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SEASONAL AND ANNUAL CHANGES IN THE CALCIUM METABOLISM OF MAN

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Variations in the capacity of an individual to absorb Ca have been recorded and commented upon by previous investigators. Those who have interested themselves in the development and mineral metabolism of children have drawn attention to their waves of growth and pointed out that these will almost certainly be accompanied by waves of Ca retention, and possibly of Ca absorption [Nicholls & Nimalasuriya, 1939]. On the pathological side, rickets, tetany and osteomalacia have often been noted to be at their worst in the late spring, and for some twenty years this seasonal incidence has been attributed to the paucity of sunlight during the winter months. This, it has been supposed, led to the formation of so little vitamin D in the skin that the clinical signs of deficiency made their appearance or became more obvious, and from what is known of the effects of vitamin D these would certainly have been accompanied if not initiated by a lowered absorption of Ca from the gut.

Some people, who have studied mineral metabolism by means of balance experiments, have noticed that the amounts of Ca (or of Fe) absorbed might vary considerably from one analytical period to the next [Ascham, 1930–1; Nicholls & Nimalasuriya, 1939; Hutchison, 1937]. These 'paper' variations have generally been attributed to real changes in the biological activity of the gut. A proportion of them, however, have certainly been due to the fact that the analytical periods were too short to allow the faecal matter of one to be properly separated from that of the next. Variations of this kind may occur, but their reality is still very much obscured by technical uncertainties.

In the course of some investigations, which were originally undertaken for another reason, large seasonal variations in the absorption of Ca have been observed in certain individuals. Changes from one year to another have also been detected. Both these belong to types hitherto undescribed, and an account of their discovery and nature forms the substance of this article.

The setting of the observations

Early in July 1940, eight persons began a study of the effect of brown bread on Ca absorption and the effect of fortifying bread with Ca and diets with vitamin D. The experiments went on almost without a break till the latter end of March 1941, and they were restarted, with some of the original party, in August 1941. The seasonal changes were first noticed in November 1940 when some of the subjects were found to be absorbing dietary Ca less freely than they had done in July. By the end of March 1941 it was clear that the Ca metabolism of three of the original subjects had changed very much since they had first come under observation. Of the others, two had apparently shown no change and one an uncertain one. No statement could be made about two, who had left the party in September to take up work in Palestine, for they had not been under observation for long enough, or about their substitutes, for the arrangements demanded by the main experiments prevented the necessary comparisons being made on them. It may be said, therefore, that the seasonal changes presently to be described have been observed in three out of a possible six people. When this type of work was restarted in August 1941, it was found that the Ca metabolism of the five subjects who had taken part in the experiments in 1940 had altered appreciably since the previous summer. These annual changes, which were all of the same type and in the same direction, were demonstrable in every subject for whom the necessary (1940) data were available.

Experimental methods

Minerals have been determined in the food and in the excreta, and throughout this paper the term 'absorption' should be taken to mean the amount in the food minus the amount in the faeces. The 'balances' may be calculated from the presented data but only the absorptions will be discussed. A full description of the way in which these experiments were carried out, and of the subjects who took part in them, have been published [McCance & Widdowson, 1942*a*, *b*]. It is only necessary to state here that flour, either white or brown, always contributed 40–50% of each person's total calories, and that the rest of the diet was freely chosen, but very similar from one experiment to the next. Most of the figures given in this paper are the results of three-week experiments, so that short-term variations and errors in faecal collection have been minimized or ruled out. Some are based upon two-week experiments and a very few on experiments which only lasted for eight days. At each season the absorption and excretion have been studied both on white bread and on brown, so that the whole series of results may be regarded as having been obtained in duplicate.

THE SEASONAL CHANGE

This effect has been observed in one man, R.M., and in two women, E.W. and B.A. The last was not under observation for quite such a long time as the other two. R.M.'s results are shown graphically in Fig. 1 and E.W.'s in Table 1. The 'negative' absorptions are an expression of the fact that the faeces sometimes had more Ca in them than the corresponding food had had.

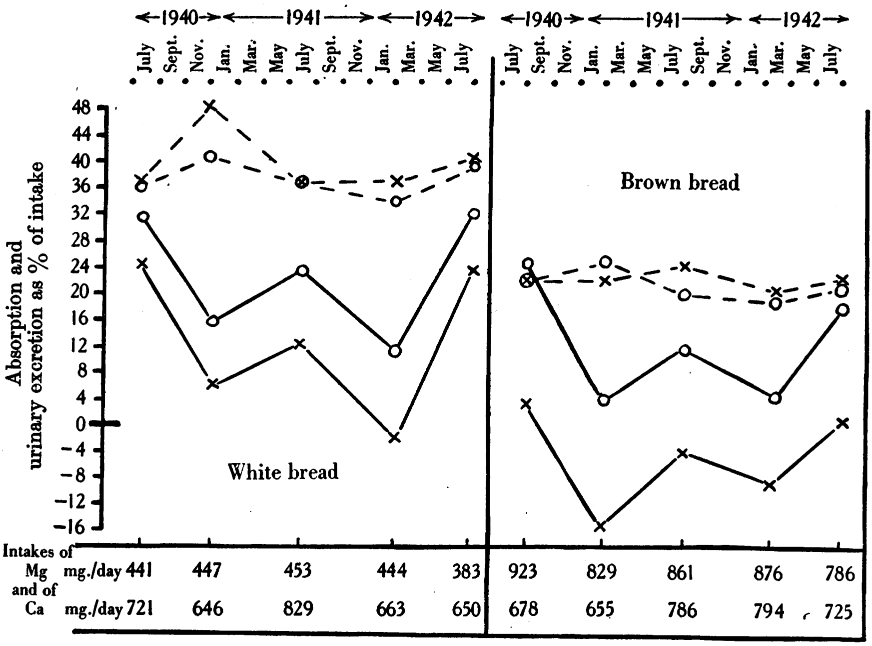

Fig. 1. R.M.'s absorption and urinary excretion of calcium and magnesium at different seasons from 1940 to 1942.

× ——— × Ca absorption. × - - - × Mg absorption.
o ——— o urinary Ca. o - - - o urinary Mg.

It will be noted that both subjects were under observation for three summers and two winters, and that throughout this time they both reacted to the seasons in precisely the same way. They absorbed Ca much more freely in July and August than they did in February and March, and the magnitudes of the differences were most striking. The seasonal effect was as clearly shown on brown bread as on white, but at any one season the absorptions were always lower on the former. Indeed, the results afford very pretty confirmation of the fact that brown bread inhibits the absorption of Ca [McCance & Widdowson, 1942 *a*, *b*]. It is interesting to point out in this connexion that the absorptions from the white bread diets became so bad in February 1942 that they were worse than the absorptions had been from the brown bread diets in August 1940.

The Mg absorptions were not affected by the seasons and showed a constancy from one experiment to the next which was really quite remarkable. R.M.'s absorptions from brown bread diets illustrate this well. Although unaffected by the seasons, the Mg absorptions were of course affected by the degree to which the flour had been milled [McCance & Widdowson, 1942 *a*, *b*].

TABLE 1. The absorption and urinary excretion of calcium and magnesium by E.W. between 1940 and 1942

		Calcium			Magnesium		
Type of diet	Date	Intake mg./day	Absorption % of intake	Urine % of intake	Intake mg./day	Absorption % of intake	Urine % of intake
White bread	July 1940	450	26	27	299	39	35
	Dec. 1940 Jan. 1941	515	6	17	323	43	39
	July 1941	600	17	25	346	28	28
	Feb. 1942	535	7	15	323	44	37
	July 1942	590	29	30	305	41	39
Brown bread	Aug. 1940	550	9	18	720	22	20
	Feb. 1941	517	−6	8	552	20	22
	Aug. 1941	600	5	12	600	19	19
	Mar. 1942	625	0	9	635	21	19
	Aug. 1942	620	16	15	595	22	18

Table 1 and Fig. 1 also uphold the views which were put forward by McCance and Widdowson [1942 *c*], and which concern the relationship of the Ca and Mg excreted by the kidney to the amounts of these minerals absorbed from the gut. An increase in Ca absorption was regularly accompanied by a rise in the urinary excretion and vice versa. E.W. was frequently and R.M. invariably in negative Ca balance on these diets: both subjects were consistently in Mg balance, or nearly so.

THE ANNUAL CHANGES

If Fig. 1 and Table 1 are examined once more it will be seen that both R.M. and E.W. absorbed Ca better in the summers of 1940 and of 1942 than they did in that of 1941. This statement is true whether the comparison is made

TABLE 2. Annual changes in the absorption and excretion of calcium

	White bread			Brown bread		
Subject and year	Intake mg./day	Absorption % of intake	Urine % of intake	Intake mg./day	Absorption % of intake	Urine % of intake
E. B. 1940	500	61	53	530	32	34
1941	477	41	47	550	16	28
A. M. 1940	—	—	—	516	14	19
1941	—	—	—	556	1	11
B. A. 1940	381	32	34	497	9	24
1941	493	22	25	517	9	11

when white bread or brown formed the basis of the diets. Table 2 summarizes the data of three other persons whose metabolism was studied in 1940 and in 1941. It will be noted that they also absorbed Ca better in 1940 than they did in 1941. B.A.'s results on brown bread should not be regarded as an exception. Her 1941 experiment was one of the very few which only lasted for 8 days, and consequently her absorption was less accurately measured than usual. Her urinary output was very much lower at that time than it had been on the same diet the year before. 1941 was evidently a worse year for Ca absorption than 1940, and R.M.'s and E.W.'s extension of these experiments suggests that 1942 was a better year than 1941 and as good as 1940. The Mg absorptions were equally good in 1940 and 1941 (see Fig. 1), and the Mg figures for E.B., B.A. and A.M. have not been given.

The absorption of phosphorus

The absorption and excretion of P have been followed in parallel with those of Ca and Mg, but no changes, either annual or seasonal, have been detected, and the figures have not been given.

Discussion

Before discussing the cause and consequences of these variations in people's ability to absorb Ca, it is essential to establish the fact of their biological reality. People unfamiliar with the accuracy with which this sort of experiment can be carried out, or unaccustomed to the almost clock-like regularity of a single person's metabolism under standardized conditions, may be inclined to dismiss them as the product of chance irregularities in the subject's behaviour or even of technical errors. The authors are satisfied as to the biological reality of the variations for the following reasons: (1) Their magnitude. The differences between the absorptions of R.M. and E.W. in the summer of 1940 and the spring of 1941 were quite outside any possible error in faecal collection or method of analysis. The annual changes were not so large as the seasonal ones, but every subject showed them and they could not have been technical in origin. (2) The confirmatory variations in the urinary Ca [McCance & Widdowson, 1942 *c*], to which reference has already been made. (3) The constancy of the Mg absorptions and urinary excretions. These acted as a check on the collections and general technique and showed up the fluctuations in Ca metabolism by providing the contrast of their own stability. (4) The duplication of the whole set of results at two levels of Ca absorption. This was the object of continuing to study the absorptions on both white and brown bread, and, looking back, the extra work would seem to have been well repaid.

The causes of these variations must next be considered. When the seasonal effects were first observed, it was thought that they were probably due to changes in the amount of vitamin D in the food or in the amount formed by the sun in the skin. This was a natural hypothesis to adopt in the light of current ideas, and the one which Havard & Reay [1925] put forward to account for the seasonal changes in the inorganic P of the serum, first observed in children by Hess & Lundagen [1922]. Accordingly, when the brown bread experiment of February 1941 was over, the diets were not relaxed and 2000 i.u. of vitamin D were administered daily to B.A., E.W. and R.M. for seven preliminary and twenty-one experimental days. The drug was given in the form of calciferol dissolved in arachis oil [McCance & Widdowson, 1942 *a*]. The effect of vitamin D on the Ca absorptions and excretions are shown in Table 3.

TABLE 3. Effect of vitamin D on the absorption and urinary excretion of calcium

	Control period Feb. 1941			Vitamin period March 1941		
Subject	Intake mg./day	Absorption % of intake	Urine % of intake	Intake mg./day	Absorption % of intake	Urine % of intake
B. A.	500	3	15	501	1	9
R. M.	655	-15	4	700	-8	4
E. W.	517	- 6	8	522	8	9

Had D acted potently, as one might have expected it to do, the absorptions certainly, and also to some extent the urinary excretions, should have increased. As it was E. W.'s absorptions improved, R. M.'s also increased a little, but there were no appreciable changes in their urinary excretions. B. A.'s absorption fell very slightly and her urinary excretion more definitely. Since it is unlikely that these three adults were deriving so much as 2000 i.u. of D per day from their summer food or from the limited amounts of sunlight to which they were able to expose themselves in the warm weather, these findings made it impossible to maintain the view that a deficiency of vitamin D was the cause of the poor winter absorptions and low urinary excretions.

It was next supposed that the variations might not be seasonal in origin but that high cereal diets taken over a long period of time—eight or nine months in this instance—might depress the absorption of Ca. This has been excluded by the passage of time, for since March 1941 E. W. has eaten very little bread except during the metabolism experiments and R. M. practically none.

Any theory as to the origin of these changes must take account of the facts that: (1) All the five subjects absorbed Ca better in 1940 than they did in 1941, but only three of the five were affected by the passage from summer to winter. Hence one must suppose that the annual and seasonal fluctuations had different metabolic origins. (2) The Mg absorptions did not change. This is important, for it excludes non-specific changes in the membranes lining the alimentary canal. The only substance known at present which influences Ca but not Mg absorption is vitamin D, and although variations in the supply of this vitamin do not seem to have been responsible for the changes which have been observed, it is tempting to try to explain all of them in terms of vitamin D. This can be done if one supposes that they were caused by variations in the resistance or in the responsiveness of these adults to the vitamin D already in the body or taken with the food. This is a reasonable hypothesis. It covers all the present observations and fits the known facts about the Ca and vitamin D metabolism of adults. Healthy men and women, who are not in need of D, are very resistant to it. This must be so, for otherwise it would not be necessary to give such enormous doses to make their Ca metabolisms alter in the characteristic way. Furthermore, children are known who respond very sluggishly to vitamin D, and there is a form of rickets which can only be cured by colossal doses. It has been shown that children with this disease absorb the vitamin [Bakwin, Bodansky & Schorr, 1940], so that in them tissue resistance is a proven fact, and one may compare it with the better known resistance to insulin, which may develop in certain diabetics. It is suggested, therefore, that both the annual and seasonal variations in the ability of these adults to absorb Ca were primarily and directly due to variations in their responsiveness to the vitamin D available to them, but that these variations in responsiveness were due to unknown and probably different metabolic origins. If an adult's responsiveness to vitamin D does alter from one time of year to another it might be possible to demonstrate that persons, whose Ca absorptions exhibited seasonal variations, were more easily affected by administered vitamin D in the summer than they were in the winter. If the response to D does vary from one year to another and from one season to another, why it does so becomes the problem, and at present there appear to be no clues at all. Seasonal changes in avian Ca metabolism are well known and might be helpful, but man is a much less seasonal animal and has a very different metabolism. Some progress might be made if these annual and seasonal phenomena were to be studied simultaneously by observers in Europe, North America, South Africa and Australia, but this would require considerable organization.

The significance of these observations seems to be twofold—practical and theoretical. From the purely practical point of view, all those interested in human Ca metabolism should be alive to the possibility of having their experiments vitiated or upset by fluctuating Ca absorptions. If the studies are to continue over a period of months, it may be necessary to run two or even more control experiments, and it is obvious that changes of the kind just described might greatly interfere with an attempt to study the effect of pregnancy on Ca metabolism. It must be remembered also that only certain persons can be expected to show seasonal instability, and at present there is no way of predicting whether any given individual is likely to do so or not. Furthermore, although 1941 was demonstrably a worse summer for Ca absorption than 1940 or 1942, it is impossible to give any estimate at present of the size of variation to be expected from any one year to the next. Theoretically these results are stimulating if not at present very constructive. The fluctuations in Ca absorption appear to be due to some factor or factors in Ca metabolism hitherto undescribed and which will ultimately have to be defined and characterized. If seasonal variations in a person's responsiveness to D should be substantiated by future findings, some similar phenomenon may very well turn out to underlie the more or less permanent differences which two perfectly normal people may exhibit in their ability to absorb Ca. The more one considers these personal differences, the more interesting they appear to be, and it is odd that they should have attracted so little attention. It is certain that the Mg absorptions are not subject to the same control—whatever it may be [McCance & Widdowson, 1942 *a*, *b*].

Summary

1. Large seasonal variations in Ca absorption have been demonstrated in three out of six people who were taking part in a metabolism experiment. Least Ca was absorbed in February and March; most in July and August.

2. All persons—five in number—who were under observation in the successive summers and autumns of 1940 and 1941, absorbed Ca more freely in the former year.

3. All changes in absorption were accompanied by corresponding changes in urinary excretion.

4. The Mg absorptions and urinary excretions did not fluctuate in the same way and remained very constant over the whole period of investigation.

5. The administration of 2000 i.u. of vitamin D in March 1941 did not materially improve the absorption or urinary excretions of Ca.

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REFERENCES

Ascham, L. [1930–1]. *J. Nutrit.* **3**, 411.
Bakwin, H., Bodansky, O. & Schorr, R. [1940]. *Amer. J. Dis. Child.* **59**, 560.
Havard, R. E. & Reay, G. A. [1925]. *Biochem. J.* **19**, 882.
Hess, A. F. & Lundagen, M. A. [1922]. *Proc. Soc. exp. Biol., N.Y.*, **19**, 380.
Hutchison, J. H. [1937]. *Arch. Dis. Child.* **12**, 305.
McCance, R. A. & Widdowson, E. M. [1942*a*]. *J. Physiol.* **101**, 44.
McCance, R. A. & Widdowson, E. M. [1942*b*]. *J. Physiol.* **101**, 304.
McCance, R. A. & Widdowson, E. M. [1942*c*]. *J. Physiol.* **101**, 350.
Nicholls, L. & Nimalasuriya, A. [1939]. *J. Nutrit.* **18**, 563.