EFFECTS OF EXCESS OF CALCIUM ON
THE SKELETON.

BY

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In my previous communications (1921-22) I determined the influence of a normal diet (N diet) or a diet deficient in fat-soluble factor (-A diet) upon the composition and structure of the skeleton of rats. These diets contained 0.25 to 0.26 per cent. Ca (about 0.4 per cent. in air-dry diet). This amount of calcium was acknowledged to be sufficient but not excessive, being rather near to the border-line of the physiological requirements of the organism.

There is a form of rickets induced solely by a deficiency of calcium in the diet—"rickets from calcium starvation." This is completely cured by the addition of calcium salts to the diet. Other forms of rickets develop on diets containing a sufficient amount of calcium, and the ingestion of even excessive amounts of lime salts is not usually followed by a complete cure. In Orgler's (1911) opinion the increased introduction of calcium is useless, as the capacity to deposit calcium in the bones is lost during the active stage of the disease. Grosser (1920), however, found that considerable retention occurred in rickety children when the calcium was introduced subcutaneously in the form of a glycerophosphate.

The question is, to which of these two groups of rickets do the affections of the skeleton, obtained by me (1921-22) in rats by means of -A diet, belong? It is also an interesting question whether, and to what extent, it is possible to increase the calcium content of the skeleton of a normal animal kept on the normal (N) diet used by me by the ingestion of large quantities of calcium.

For the purpose of solving these questions I conducted seven experiments. They were conducted on 39 rats, belonging to seven litters. The technique of the experiments was, on the whole, similar to that used by me in my previous experiments. The rats were fed on the same basal diets: (1) normal (N), containing a liberal amount of fat-soluble factor; (2) deficient in this factor (-A). The different conditions introduced into the present experiments, and clearly seen from Table I, were as follows: (1) In diets N 2, N 3, -A 2, -A 3, the amount of calcium was increased by the addition of CaCO_3 , and (2) the normal diet of some rats contained as the source of fat-soluble factor butter only, without any cod-liver oil (N B).

TABLE I.

Diet.	Percentage of Fat in Fresh Diet.	Amount of Calcium in Fresh Paste.	Amount of Calcium in Air-dry Diet.
NB	11 per cent. butter	Per cent. 0.26	Per cent. 0.4
N 1	8 per cent. butter + 2 per cent. cod-liver oil	0.25	0.4
N 2	Ditto	0.52	0.8
N 3	Ditto	0.77	1.18
-A 1	10 per cent. cottonseed oil (no fat-soluble factor)	0.26	0.4
-A 2	Ditto	0.52	0.8
-A 3	Ditto	0.77	1.18

In all of the above diets about 0.5-0.51 per cent. phosphorus was present in fresh paste and about 0.77 per cent. phosphorus in the air-dry diet. The amount of calcium in the different diets was determined by McCrudden's method, that of phosphorus by A. Neumann's method. Shipley, Park, McCollum, Simmonds, and Kinney (1922) consider the optimum calcium content in air-dry diet about 0.67 per cent.; in their opinion, about 0.4 per cent. phosphorus represents the minimal content on which optimal development can take place. For comparison with the figures of these authors, my figures in Table I, "in air-dry diet," should be used.

Details of the experiments are shown in Tables II to V. The average consumption of food per diem by the different litters of rats was as follows:

	NB.	N 1.	N 2.	N 3.	-A 1.	-A 2.	-A 3.
Litter 638 ...	grm. 17	grm. 17.5	grm. 20	grm. 20	grm. 11.5	grm. 13	grm. 14
Litter 640 ...	24	18	16	15	10	12	11
Litters A, B, C ...	15	18	16	15	10	12	11
Litter 689 ...	—	—	—	—	—	—	6-7
Litter of rats 701-705 ...	—	—	—	—	11.5	13	14

In some cases it was observed that the average consumption was greater when the food contained a greater amount of calcium.

Results of Chemical Investigation.

An examination of the figures in Tables II to VI shows the following:

TABLE II.

Changes in the skeleton of two litters (638 and 640) of rats kept on normal diets. Litters 638 and 640 aged at the beginning of diet 39 and 49 days respectively; final age, 101 and 110 days; duration of feeding, 61 days.

No. of Rat.	Diet.	In Dry Bone.	No. of Rat.	Diet.	In Dry Bone.
638 A...	N 1	Ca % 22.0	638 D...	N 2	Ca % 23.5
638 B...	"	22.8	638 E...	"	23.7
640 A...	"	22.3	638 H...	"	22.8
Average ..		22.4	640 B...	"	22.0
638 G...	N 3	23.6	Average ...		23.0
638 K...	"	22.8			
Average ...		23.2			

TABLE III.

Changes in the skeleton of three litters (A, B, and C) of rats kept on normal diets. Litters A, B, and C when put on diets, aged 22, 24, and 26 days respectively; final age—82, 84, and 86 days; duration of feeding—60 days.

No. of Rat.	Diet.	In Dry Bone.	No. of Rat.	Diet.	In Dry Bone.
668 A...	NB	Ca % 21.3	666 A...	N 2	Ca % 21.2
675 B...	"	21.3	673 B...	"	21.4
682 C...	"	21.3	680 C...	"	21.6
Average ...		21.3	Average ...		21.4
655 A...	N 1	21.2	667 A...	N 3	22.6
672 B...	"	21.4	674 B...	"	21.4
686 C...	"	21.7	681 C...	"	22.5
Average ...		21.4	Average ...		22.2

TABLE IV.

Changes in the skeleton of rats taken from the same three litters, shown in Table No. 3 but kept on -A diet.

No. of Rat.	Diet.	In Dry Bone.	No. of Rat.	Diet.	In Dry Bone.
669 A...	-A 1	Ca % 11.2	671 A...	-A 3	Ca % 18.1
676 B...	"	15.8	678 B...	"	14.2
683 C...	"	14.8	685 C...	"	15.5
Average ...		13.9	Average ...		15.9
670 A...	-A 2	16.7			
677 B...	"	17.7			
684 C...	"	15.3			
Average ...		16.6			

TABLE V.

Changes in the skeleton of rats 701-705, kept on -A diet. Litter, when put on diet, aged 27 days; final age, 65 days. Duration of feeding, 49 days.

No. of Rat.	Diet.	In Dry Bone.	No. of Rat.	Diet.	In Dry Bone.
Normal rats of same age	N 1	Ca % 20.5	703	-A 2	Ca % 18.7
701	-A 1	16.9	704	-A 2	17.7
702	-A 1	16.9	Average		18.2
Average ...		16.9	705	-A 3	17.5

TABLE VI.

Changes in the skeleton of litter 689 of rats kept on -A 3 diet. Litter 689, when put on -A 3 diet, aged 24 days; final age, 65 days; duration of feeding, 41 days. Mother kept on the same diet -A 3 during lactation.

No. of Rat.	Diet.	In Dry Bone.
Normal rats of the same age ...	N 1	Ca % 20.4
689 C	-A 3	13.2
" D	"	14.2
" E	"	12.5
" F	"	12.8
Average		13.2

Normal Diet NB, without Cod-liver Oil.—As is seen from Table III, when butter alone was used as a fat-soluble factor in the diet, and when the calcium content in fresh diet reached about 0.26 per cent., the calcification of the skeleton did not differ from that in rats fed on the same diet but with cod-liver oil substituted for part of the butter ration. The result was the same even when the calcium content in the latter diet was doubled (N 2 diet, see Table III). That is to say, some samples of butter, even when bought in winter, may contain such an amount of the antirachitic principle that even the addition of cod-liver oil to the diet does not increase the calcification of the skeleton.

Normal Diets, N 1, N 2, and N 3, with Cod-liver Oil (Tables II and III).—In these normal diets, containing butter and cod-liver oil as sources of the fat-soluble factor, the increase to double (N 2) or treble the amount (N 3) resulted either in no increase whatever in the calcium content of the skeleton, or in the calcification of the latter being increased very slightly (within the limits of physiological fluctuations).

Diets Deficient in the Fat-soluble Factor.—Among all the rats fed on such diets there was not a single case where the increase of calcium from 0.4 per cent. (in air-dry diet) to 0.8 per cent. (-A 2 diet), and even to about 1.2 per cent. (-A 3 diet), could restore the calcium content of the skeleton to the normal.

A great increase of calcium in the skeleton, in connexion with its increased content in the diet, was observed only in one litter (A, Table IV); but even in this case, as compared with the corresponding normal rat 667 A, in rat 671 A (on -A 3 diet) the calcium content of the skeleton was 27 per cent. less in fresh bone and 16 per cent. in dry. I came across a similar decrease in the calcification of the skeleton of rats kept on -A diet in other experiments (Korenchevsky, 1922, 3, p. 83). In another rat (670 A) from the same litter A, the calcium deficiency in the skeleton as compared with the normal rat 666 A was still more marked, being 31 per cent. (fresh bone) and 21 per cent. (dry bone). Besides this, in connexion with litter A it is necessary to mention the following. This litter was obtained from a dealer, and not reared in the Lister Institute, as was usually the case in my experiments. The diet of the mother rat during lactation, and of the young until weaned, was deficient in calcium (kitchen refuse, bread). This would explain the low calcium content of the skeleton of rat 669 (Table IV) of this litter on -A diet, such as I have never observed in rats fed on a normal diet during lactation, and which occurs only when the mother's diet during lactation is deficient in calcium or fat-soluble factor (Korenchevsky, 1922, C). In that case it is quite comprehensible that the ingestion of larger quantities of calcium caused a more rapid increase in the calcium content of the skeleton to the level

observed in rats on -A diet. The special experiment conducted by me and described elsewhere (1922, C, pp. 105-108) shows this very clearly.

In the case of four rats (677, 678, 684, 685) of litters B and C (Table IV), with an increased amount of calcium in the diet -A 2 and -A 3, the fluctuations of the calcium content in the skeleton kept within limits frequently observed in different rats of the same litter. For instance, in rat 678 on -A 3—that is, with the greatest amount of calcium—the calcium content in the skeleton was lower than that of rats 676 and 677 of the same litter, fed on -A 1 and -A 2 diets respectively.

In litter of rats 701 to 705 (Table V) there was slight increase in the calcium content of the skeleton of rats kept on -A 2 and -A 3 diets as compared with that of rats kept on -A 1 diet. These rats were born from a rat kept during pregnancy and lactation on a diet rich in fat-soluble factor. Therefore, owing to a congenital store of fat-soluble factor in their bodies they continued to grow fairly well, notwithstanding -A diet during the experiment. On autopsy they were found to be fat, well nourished, and with no signs of any macroscopical lesions in the skeleton. It is possible to suggest that some amount of fat-soluble factor, stored in the body of these rats, had enabled them to assimilate a larger, *although not normal*, amount of calcium when fed on diets containing an excess of calcium.

In contrast to this experiment was a cross experiment with litter 689 (Table VI) in whom the storage of fat-soluble factor was reduced to a minimum by feeding their mother rat during lactation on diet deficient in this factor, although rich in calcium (-A 3 diet). Notwithstanding the presence of an excess of calcium in diet -A 3 the calcium content of the skeleton of litter 689 was strikingly decreased (about 50 per cent. in fresh bone and about 35 per cent. in dry bone, below normal).

These two experiments indicate that even in the case of abnormally lowered calcium assimilation in rats kept on diets deficient in fat-soluble factor the degree of this assimilation depends upon a more or less complete exhaustion of the fat-soluble factor in the organism. Apparently an excess of calcium in the diet could be followed by slightly increased, *although far from normal*, assimilation of calcium, if the fat-soluble factor is not completely exhausted in the organism.

Histological Results.

Histological structure of the skeleton of rats kept on N B, N 1, N 2, and N 3 diets was normal and similar in all cases. I have mentioned in my previous communications that the ribs of rats kept on N 1 diet sometimes show slight concave flexure of the costo-chondral junction. I have observed this same feature in the ribs of some rats kept on normal diets containing a double or treble amount of calcium. Rat 682 on NB diet, which contained the smallest amount of calcium and no cod-liver oil, showed the most classical picture of normal skeleton.

In the experiments with litters A, B, and C (Table IV) the structure of the skeleton of rats on -A 2 diet was similar to that of rats kept on -A 1 diet. I described this picture several times. In rats of the same litters, kept on -A 3 diet, the histological changes in the bones were less pronounced, but these changes always vary on -A diet. In any case, the double amount of calcium (corresponding to McCollum's optimum amount of calcium in rat's food) had no influence on the structure of the skeleton. In these experiments histological changes in the bones of litters A, B, and C were found to be typical of *late rickets*—that is, without increase of the proliferating cartilage with some osteoporosis. This type of late rickets, slight or very slight, was also found in rats 701 to 705 (Table V). In litter 689 (Table VI), kept on -A 3 diet, but with an exhausted store of fat-soluble factor, moderately severe rickets was found. In these rats proliferating cartilage was two to four times more than normally increased, calcium deposition in the zone of provisional calcification was deficient, and the bones were as well osteoporotic. Therefore, the results of histological investigation were completely analogous to those of the chemical analysis and showed the importance of the exhaustion of fat-soluble factor from the organism in the development of rickets.

On the basis of the results of the experiments described above I think it possible to draw the following conclusions:

1. Butter bought in winter may contain a considerable amount of the antirachitic principle.
2. When the amount of calcium in a normal diet containing 8 per cent. butter and 2 per cent. cod-liver oil was increased

two or three times the calcification of the skeleton was either not increased at all or only slightly.

3. The ingestion of even very large quantities of calcium did not cure the rachitic calcium impoverishment of the skeleton of rats on a diet deficient in the fat-soluble factor.

4. When the exhaustion of the fat-soluble factor in the body of rats is not complete, an excess of calcium in diets deficient in fat-soluble factor may in some cases slightly increase the amount of calcium in the skeleton, though never sufficient to make the calcification normal.

5. On the basis of the data of the chemical and histological examination, the skeletal affections in rats on —A diet must be classed in the group of rachitic affections, which develop even with an excess of calcium in the diet.

INTUSSUSCEPTION SUPERVENING ON CONGENITAL STENOSIS OF THE ILEUM.

BY

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Cases of intussusception as the result of congenital constriction of the small intestine form a group often emphasized in textbooks, but records of such cases are comparatively infrequent. In a series of 400 cases of intussusception at the London Hospital, Perrin and Lindsay¹ found only two due to this cause. According to Leichtenstern² intussusception as a result of congenital stricture is uncommon, as the dilated hypertrophied proximal segment is not easily invaginated into the small empty distal portion. The following case, therefore, seems of sufficient interest to record. I am indebted to the late Mr. T. H. Kellock for permission to publish it.

A boy aged 11 years returned home from school on June 30th, 1922, complaining of pains in the abdomen; administration of castor oil was followed by vomiting; the sickness and pain continued throughout the night; next day the vomiting ceased though the pain persisted, becoming more severe at night. His condition became progressively worse, vomiting recurred, and he was admitted to the Middlesex Hospital on July 3rd. He was a tall thin boy of poor muscular development; his face was pale, drawn, and anxious, the tongue dry and furred, the lips and teeth were crusty. The temperature was 97°, pulse 124, respirations 28. The abdomen was distended and tender, especially in the lower part, and showed no movement on respiration. In the centre of the lower part of the abdomen was an indefinite swelling dull to percussion. No note was made as to visible peristalsis.

Operation (by Mr. Kellock).

A right paramedial incision, 4 inches long, was made below the level of the umbilicus. The peritoneum was injected, and the cavity contained much blood-stained fluid. The distended and engorged small intestine which presented was followed down until the cause of the obstruction was reached in the lower ileum. This proved to be an intussusception. The greater part of it was reduced, but a portion some 4 inches long was irreducible, and showed gangrenous patches. Resection of this part was performed, and, as the patient's condition was bad, anastomosis was effected by a Murphy's button. The abdomen was closed except for a small gauze drain.

On the evening of that day the temperature rose to 99.4°, the pulse and respiration rate being 140 and 28. His condition remained critical for some days. Removal of the gauze drain on the fifth day released a discharge with faecal odour. By the eighth day the general condition showed slight improvement, but a fistula, freely discharging intestinal contents, had developed. The Murphy's button was not recovered until the twenty-eighth day. The escape of intestinal contents slowly diminished and the surrounding skin, which had been reddened and excoriated, began to heal.

The patient was discharged to a convalescent home seven weeks after the operation, with the fistula practically closed. His general condition was very satisfactory. He is now completely recovered, has put on weight, and looks robust and well.

The grant of the Medical Research Council and the hospitality of the laboratories of the Lister Institute have enabled me to carry out this work, and to them my thanks are due. I wish also to express my sincere gratitude to Professor C. J. Martin for his continuous support in this investigation, and to Miss M. Carr for her assistance in chemical analyses.

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The Specimen.

Examination of the specimen removed showed a pure enteric intussusception. When the two outer coats were divided longitudinally it was found that the intussusception had commenced by the invagination of a portion which was the seat of a congenital stricture into the part below. The stricture was over 2 inches in length, and the lumen of the gut at its narrowest part was not more than an eighth of an inch in diameter. The wall of the gut at the stricture is not much thickened, the external diameter being about a quarter of an inch. A nodule about the size of a hazel nut, which was incorporated in the wall of the gut, appeared to be the most advanced point of the entering layer; it was an effusion of blood into the tissues, probably secondary to the intussusception.

The whole specimen showed the congestion and ulceration usual in cases of intussusception of some days' standing.

The different ways in which a marked congenital stricture of the ileum may affect the life and health of an individual are well shown in the notes on three specimens in the Middlesex Hospital museum. Bland-Sutton,³ who applies the name "im-perforate ileum" to such deformities, has illustrated two of the specimens in his article in the *American Journal of the Medical Sciences* and in his book on tumours. In the first

specimen, which shows the condition to which he gives the name "septate ileum," the lumen is interrupted 36 inches above the ileo-caecal valve by a perforated diaphragm which reduces the diameter of the channel to a quarter of an inch. Externally a slight constriction marks its site. This septum had caused no symptoms, and was found *post mortem* in a man, aged 62, who had died from myocarditis and emphysema. The second specimen shows complete interruption of the ileum in an infant; the patient was under the care of Sir John Bland-Sutton, who diagnosed the condition and operated; death occurred, as it almost

The specimen removed at operation. (From a drawing by Miss D. Clephan.) The outer and middle layers of the intussusception have been opened up to show the congenital constriction, A, in position. The most advanced point, B, shows a rounded nodule projecting on the peritoneal surface; this on section consisted of blood clot, C, ulcerated or gangrenous portion of the outer layer.

invariably does. Only two cases are recorded in which an infant with complete stenosis in this region has recovered. In both of these the lesion was single, and it was possible to perform entero-anastomosis. When the condition is multiple death has so far invariably been the result. In many cases, according to Clogg,⁴ even where the lesion is single, the lumen beyond the occlusion is either blocked with inspissated mucus or so narrow that the passage of meconium along it is still prevented.

The third specimen, recorded by Leopold Hudson,⁵ was obtained *post mortem* from a boy aged 8, who died of peritonitis; until twelve months previous to his death the boy had been perfectly healthy and free from abdominal trouble. The specimen shows a segment of gut situated 38 inches above the ileo-caecal valve, so narrow for a length of three-quarters of an inch that it barely admitted a probe. This stenosed segment connected a hypertrophied and distended proximal portion of small intestine with a distal part apparently normal. A small perforation had occurred just above the narrow segment, causing a fatal result. The autopsy revealed an intussusception considered agonal in nature, formed by the invagination of the upper loop into the lower for a distance of approximately 2 inches.

Sir Arthur Keith⁶ collected and grouped specimens of constrictions and occlusions of the alimentary tract of congenital