STUDIES ON CALCIUM AND MAGNESIUM METABOLISM IN DISEASE.

I. Calcium and Magnesium Metabolism in Leprosy.

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In a preliminary paper by Honeij[1] on bone changes in leprosy it was shown that in this disease there is a definite absorption of bone salts. The idea seems prevalent that the bony changes in leprosy are due to suppurative processes or to nerve lesions, and hence little attention has been paid to them. This view-point is, however, entirely erroneous, for although bony changes may bear a relation to suppurative processes and to nerve lesions, Honeij points out that this kind of reaction plays no part in the true type of bone absorption which is part of the general disease. Thus, in the cases of leprosy with absence of suppuration and nerve disturbances the absorption of bone salts is demonstrable. Again, in progressive cases without any marked evidence of nerve involvement and distinctly without indication of suppuration the absorption of bone salts and consequent changes are most noticeable.

From the foregoing considerations it is apparent that a study of the calcium and magnesium exchange in leprosy would possibly afford a better conception of the processes involved in the abnormal condition under discussion. Indeed, the possibility exists that such a study might lead to improvement in treatment or prognosis as well as be of importance in the classification of the various types of leprosy.

[1] Honeij, J. A., *Am. J. Roentgenol.*, 1917, iv, N. S., 494.

Plan of Investigation.

Experience has demonstrated that simple determination of the balance of calcium and magnesium in the body does not always lead to convincing conclusions. This is due in large measure to the fact that it is difficult to obtain approximately perfect balances, and even though attained this maintenance is not easy. An attempt to draw definite conclusions from the balances alone is even more difficult in diseased conditions wherein the elements concerned exert a disturbing influence.

Therefore in the present investigation, although due weight has been given to the calcium and magnesium balances, more significance has been attached to giving the diseased organism a distinct task to perform and observing the manner in which this is accomplished. Stated differently, the general plan of procedure has been to maintain diseased individuals upon a restricted diet low in calcium and magnesium and then for a period to increase the calcium or magnesium either by administration of food rich in the element or directly as a salt. From the data so obtained various ratios were calculated. A comparison was then made with the ratios obtained from normal individuals maintained under similar experimental conditions. In this manner deviations from normal behavior are readily detected, inasmuch as usually, when perverted calcium or magnesium exchange occurs, the evidence is quite noticeable.

Method.—The dietary was limited in the kind of food, and, as has been stated previously, was so selected as to be poor in calcium and magnesium quantitatively. The dietary was restricted within certain limits but was not a constant diet. Calcium was added to this diet in the form of milk, magnesium as magnesium citrate. The investigation was divided into four periods. Previous to the first period all subjects were maintained upon the diet of Period 1 for 3 days. Period 1 was arranged so as to represent a calcium-magnesium-low interval. Period 2 represented a calcium-rich but magnesium-low period. This was accomplished by the addition of varying quantities of milk. Period 3 was approximately identical with Period 1; that is, a period low in both calcium and magnesium, milk being withdrawn from the dietary. Period 4 was essentially the same as Period 3 except that 2 gm. of magnesium citrate, equivalent to 205 mg. of magnesium, were admin-

istered in three equal doses daily. In other words, Period 4 was an interval of low calcium and high magnesium.

The experimental periods were marked off in the feces by the employment of carmine. Calcium and magnesium were determined in the food, urine, and feces by the methods of McCrudden.[2]

Description of Subjects.

Normal Individuals.

Subject 1.—M. A., female, age 25 years; engaged in laboratory work. The experiment was so planned that menstrual periods were avoided.

Subject 2.—G. S., male, age 28 years; engaged in laboratory work.

Leprous Cases.

Case 1.—M. T., male, age 31 years; single; laborer; born in Greece. December 1, 1916. Admitted to the New Haven Hospital.

Complaint.—"Red spots on body." A few spots first appeared on the face, resembling lesion now present. These lesions were at first small and red, later became browner and larger. Cheeks were at first affected, then the feet, following these the arms and hands. Lesions are not painful, have never itched, never broken down to form ulcers. Patient claims he feels well. For less than a year the left side of the nose has been almost completely blocked; no catarrh previously.

Family History.—Negative.

Past History.—Negative.

Physical Examination.—Negative except in the following respects. The nose shows thickening of the septum on the left side, with whitish color and several small whitish nodules. Glands of the cervical, axillary, epitrochlear, and inguinal regions are all moderately enlarged. The skin shows the greatest changes. On the face and forehead rather numerous, flat papules 2 to 4 mm. in size and of a brownish color. An infiltrated area 1 cm. in diameter seen on right cheek and two similar areas on left cheek. Pigmented areas also seen. A nodule 1.5 cm. in diameter on left forehead, involving skin and subcutaneous tissue. The same lesions are found on forearm, elbows, buttocks, thighs, and lower legs, mostly on extensor surfaces. The nerves are thickened; the ulnar nerves, peroneal, and popliteal are also affected. Many large papules and a large area on left shin are anesthetic. Many pigmented areas are slightly affected. The blood examination on November 8, 1917, shows 63 per cent hemoglobin and 8.4 per cent white cells, mostly polymorphonuclears. Wassermann reaction +++. Later the white cell blood count was 11,000 with 75 per cent polymorphonuclears. Achroma also.

[2] McCrudden, F. M., *J. Biol. Chem.*, 1909–10, vii, 83; 1911–12, x, 187.

Renal functional test, December 18, 1917, shows 54 per cent excretion 2 hours after phenolsulfonephthalein. The urine examination gave a specific gravity of 1,015; the color was amber; clear; acid reaction; slight possible trace of albumin; no sugar; few epithelial cells on microscopic examination.

The radiographic gastrointestinal examination was negative except for some colonic stasis.

The patient was under treatment for 1 year and on special diet from June 26 to July 25, 1917.

Diagnosis.—Leprosy of the nodular, anesthetic type.

Case 2.—G. C., male, age 21 years; single; laborer; born in Italy. January 2, 1918. Admitted to the New Haven Hospital.

Complaint.—Difficulty in breathing through nose. Patient has been troubled with a dry feeling in his nose for the last 2 years. Has expelled by force scab-like masses which are now and then accompanied by slight epistaxis. Has always had a biting sensation in his nose. Patient is not subject to colds. Throat troubles him also. Headaches are frequent and quite frequently has cold sweats. Every now and then his upper extremity "falls asleep," giving tingling sensation. Itchy feeling when body becomes warm.

Family History.—Negative.

Past History.—Negative.

Physical Examination.—Negative except in the following respects. The nose shows both anterior nares almost entirely occluded by atrophic scabs. On removing them a perforation of the septum is seen 3 by 2 cm.; it does not seem to include the bony portion of the septum. The turbinates are difficult to determine. The eyes show a slight conjunctivitis and areas of anesthesia which also occur on lids. A small nodule is seen at the sclera-corneal margin of both eyes. The glands of the cervical, axillary, and inguinal regions are enlarged. The examination of the body is negative except for areas of anesthesia, fairly symmetrical in their distribution, occurring on body and on extremities, face, and ears. The hands and feet are cyanotic. The patient perspires freely. The nerves are thickened. The ulnar and anterior tibial nerves are considerably thickened. Areas of discoloration and pigmentation seen on the buttocks; here there are also some nodules. The blood examination on October 16, 1918, shows a white blood count of 8,400 and on October 21 a count of 13,600. The urine examination on October 15 gave a specific gravity of 1,032; normal color; clear; acid reaction. Microscopic examination showed a rare leucocyte.

Diagnosis.—Leprosy of the anesthetic type. An earlier case of the disease than Case 1.

Dietary.

The diet for all subjects consisted of varying but definite quantities of the foodstuffs presented in Table I. The calcium content and magnesium content are also given. In order to save space the quantities of food consumed daily are omitted.

TABLE I.

Dietary.

Food.	Calcium content.	Magnesium content.
	per cent	*per cent*
Bread	0.032	0.036
Orange	0.056	0.015
Egg	0.073	0.015
Sugar		
Baked potato	0.005	0.020
Chopped beef	0.007	0.018
Banana	0.013	0.021
Prunes	0.042	0.018
Boiled rice	0.002	0.005
Fresh strawberries	0.041	0.019
Milk	0.179 0.199	0.016 0.014

Calcium and Magnesium Balances.

In Tables II to V are presented the data relative to the calcium and magnesium exchange in the four subjects of investigation. The first period shows the two normal subjects to be in a distinct negative calcium balance, but on the other hand, the magnesium balance is positive. Added calcium, in the form of milk, in the second period causes both subjects to approach an equilibrium. In Subject 1 the added calcium exerted little or no influence upon the magnesium balance, whereas with the other normal individual, Subject 2, a distinct negative magnesium balance was exhibited. Withdrawal of the additional calcium in the third period resulted with the two normal subjects in a distinct negative calcium balance; the negative magnesium balance in this period was not so marked. In the fourth period where magnesium citrate was added to the diet a significant

TABLE II.

Subject 1; Normal. Calcium and Magnesium Balances.

Period.	Diet.	Date.	Calcium. Intake.	Calcium. Output. Urine.	Calcium. Output. Feces.	Calcium. Output.	Calcium. Balance.	Magnesium. Intake.	Magnesium. Output. Urine.	Magnesium. Output. Feces.	Magnesium. Output.	Magnesium. Balance.
		1919	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*
1	Calcium-low and magnesium-low.	Jan. 4	317	316				228	67			
		" 5	349	300				239	93			
		" 6	333	335				263	96			
		" 7	342	395				275	88			
Total			1,341	1,346	885	2,231	−890	1,005	344	585	929	+76
Average per day			335	336	221	557	−222	251	86	146	232	+19
2	Calcium-high and magnesium-low.	Jan. 8	1,324	469				341	109			
		" 9	1,333	508				361	110			
		" 10	1,339	618				392	134			
Total			3,996	1,595	2,500	4,095	−99	1,094	353	676	1,029	+65
Average per day			1,332	532	833	1,365	−33	364	117	225	343	+22
3	Calcium-low and magnesium-low.	Jan. 11	365	325				294	108			
		" 12	329	352				277	124			
		" 13	358	343				271	114			
Total			1,052	1,020	881	1,901	−849	842	346	691	1,037	−195
Average per day			351	340	293	633	−283	280	115	230	345	−65
4	Calcium-low and magnesium-high.	Jan. 14	367	351				487	128			
		" 15	419	426				507	152			
		" 16	408	408				533	148			
Total			1,194	1,185	1,031	2,216	−1,022	1,527	428	710	1,138	+389
Average per day			398	395	343	738	−341	509	142	236	379	+130

TABLE III.

Subject 2; Normal. Calcium and Magnesium Balances.

Period.	Diet.	Date.	Calcium. Intake.	Calcium. Output. Urine.	Calcium. Output. Feces.	Calcium. Balance.	Magnesium. Intake.	Magnesium. Output. Urine.	Magnesium. Output. Feces.	Magnesium. Balance.
		1919	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*
1	Calcium-low and magnesium-low.	Jan. 4	506	149			345	128		
		" 5	542	215			398	124		
		" 6	537	213			369	112		
		" 7	584	242			429	104		
		" 8	525	359			377	161		
Total			2,694	1,178	2,264	−748	1,918	629	1,257	+32
				3,442				1,886		
Average per day			539	235	452	−150	383	125	251	+6
				688				377		
2	Calcium-high and magnesium-low.	Jan. 9	1,539	295			494	176		
		" 10	1,467	304			450	183		
		" 11	1,499	400			489	165		
Total			4,505	999	3,479	+27	1,433	524	1,132	−223
				4,478				1,656		
Average per day			1,501	333	1,159	+9	477	174	377	−74
				1,492				552		
3	Calcium-low and magnesium-low.	Jan. 12	444	207			363	134		
		" 13	502	215			382	145		
		" 14	537	415			417	110		
Total			1,483	837	1,735	−1,089	1,162	389	822	−49
				2,572				1,211		
Average per day			494	279	578	−363	387	129	274	−16
				857				403		
4	Calcium-low and magnesium-high.	Jan. 15	544	280			612	185		
		" 16	472	382			560	169		
		" 17	592	772			595	101		
Total			1,608	1,434	1,390	−1,216	1,767	455	976	+336
				2,824				1,431		
Average per day			536	478	463	−405	589	151	325	+112
				941				477		

TABLE IV.

Case 1; Leprosy. Calcium and Magnesium Balances.

Period.	Diet.	Date.	Calcium. Intake.	Calcium. Output. Urine.	Calcium. Output. Feces.	Calcium. Balance.	Magnesium. Intake.	Magnesium. Output. Urine.	Magnesium. Output. Feces.	Magnesium. Balance.
		1917	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*
1	Calcium-low and magnesium-low.	June 30	290	22			194	60		
		July 1	217	21			174	77		
		" 2	277	23			198	77		
		" 3	299	23			184	69		
Total			1,083	89	560	+434	750	283	223	+244
				649				506		
Average per day			271	22	140	+108	187	71	56	+61
				162				126		
2	Calcium-high and magnesium-low.	July 4	894	23			204	89		
		" 5	1,005	20			214	81		
		" 6	976	25			226	100		
Total			2,875	68	1,083	+1,724	644	270	230	+144
				1,151				500		
Average per day			958	22	361	+574	214	90	76	+48
				383				166		
3	Calcium-low and magnesium-low.	July 7	203	12			126	63		
		" 8	265	28			171	75		
		" 9	177	25			127	77		
Total			645	65	931	−351	424	215	299	−90
				996				514		
Average per day			215	22	310	−117	141	71	99	−30
				332				171		
4	Calcium-low and magnesium-high.	July 10	286	27			408	94		
		" 11	253	27			362	95		
		" 12	257	28			395	92		
Total			796	82	761	−47	1,165	281	490	+394
				843				771		
Average per day			265	27	253	−15	388	93	163	+131
				281				257		

TABLE V.

Case 2; Leprosy. Calcium and Magnesium Balances.

Period.	Diet.	Date.	Calcium. Intake.	Calcium. Output. Urine.	Calcium. Output. Feces.	Calcium. Balance.	Magnesium. Intake.	Magnesium. Output. Urine.	Magnesium. Output. Feces.	Magnesium. Balance.
		1917	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*
1	Calcium-low and magnesium-low.	Feb. 10	523	103			324	114		
		" 11	522	129			344	139		
		" 12	486	153			339	106		
		" 13	496	119			331	87		
Total			2,027	504	1,538	−15	1,338	446	994	−102
				2,042				1,440		
Average per day			506	126	384	−4	334	111	248	−26
				510				360		
2	Calcium-high and magnesium-low.	Feb. 14	1,519	207			381	122		
		" 15	1,466	179			362	126		
		" 16	1,929	189			448	126		
Total			4,914	575	2,944	+395	1,191	374	981	−164
				3,519				1,355		
Average per day			1,638	192	981	+131	397	124	327	−54
				1,173				451		
3	Calcium-low and magnesium-low.	Feb. 17	492	135			339	109		
		" 18	517	159			353	124		
		" 19	515	161			379	115		
Total			1,524	455	1,169	−100	1,071	348	852	−129
				1,624				1,200		
Average per day			508	151	389	−33	357	116	284	−43
				541				400		
4	Calcium-low and magnesium high.	Feb. 20	562	145			592	144		
		" 21	514	152			580	148		
		" 22	525	138			542	151		
Total			1,601	435	1,137	+29	1,714	443	1,122	+149
				1,572				1,565		
Average per day			533	145	379	+9	571	147	374	+49
				524				521		

negative calcium balance persisted, but the magnesium balance became positive.

It is therefore evident that with normal subjects in negative calcium balance added calcium causes the balance to become positive and that the additional calcium exerts little or no influence upon the magnesium balance. The influence of the added calcium is, however, only temporary, since its withdrawal results in a resumption of a significant negative calcium balance. Added magnesium changes a slightly negative magnesium balance to a strongly positive one without a very significant influence upon the calcium balance.

With the leprosy cases a different picture is presented. Although both subjects were maintained on a low calcium intake in Period 1, Case 1 was in positive calcium balance and Case 2 was almost in perfect equilibrium. Case 1 was also in positive magnesium balance, whereas Case 2 showed a negative balance. Administration of added calcium in Period 2 demonstrated in both instances retention of calcium, greater in Case 1 than in Case 2. With Case 1 the magnesium balance was little altered, whereas with Case 2 the balance was more strongly negative than it was in Period 1. In Period 3, during which the additional calcium was eliminated, both calcium and magnesium were negative with respect to equilibrium. In the fourth period added magnesium caused a positive magnesium balance, and with Case 2 a positive calcium balance was also obtained. With Case 1 an approach to calcium equilibrium was evident.

A comparison of these results with those of the normal subjects shows that there is an apparent tendency for the leprosy subjects to remain in positive balance with respect to calcium, and in Case 1 in magnesium balance also. It is also evident that this tendency is, with respect to calcium, greater in the more advanced case, No. 1, than in the other patient. It is therefore indicated that in leprosy the organism exhibits a tendency to retain calcium whether maintained upon a diet containing little or much of this element, the more advanced the pathological condition clinically the more evident does this tendency to retention become.

In leprosy the organism may or may not retain a large portion of the added magnesium. Where retention was in evidence its degree was not strikingly greater than in the normal individuals maintained under similar conditions.

Further Analysis of the Data.

Calcium Metabolism.

In order to ascertain the correctness of the statement that in leprosy there is a tendency to retain calcium, the data have been subjected to further analysis.

Excretion of Added Calcium.—If one calculates the percentage of added calcium eliminated from the body during the period of administration, *i.e.* Period 2, it will be found that in leprosy the figures are different from those for normal individuals (Table VI).

TABLE VI.

Excretion of Added Calcium.

Subject.	Excretion of added calcium.*
	per cent
Subject 1; normal	100+
" 2; "	92+
Case 1; leper	38+
" 2; "	62+

* Period 2; calcium added as milk.

From these figures it is apparent that normal individuals in negative calcium balance promptly eliminate added calcium almost quantitatively, only a small amount of added calcium being retained; this leads to a corresponding approach to calcium equilibrium. In leprosy added calcium is retained in large measure. In the two individuals studied a marked difference was observed in the ability of the body to retain calcium. The query is pertinent whether this difference in behavior is due to a difference in the stage of the disease. Clinically the two cases are distinct, Case 1 being in a more advanced stage than Case 2. From the fact that the more advanced case shows the greater retention of calcium it may be argued that this subject has the greater need for this element.

Relation of Calcium Output to Intake.—From an inspection of Table VII it is apparent that in leprosy calcium exchange is different from that found in normal individuals. Placed upon a low calcium

diet the leprous subjects exhibited a distinct tendency to retain calcium, the retention being especially marked in Case 1, the more advanced case. When placed upon a calcium-rich diet Case 1 retained enormous quantities of calcium, the other subject, Case 2, exhibiting this behavior to a much less marked degree. When again placed upon a calcium-poor diet both subjects tended to approach the normal individuals in their behavior. On the other hand, the

TABLE VII.

Relation of Calcium Output to Intake.

Ratio: $\frac{\text{Calcium Output}}{\text{Calcium Intake}}$.

Subject.	Period.			
	1	2	3	4
Subject 1; normal	1.6	1.0	1.8	1.9
" 2; "	1.2	0.9	1.7	1.7
Case 1; leper	0.6	0.4	1.5	1.0
" 2; "	1.0	0.7	1.0	0.9

excretion was less marked again in the fourth period, and evidence of a tendency to retention is to be observed. This approach to a normal type of excretion may perhaps be interpreted to mean that the leprous organism once having a sufficiency of calcium for its present needs rather slowly parts with the excess.

Relation of Output to Intake for the Entire Period.—Comparison (Table VIII) of the total output in relation to intake for the entire

TABLE VIII.

Relation of Calcium Output to Intake for the Entire Period.

Subject.	Calcium.		
	Output.	Intake.	Difference.
	mg.	*mg.*	*mg.*
Subject 1; normal	10,443	7,583	−2,860
" 2; "	12,626 (13 days).	9,752	−2,874
Case 1; leper	3,639	5,399	+1,760
" 2; "	8,757	10,066	+1,309

period of investigation in the four subjects brings out the fact already alluded to; namely, a significant calcium retention in leprosy, even though the subjects were maintained for three periods out of four on a calcium-low diet. Again the fact is emphasized that in the more advanced patient, Case 1, the retention is greater than in the less advanced patient, Case 2. The normal subjects, on the other hand, exhibited a marked loss of calcium.

Relation of Calcium Intake and Output to Body Weight.—The weights of the individuals under experimentation varied widely and it is possible that this variation may bear a relation to the interpretation of the facts discussed above. With this idea in mind the relation of the total intake and output of calcium to body weight

TABLE IX.

Relation of Calcium Intake and Output to Body Weight.

Subject.	Body weight.	Calcium.		Calcium per pound of body weight.	
		Intake.	Output.	Intake.	Output.
	lbs.	*mg.*	*mg.*	*mg.*	*mg.*
Subject 1; normal	105	7,583	10,443	72	99
" 2; "	150 (13 days).	9,752	12,626	65	84
Case 1; leper	117	5,399	3,639	46	31
" 2; "	147	10,066	8,757	68	59

has been expressed numerically in Table IX. Inspection of these data will show at once the same general type of differences already discussed, so that it may be concluded that variations in body weight do not account for the fact that in leprosy calcium is used differently than in the normal organism.

Absorption of Calcium.—A point of considerable interest in the interpretation of the data presented relates to the question of variation in absorption of the introduced calcium. It is obvious that this question does not lend itself readily to dogmatic statements, since it is probable that calcium is excreted in variable degree by both the kidney and intestine under diverse circumstances. However, in the present discussion it is pertinent to compare the absorption of calcium in leprosy with that of normal individuals. In this

consideration the excretion of calcium through the urine is taken tentatively as evidence of absorption; the passage of calcium from the body through the feces as unabsorbed calcium. This is obviously incorrect, since undoubtedly part of the calcium eliminated with the feces is calcium which underwent absorption and is merely excreted by the intestine. For a comparative study of absorption, however, such a hypothesis may be employed.

On the basis of this hypothesis, with the necessary limitations involved, a study of the excretion of calcium by way of the urine in relation to the intake shows some noteworthy features (Table X). With the normal individuals on a calcium-low diet from approximately one-half to a quantity equal to the ingested calcium is excreted

TABLE X.

Relation of Urinary Calcium Excretion to Calcium Intake.

Ratio: $\frac{\textit{Calcium of Urine}}{\textit{Calcium of Food}}$.

Subject.	Period.			
	1	2	3	4
Subject 1; normal	1.0	0.4	1.0	1.0
" 2; "	0.4	0.2	0.5	0.8
Case 1; leper	0.08	0.02	0.1	0.1
" 2; "	0.2	0.1	0.3	0.2

by way of the kidney. As a calcium-rich diet is introduced the relative quantity of food calcium absorbed diminishes to a perceptible degree. Withdrawal of the calcium-rich diet causes the relation between the calcium excreted by the kidney and that ingested to resume the status which obtained in the calcium-poor period previously.

With the cases of leprosy the ratio is radically different from that of the normal individuals. In both cases relatively little calcium is eliminated by way of the urine. This is especially noticeable with the more advanced patient, Case 1. On a calcium-rich diet both subjects follow the general type of behavior of normal subjects; the degree of deviation is markedly different. The same fact holds when the calcium-poor diet is again introduced.

Relation of Fecal Calcium to Calcium Intake.—The figures given, when applied to the hypothesis outlined above, would lead one to conclude that very much less calcium was absorbed in the leprous cases than in the normal individuals. However, before positive conclusions can be drawn relative to this point a study should be made of the relation of calcium excretion by way of the feces to the calcium intake. This has been done and the results are expressed in Table XI. These figures demonstrate that normal conditions exist with respect to calcium elimination by the intestine in leprosy when these subjects are placed upon a calcium-poor diet. Addition of calcium to the diet results in a relatively smaller quantity

TABLE XI.

Relation of Fecal Calcium to Calcium Intake.

Ratio: $\frac{\textit{Calcium of Feces}}{\textit{Calcium of Food}}$.

Subject.	Period.			
	1	2	3	4
Subject 1; normal	0.6	0.6	0.8	0.8
" 2; "	0.8	0.7	1.1	0.8
Case 1; leper	0.5	0.3	1.4	0.9
" 2; "	0.7	0.6	0.7	0.7

appearing in the feces during this period. Since in this period there is no increase in either the urinary or fecal excretion of calcium it is obvious that the added calcium was absorbed in large measure. This theory is supported by the fact that in the later periods upon a calcium-poor diet some of the retained calcium is excreted by both the urine and feces (see Periods 3 and 4, Tables X and XI). The conclusion is therefore warranted that the behavior of leprous subjects with respect to urinary calcium excretion cannot be ascribed to lack of absorption of this element. Moreover, absorption of calcium in the leprous condition seems even better than in the normal individual. This is especially true with the more advanced patient, Case 1.

Relation of Urinary Calcium to Fecal Calcium.—If a comparison is made of the output of calcium in the urine and feces it becomes evident (Table XII) that only a small proportion of absorbed calcium is excreted in the more advanced case of leprosy. With the less advanced case the behavior is more nearly normal.

TABLE XII.

Relation of Urinary and Fecal Calcium.

$$Ratio: \frac{Calcium\ of\ Urine}{Calcium\ of\ Feces}.$$

Subject.	Period.			
	1	2	3	4
Subject 1; normal	1.5	0.6	1.1	1.1
" 2; "	0.5	0.2	0.4	1.0
Case 1; leper	0.1	0.06	0.07	0.1
" 2; "	0.3	0.2	0.4	0.3

When compared to normal individuals under the same experimental conditions leprous patients retain calcium in relatively large quantities whether the individual is maintained upon a calcium-poor or a calcium-rich diet, and the greater the intake the greater is the relative retention. In the more advanced stage of the disease the degree of retention is greater than in the early phase. This retention cannot be explained by differences of calcium intake, or by variation in the power of absorption. It is apparently an evidence of metabolic demand for calcium induced by the disease. Clinically, it may be inferred that there is a need for calcium; experimentally, the organism gives demonstration of this need by retention of calcium administered.

It is perhaps self-evident that the loss of bone salts in leprosy is but a manifestation of the disease processes. Nevertheless, it is conceivable that under dietary conditions in which calcium is not particularly abundant the lack of this element may play a material part in the rapidity of the progress of the disease. Conversely, the suggestion is pertinent that the progress of the disease may be greatly retarded or perhaps even alleviated if an abundance of calcium is

present in the diet. The suggestion that plenty of calcium should be supplied in the food as a therapeutic measure is at least worthy of trial.

Magnesium Metabolism.

Excretion of Added Magnesium.—From the figures in Table XIII it is apparent that normal individuals in a slightly negative magnesium balance retain more than one-half the magnesium added to a diet relatively low in this element. Of the leprosy patients, Case 1 behaved in a manner very similar to the normal individuals, whereas in the less advanced patient, Case 2, three-quarters of the administered magnesium was promptly eliminated.

TABLE XIII.

Excretion of Added Magnesium.

Subject.	Excretion of added magnesium.
	per cent
Subject 1; normal	36
" 2; "	45
Case 1; leper	36
" 2; "	75

Relation of Magnesium Output to Intake.—As may be seen from an inspection of Table XIV leprous individuals differ little from normal individuals in the manner in which magnesium is eliminated from the body, whether these subjects are maintained upon a diet low or rich in magnesium.

TABLE XIV.

Relation of Magnesium Output to Intake.

Ratio: $\frac{\textit{Magnesium Output}}{\textit{Magnesium Intake}}$

Subject.	Period.			
	1	2	3	4
Subject 1; normal	0.9	0.9	1.2	0.7
" 2; "	0.9	1.1	1.0	0.8
Case 1; leper	0.6	0.8	1.2	0.7
" 2; "	1.0	1.1	1.1	0.9

Relation of Output to Intake for the Entire Period.—It is only when comparison is made between the total output and total intake of magnesium that a marked difference can be observed between normal individuals and leprous subjects. From Table XV it is seen that in spite of the fact that Case 1 ingested only about one-half or less of the magnesium taken in by the normal subjects, yet the absolute quantity of magnesium retained was more than double that of the normal subject retaining the most. It would appear, therefore, that in this case there is indication of a distinct magnesium retention. This would naturally be expected, since clinically in this patient there was evidence of considerable bone absorption. In Case 2, however, evidence of bone absorption was less apparent. With this

TABLE XV.

Relation of Magnesium Output to Intake for the Entire Period.

Subject.	Magnesium.		
	Output.	Intake.	Difference.
	mg.	*mg.*	*mg.*
Subject 1; normal	4,133	4,468	+335
" 2; " (13 days)	5,806	5,894	−88
Case 1; leper	2,291	2,983	+692
" 2; "	5,560	5,314	−246

subject there is a small loss of magnesium rather than a retention. It is therefore probable that in the advanced stages of leprosy the organism conserves its magnesium store, since it retains a considerable quantity. Although the advanced case of leprosy retained about the same percentage of food magnesium, the absolute amount retained was much greater, as may be seen from Table XV.

Relation of Magnesium Intake and Output to Body Weight.—When a comparison is made of the intake and output of magnesium to body weight it may be seen (Table XVI) that although the intake of the advanced leprous patient, Case 1, was much smaller than that of either the normal subjects or the other patient, nevertheless more magnesium was stored.

TABLE XVI.

Relation of Magnesium Intake and Output to Body Weight.

Subject.	Body weight.	Magnesium.		Magnesium per pound of body weight.	
		Intake.	Output.	Intake.	Output.
	lbs.	*mg.*	*mg.*	*mg.*	*mg.*
Subject 1; normal	105	4,468	4,133	42	39
" 2; "	150 (13 days).	5,894	5,806	39	38
Case 1; leper	117	2,983	2,291	25	19
" 2; "	147	5,314	5,560	36	38

Absorption of Magnesium.—From a study of Tables XVII and XVIII it is evident that the absorption of magnesium in leprosy falls within normal limits.

TABLE XVII.

Relation of Urinary Magnesium Excretion to Magnesium Intake.

$$\textit{Ratio: } \frac{\textit{Magnesium of Urine}}{\textit{Magnesium of Food}}.$$

Subject.	Period.			
	1	2	3	4
Subject 1; normal	0.3	0.3	0.4	0.2
" 2; "	0.3	0.3	0.3	0.2
Case 1; leper	0.3	0.4	0.5	0.2
" 2; "	0.3	0.3	0.3	0.2

TABLE XVIII.

Relation of Fecal Magnesium to Magnesium Intake.

$$\textit{Ratio: } \frac{\textit{Magnesium of Feces}}{\textit{Magnesium of Food}}.$$

Subject.	Period.			
	1	2	3	4
Subject 1; normal	0.5	0.6	0.8	0.4
" 2; "	0.6	0.8	0.7	0.5
Case 1; leper	0.3	0.3	0.7	0.4
" 2; "	0.7	0.8	0.8	0.6

Relation of Urinary Magnesium to Fecal Magnesium.—A comparison of the ratio of urinary magnesium to fecal magnesium demonstrates a marked difference in the case of advanced leprosy from that of the other subjects (Table XIX). In the normal individuals studied approximately one-third of the total magnesium excretion is by way of the urine. This relation holds fairly constant whether the individual is maintained on a low magnesium diet or whether additional magnesium has been administered. In general, with Case 1, on the other hand, almost as much or somewhat more magnesium is excreted by the urine than by the feces as long as the individual is on a magnesium-poor diet. When this element is added to the diet the ratio characteristic of the normal individual is obtained.

TABLE XIX.

Relation of Urinary and Fecal Magnesium.

Ratio: $\frac{\textit{Magnesium of Urine}}{\textit{Magnesium of Feces}}$.

Subject.	Period.			
	1	2	3	4
Subject 1; normal	0.6	0.5	0.5	0.6
" 2; "	0.5	0.4	0.4	0.4
Case 1; leper	1.2	1.2	0.7	0.6
" 2; "	0.4	0.4	0.4	0.4

A study of magnesium exchange in normal and leprous subjects demonstrates that in the advanced stage of leprosy there is a tendency for a retention of magnesium. This behavior is, however, not strikingly different from that of normal individuals maintained under similar dietary conditions.

Relation of Calcium to Magnesium.

Relation of Calcium and Magnesium in the Food.—In Table XX may be found the ratio of food calcium to food magnesium. Inspection of these data will demonstrate that in the first calcium-poor period, that is Period 1, the ratio is remarkably constant. In the second period, that in which calcium was added in the form of milk,

the ratio in the normal individuals changes markedly, but in the two instances is quite constant. With the leprosy subjects there is the same type of uniformity in the two individuals, but the ratio varies even further from that of Period 1 than in the normal subjects. With a return to a calcium-poor diet there is little variation in any subject from the figures for the first period. Added magnesium naturally lowers this ratio somewhat, but in no subject does it result in a perverted variation.

TABLE XX.

Relation of Calcium and Magnesium Intake.

Ratio: $\frac{\textit{Calcium of Food}}{\textit{Magnesium of Food}}$.

Subject.	Period.			
	1	2	3	4
Subject 1; normal	1.3	3.6	1.2	0.8
" 2; "	1.4	3.1	1.2	0.9
Case 1; leper	1.4	4.3	1.5	0.7
" 2; "	1.5	4.1	1.4	0.9

Relation of Calcium and Magnesium in the Urine.—In the first calcium-poor period, in spite of the fact that the calcium-magnesium ratio in the food was fairly constant, there is a considerable variation in the ratio of urinary elimination of these substances even in normal individuals (Table XXI).

TABLE XXI.

Relation of Calcium and Magnesium in the Urine.

Ratio: $\frac{\textit{Calcium of Urine}}{\textit{Magnesium of Urine}}$.

Subject.	Period.			
	1	2	3	4
Subject 1; normal	3.9	4.5	2.9	2.7
" 2; "	1.8	1.9	2.1	3.1
Case 1; leper	0.3	0.2	0.3	0.3
" 2; "	1.1	1.6	1.0	1.0

In the leprosy cases the ratio is distinctly perverted, especially in the advanced case. This perversion, however, may be explained by the retention of calcium by these subjects. When a calcium-rich diet is given the ratios vary more widely in the normal subjects than they do in the leprosy cases. Addition of magnesium does not alter the ratios in any determinable manner.

The most significant feature with respect to the ratio of calcium and magnesium in the urine is that a change from a calcium-poor diet to one rich in calcium, or the reverse, or a change from a magnesium-poor diet to a magnesium-rich diet does not induce any significant alteration in the unusual ratio of calcium to magnesium in the urine in the advanced case of leprosy, Case 1.

Relation of Calcium and Magnesium in the Feces.—As may be seen from inspection of Table XXII the relation between the calcium and

TABLE XXII.

Relation of Calcium and Magnesium in the Feces.

$$\text{Ratio: } \frac{\text{Calcium of Feces}}{\text{Magnesium of Feces}}.$$

Subject.	Period.			
	1	2	3	4
Subject 1; normal	1.5	3.7	1.2	1.4
" 2; "	1.8	3.0	2.1	1.3
Case 1; leper	2.5	4.6	3.1	1.5
" 2; "	1.5	3.0	1.3	1.0

magnesium of the feces in leprosy does not differ widely from that in normal individuals. The greatest variation is in Case 1 and is caused by the fact that relatively less magnesium is eliminated through the feces than in the other subjects.

A study of the relations existing between the calcium and magnesium of the food, urine, and feces demonstrates that even in normal subjects, although the relation of food calcium and magnesium may be quite constant, nevertheless a decided variation may exist in the relation of these elements in the urine and feces, especially in the former. This fact is undoubtedly explained by the extent of retention of one or the other of these elements.

In leprosy the perversion of ratios is much more noticeable, especially in the advanced case. Inasmuch as relatively large quantities of calcium and much smaller quantities of magnesium were retained in the body it is evident that the greater retention of these elements in leprosy is sufficient to explain the peculiar ratios observed, for instance, in Table XXI.

CONCLUSIONS.

In leprosy there is a definite retention of calcium.

The more advanced the stage of the disease the greater is the degree of retention.

This behavior on the part of leprous individuals may be taken as an indication that the organism is in need of calcium.

Magnesium may also be retained in leprosy, but the degree of retention is much less marked than in the case of calcium.

With the exception of the retention of calcium and magnesium the leprous organism responds to changes in the intake of calcium and magnesium in the same manner as normal individuals.

The results of this investigation suggest that in leprosy administration of calcium may be of benefit as an additional therapeutic measure in an endeavor to retard or arrest the progress of the bone changes characteristic of the disease.