranged from 106·2 to 164·5 mg. in the 14 days (7·6–11·7 mg./day). In addition to this, 98 mg. in all were administered to each subject intravenously (7 mg./day). Turning to the output it will be noted that the urinary iron was higher in each subject during this stage and that the total quantity in the urine was about twice what it had been in stages 1 and 2. This is not surprising, since it has been known for a long time [Jacobi, 1891; Henriques & Roland, 1928] that if iron is administered intravenously, some of it tends to find its way into the urine. The amount of iron so excreted, however, in this experiment was about 1·4 p.c. of the amount injected and it is almost certainly of no practical importance, since no extra iron is excreted by this route when large doses of iron are taken by mouth and large quantities of iron are being absorbed. This excretion therefore probably takes place while the injection is actually being made and before the injected iron has been removed from the plasma. The amount of iron in the faeces was in all subjects close to the amount in the food. This discovery was the culminating point of the whole experiment. Actually, if the injected iron is neglected altogether, two of the subjects were in slight positive balance and four in slight negative balance. The group balance of −13·6 mg. on an intake by mouth of 806 mg. is well within experimental error, and even this negative balance is subject to a correction for the extra iron found in the urine. Making this correction by using the figure for urinary iron found in stage 1 the group balance becomes −4·8 mg. It may be concluded, therefore, that *none* of the injected iron was excreted by the gastro-intestinal tract. Since the subjects were known to be in iron equilibrium beforehand and fully saturated with iron up to normal capacity, the injected iron should have been excreted into the gut in reasonably large amounts if the gut plays any real part in regulating the amount of iron in the body. The present results are entirely in agreement with the new theory according to which the capacity of the body to excrete iron is strictly limited and probably negligible.

Implications and conclusion

These experiments raise a number of interesting points. In the first place it is curious that the three normal women were not in positive iron balance in their intermenstrual periods. Assuming these women to lose 20 mg. of iron/month [Ohlson & Daum, 1935; Barer & Fowler, 1936] they might be expected to absorb 10 mg./fortnight to make good this loss, i.e. 60 mg. between them in stages 1 and 2. In these two stages, however, their joint positive balance was only 10·4 mg. It would be interesting to know at what time during the menstrual cycle these women absorbed the iron necessary to make good their loss. In the second place, now that it has been shown that the intestine does not excrete iron, is it wise to adhere without question to the belief that it regulates by excretion the amount of calcium or magnesium in the body, or indeed the amounts of any of the physiological or non-physiological metals? It would be premature at the moment to go into this interesting possibility, but the matter is being investigated. Should it be proved that the gut does not excrete these metals, work on the metabolism of the divalent metals will be immensely facilitated.

Summary

1. In the first stage of this experiment three men and three women were placed upon diets containing 5·9–8·6 mg. of iron/day and shown to be in balance.

2. In the second stage the oral intakes were raised to 12–16 mg. of iron/day and the subjects were again shown to be in balance, i.e. all the supplementary iron was excreted.

3. In the third stage 7 mg. of iron were injected intravenously every day into the same subjects, whose intakes by mouth now ranged from 7·6 to 11·7 mg./day. Within the limits of experimental error none of the injected iron was excreted into the gastro-intestinal tract. About 1·4 p.c. of it was excreted in the urine, but reasons are given for believing that this is of no practical significance in iron metabolism.

4. These results are considered to confirm the theory that the intestine has no power of regulating by excretion the amount of iron in the body.

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