

The Archives of Internal Medicine

Vol. IX

MARCH, 1912

No. 3

STUDIES IN BONE METABOLISM: THE ETIOLOGY OF NON-PUERPERAL OSTEOMALACIA*

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The present investigation is a further contribution to the study of mineral metabolism and is designed to throw more light on the etiology and process in osteomalacia. A correct interpretation of this process is of the greatest importance in an understanding of the metabolism of bone since the two views regarding the nature of the osteoid tissue in osteomalacia — the one, that it is an old bone from which the mineral constituents have been dissolved out, and the other that it is new bone poor in mineral constituents — are based respectively on the two opposing views regarding the metabolism of bone — the one, that bone is dead tissue not undergoing metabolism, the other, that it does have a metabolism. Anatomical investigations not having been successful in deciding between these two views, chemical methods were applied, which led to the conclusion that bony tissue, like other tissue, is continuously being destroyed and replaced by new, and that osteomalacia is due to a disturbance of the balance whereby the new tissue is poor in calcium salts and therefore soft.¹ A study of the etiology led to the conclusion that the starting point is an increased catabolism of bony tissue due to a need of calcium salts elsewhere and that the tendency of physiological activity to overproduction which is responsible for the production of antitoxins and acquired immunity, is also an important factor in leading to the long-continued, increased catabolism of calcium after the original need

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1. In view of these findings it is interesting to note that v. Recklingshausen has recently been obliged to retract his interpretation of the *Gitterfiguren*, which was largely responsible in upholding the opposing theory, and to admit that it is not possible to differentiate morphologically between old bone from which the mineral salts have been removed and new bone poor in lime salts (von Recklingshausen: *Untersuchungen über Rhachitis und Osteomalacie*, 1910. See especially Chapter xiii and pages 343 and 346).

has ceased to exist.² The present investigation is the result of an excellent opportunity of studying a rare case of non-puerperal osteomalacia and was designed to test the above theory of the nature of the process, and to investigate the relation of the need of calcium salts and the tendency of overproduction to the etiology.

The following is an extract of her history and physical examination:³

CASE REPORT

History.—The patient, a woman aged 42 and unmarried, dates her illness to 1891 when she noted a hard, painless nodule about the size of a bean on the right side of the lower jaw. Six months later the growth, which had by then increased to the size of a hen's egg, was removed together with a piece of the jaw. In 1895 she began to suffer from loss of appetite, vomiting, obstinate constipation and severe neuralgia in the face and upper jaw and began to walk with difficulty. She noticed that her ankles would "bend in and out" on walking "as if they were made of rubber." Then a gradual stiffening of the back and stiffness and creaking of the knees developed, so that, after five months, she could get about only with the greatest difficulty. In the fall of this year small, hard, painless nodules were noticed on her shin-bones. The largest, on the left, was about the size of a walnut. In 1897 she was forced to give up work entirely. A year later, while riding a low tricycle, she fell and fractured the right thigh. This fracture, which she describes as causing her surprisingly little pain, laid her up seven weeks after which, and until ten weeks ago, she was able to move about by leaning on a chair. While laid up she had an attack of renal colic, i. e., intense colicky pain, radiating downward from her right kidney region. Three weeks later she passed several small,

2. McCrudden: Chemical Analysis of Bone from a Case of Human Adolescent Osteomalacia, *Jour. Biol. Chem.*, 1910, vii, 199; The Composition of Bone in Osteomalacia, *Am. Jour. Physiol.*, 1906, xvii, 32; A Study of the Metabolism in Osteomalacia, *Am. Jour. Physiol.*, 1905, xiv, 211; The Effect of Castration on the Metabolism, *Jour. Biol. Chem.*, 1910, vii, 185; The Effect of Castration on the Metabolism in Osteomalacia, *Am. Jour. Physiol.*, 1906, xvii, 211; Studies of Bone Metabolism, Especially the Pathological Process, Etiology and Treatment of Osteomalacia, *THE ARCHIVES INT. MED.*, 1910, v, 596.

The gynecologists are at present inclined to the hypothesis that osteomalacia is a disease of the adrenals. The original basis for this hypothesis was the experience of Bossi, an Italian physician, who, on Dec. 16, 1906, and on four successive days, administered epinephrin in a case of osteomalacia. At the end of that time the patient had much less pain and was therefore discharged as cured. *Within four weeks of the first treatment* the journal containing publication of the results appeared. (Bossi: *Nebonniere und Osteomalakie*, *Centralbl. f. Gynäk.*, Jan. 19, 1907, No. 31, p. 69.) A number of other just such experiments have since been reported in the literature. In all cases "cure" was reported soon after treatment and meant simply relief from pain. The rapidity with which tenderness and pain disappear at times, even without treatment in osteomalacia, is well known and does not indicate a cure of the disease. The case reported by Kaessman (*Ein Beitrag zur Adrenalin Behandlung des Osteomalakie nach Bossi*, *Centralbl. f. Gynäk.*, 1907, xxxi, 1376) may be typical of what happens to some of these patients. Kaessman administered epinephrin daily from Sept. 6 to Sept. 11, 1907, and, on September 14, sent the patient away better but with instructions to keep up the treatment. Nine days later, on September 23, the patient returned worse than ever. The suprarenal theory does not seem worthy of very serious consideration.

3. She was under the direct care of Dr. Henry K. Marks of this hospital.

gray stones. These attacks of pain recurred, at intervals of six to eight months. Usually, about three weeks after each attack, she would pass a stone about the size of a pea. Since May, 1904, she has had no attacks. Between 1900 and 1905

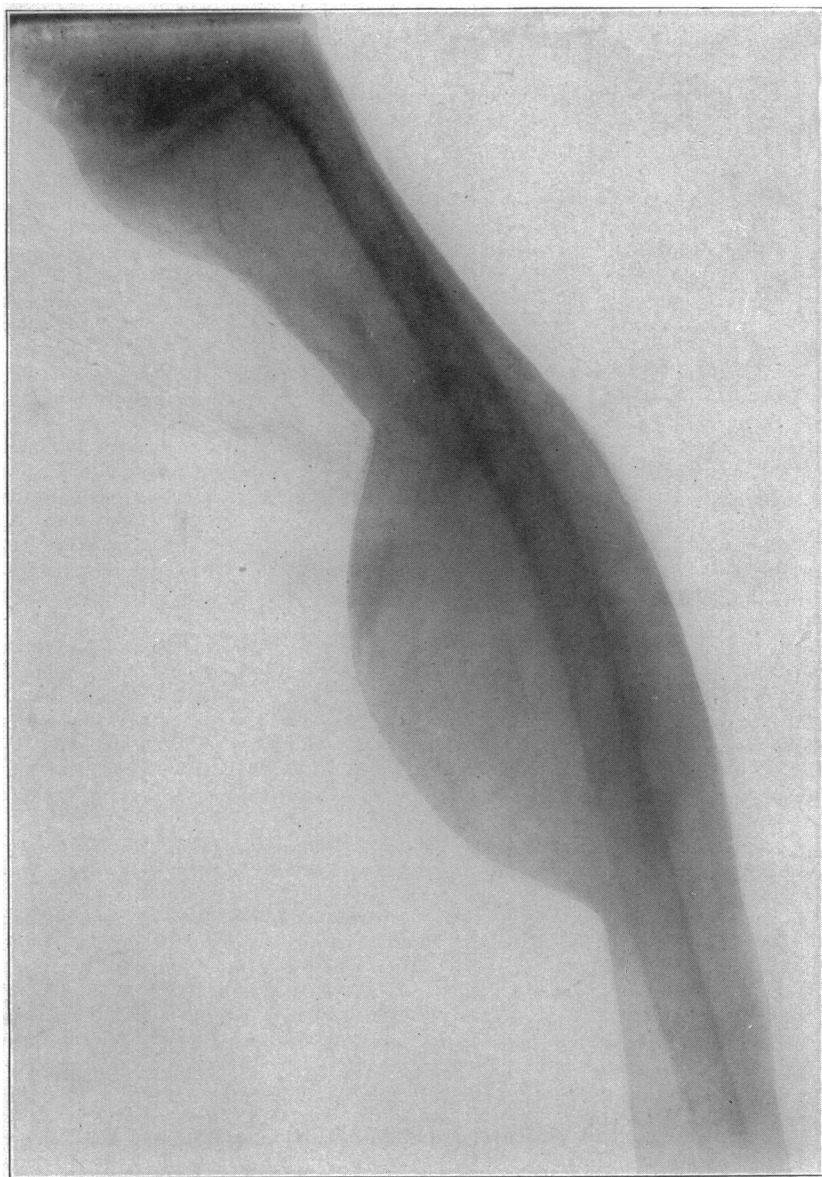


Fig. 1.—X-ray plate showing bony tumor from the left shin of a patient suffering from osteomalacia.

her symptoms did not progress. Then the stiffness of her knees and back increased and she noticed a painless enlargement near the lower edge of the spine. In 1907

she began to grow deaf in the right ear. A year later there was difficulty in breathing following the appearance of a bony growth in the right nostril. In the spring of 1909 it was noticed that her left eyeball protruded and she complained of dimness of vision and seeing double. There was no pain. In 1909 small nodules were noticed on her forehead. About this time she fractured the second metacarpal bone of the right hand by shaking hands with a friend. In August, 1910,



Fig. 2.—Rarefaction in the second phalange of the index- and third fingers and in the fifth metacarpal bone of patient with osteomalacia.

while washing her hands, she dislocated the terminal phalanx of the left index finger. For the last ten weeks she has been bedridden on account of increasing stiffness and weakness. She feels no pain on lying still but only on movement or when handled.

Physical Examination of the Osseous System.—The patient is a poorly nourished, emaciated, distorted, middle-aged woman. She lies comfortably in bed except when she attempts to move. A slight ridge can be felt extending along the suture lines of the skull. There is a hard nodule about the size of a pea on the temporal bone behind the right ear, an indefinite firm swelling behind the left ear, and three small firm nodules on the frontal bone. The nodules are not tender and not movable. There are two firm swellings on either side of the raphé between the hard and soft palate. There is a sharp, bony exostosis on the outer edge of the outer third of the right clavicle. There is a marked rosary. The right costal margin is somewhat depressed. At the left over the costochondral margin there is an elevation which is tender. There is moderate kyphosis of cervical and upper dorsal vertebræ and marked scoliosis. The sacrum is very prominent. The iliac wings are thickened and nodular. The absence of about an inch of the lower jaw gives the face an asymmetrical appearance. The legs are emaciated. The left leg is somewhat longer than the right, owing to bowing out of the right femur just above the middle (site of the old fracture, over which is a large callus). The surfaces of both shins are roughened. Just below the middle of the left tibia, and involving chiefly the inner surface, is a hard, oval, bone-like mass 11 cm. long, and 13 cm. wide. It is not tender or movable and the skin is not adherent. On the second metacarpal joints of both hands, there are hard swellings. The terminal phalanx of the left index-finger is movable laterally.

X-Ray Pictures.—Examples of the bony tumors and bone rarefactions are seen in Figures 1 and 2, respectively. Figure 1 shows a tumor from the left shin. In Figure 2 examples of rarefaction may be seen in the second phalanges of the index-finger and third finger and in the fifth metacarpal bone.

Briefly summarized, the condition is one of osteomalacia following the appearance of multiple bony tumors.

EXPERIMENTAL DATA

A complete metabolism experiment of ten days' duration, in which the intake and outgo of nitrogen, calcium, magnesium, sulphur and phosphorus was determined, was carried out. The diet consisted of the mixed diet of the hospital, only foods that were not homogeneous enough to sample properly being excluded. The diet for a week preceding the experiment was the same as that used in the experiment, so that there was no abrupt change. The details of feeding, collecting excreta, sampling and analyzing have been described in earlier papers.² The diet follows:

NOVEMBER 17.—*Breakfast:* White bread, 51.8 gm.; oatmeal, 104.4 gm.; scrambled eggs, 32.9 gm.; coffee, 40.0 c.c.; milk, 430.0 c.c.; water, 200.0 c.c. *Luncheon:* Potatoes, 51.2 gm.; rice, 98.5 gm.; ham, 23.1 gm.; custard, 112.4 gm.; milk, 205.0 c.c.; chicken broth, 160.0 c.c.; water, 200.0 c.c. At 3:30 p. m.: milk, 250.0 c.c. *Supper:* Hamburg steak, 34.2 gm.; sweet potatoes, 23.6 gm.; banana, 44 gm.; milk, 130.0 c.c.; water, 228.0 c.c.

NOVEMBER 18.—*Breakfast:* Graham bread and butter from stock; oatmeal, 96.4 gm.; lamb chop meat, 14.6 gm.; coffee, 50.0 c.c.; milk, 470.0 c.c.; water, 360.0 c.c.; water (injection*), 300.0 c.c. *Luncheon:* Bread and butter from stock; chicken meat, 23.3 gm.; spinach, 29.7 gm.; rice, 41.4 gm.; water, 250.0 c.c.; chicken

*It was occasionally necessary to give an enema to move the bowels. Tap water was used and the amount used added to the food to be analyzed.

broth, 160.0 c.c.; milk, 150.0 c.c. *Supper*: Bread and butter from stock; meat, 26.5 gm.; junket, 114.6 gm.; chicken broth, 100.0 c.c.; milk, 150.0 c.c.; water, 450.0 c.c.

NOVEMBER 19.—*Breakfast*: Oatmeal, 85.0 gm.; sausage, 33.0 gm.; water, 200.0 c.c.; coffee, 60.0 c.c.; milk, 100.0 c.c. *Luncheon*: Chicken, 25.9 gm.; rice, 79.2 gm.; custard, 48.1 gm.; Graham bread and butter from stock; water, 210.0 c.c.; milk, 210.0 c.c.; soup, 170.0 c.c.; gravy, 50.0 c.c. *Middle Afternoon*: milk, 250.0 c.c.; water, 390.0 c.c. *Supper*: Meat, 23.9 gm.; banana, 40.3 gm.; water, 150.0 c.c.; milk, 200.0 c.c.; soup, 160.0 c.c.

NOVEMBER 20.—*Breakfast*: Oatmeal, 93.2 gm.; eggs, 40.6 gm.; brown bread and butter from stock; water, 200.0 c.c.; coffee, 140.0 c.c.; milk, 355.0 c.c.; water (injection), 240.0 c.c. *Luncheon*: Brown bread and butter from stock; chicken, 46.9 gm.; rice, 63.8 gm.; spinach, 46.3 gm.; ice-cream, 41.0 gm.; soup, 135 c.c.; water, 200.0 c.c.; milk, 250.0 c.c. *Supper*: Brown bread and butter from stock; soup, 170.0 c.c.; milk, 500.0 c.c.; water, 200.0 c.c.

NOVEMBER 21.—*Breakfast*: Brown bread and butter from stock; oatmeal, 97.1 gm.; water, 200.0 c.c.; milk, 250.0 c.c.; coffee, 70.0 c.c. *Luncheon*: Beefsteak, 25.7 gm.; rice, 71.3 gm.; apple sauce, 112.3 gm.; bread and butter from stock; water, 200.0 c.c.; milk, 400.0 c.c.; soup, 170.0 c.c. *Supper*: milk, 185.0 c.c.; oyster soup, 170.0 c.c.; water, 200.0 c.c.

NOVEMBER 22.—*Breakfast*: Banana, 37.4 gm.; oatmeal, 88.5 gm.; water, 180.0 c.c.; milk, 350.0 c.c.; coffee, 70.0 c.c.; water (injection), 315.0 c.c. *Luncheon*: Chicken, 33.0 gm.; rice, 76.0 gm.; custard, 93.8 gm.; bread and butter from stock; water, 180.0 c.c.; soup, 180.0 c.c.; milk, 250.0 c.c. *Supper*: Meat, 21.8 gm.; sweet potato, 51.7 gm.; water, 200.0 c.c.; milk, 470 c.c.; broth, 150 c.c.

NOVEMBER 23.—*Breakfast*: Bread and butter from stock; oatmeal, 91.1 gm.; egg-milk-sherry mixture, 215.0 c.c.; water, 120.0 c.c.; coffee, 70.0 c.c.; milk, 350.0 c.c. *Luncheon*: Bread and butter from stock; rice, 91.1 gm.; custard, 93.1 gm.; chicken, 32.2 gm.; water, 200.0 c.c.; soup, 170.0 c.c.; milk, 250.0 c.c.; gravy, 25.0 c.c. *Supper*: Water, 200.0 c.c.; egg-milk-sherry, 235.0 c.c.; soup, 170.0 c.c.

NOVEMBER 24.—*Breakfast*: Bread and butter from stock; banana, 42.7 gm.; water, 220.0 c.c.; sausage, 49.4 gm.; coffee, 70.0 c.c.; milk, 100.0 c.c. *Luncheon*: Rice, 88.0 gm.; peas, 52.3 gm.; turkey, 41.5 gm.; milk, 225.0 c.c.; water, 210.0 c.c.; broth, 180.0 c.c. *During Afternoon*: milk, 250.0 c.c. *Supper*: Chicken, 24.3 gm.; apple sauce, 76.7 gm.; milk, 470.0 c.c.; broth, 80.0 c.c.; water, 210.0 c.c.

NOVEMBER 25.—*Breakfast*: Banana, 42.8 gm.; oatmeal, 94.6 gm.; water, 210.0 c.c.; milk, 510.0 c.c.; coffee, 70.0 c.c. *Luncheon*: Rice, 47.8 gm.; spinach, 43.8 gm.; chicken, 33.1 gm.; water, 210.0 c.c.; broth, 170.0 c.c.; milk, 250.0 c.c.; gravy, 55.0 c.c. *During morning*: Milk, 250. c.c. *Supper*: Bread, 16.4 gm.; lamb, 23.8 gm.; peaches, 64.0 gm.; egg-milk-sherry mixture, 230.0 c.c.; milk, 470.0 c.c.; water, 230.0 c.c.; broth, 160.0 c.c.

NOVEMBER 26.—*Breakfast*: Bread, 39.7 gm.; oatmeal, 67.0 gm.; beefsteak, 28.5 gm.; milk, 420.0 c.c.; water, 100.0 c.c.; coffee, 70.0 c.c. *Luncheon*: White sauce, 40.0 gm.; apple sauce, 68.2 gm.; bread, 25.6 gm.; water, 200.0 c.c.; milk, 225.0 c.c.; soup, 160.0 c.c. *During day*: Water, 200.0 c.c.

For the whole experiment: Graham bread, 536.6 gm.; white bread, 213.4 gm.; butter, 612.5 gm.; salt, 5.9 gm.

We neglected to weigh the patient at the end of the experiment, but she appeared to be steadily gaining in weight and strength and there was a considerable retention of nitrogen.

The accompanying tables give the results.

TABLE 1.—METHODS OF ANALYSIS AND AMOUNTS USED

	Amounts Used for Analysis			Method of Analysis
	Urine c.c.	Food* gm.	Feces† gm.	
N	5	1	1	Kjeldahl
CaO	200	10	1	McCrudden ⁴
MgO	200	10	1	McCrudden ⁴
S	50	2	2	Folin ⁵
P ₂ O ₅	50	2	1	Neumann ⁶

* Total weight 3104.7 gm.

† Total weight 246.7 gm.

TABLE 2.—ANALYSIS OF URINE DAY BY DAY *

Day	N gm.	CaO gm.	MgO gm.	S gm.	P ₂ O ₅ gm.
1.....	8.08	0.291	0.106	0.590	1.692
2.....	8.40	0.293	0.119	0.648	1.680
3.....	10.28	0.333	0.139	0.734	1.840
4.....	10.08	0.379	0.107	0.716	2.020
5.....	9.56	0.315	0.123	0.656	1.948
6.....	10.56	0.350	0.131	0.730	1.880
7.....	10.92	0.330	0.129	0.804	2.072
8.....	11.52	0.298	0.129	0.762	1.996
9.....	10.76	0.477	0.045	0.788	2.048
10.....	9.52	0.278	0.123	0.684	1.936
Total..	99.68	3.344	1.151	7.112	19.112

* The urine analyses were made in duplicate.

TABLE 3.—COMPARISON OF ANALYSES OF URINE, FOOD AND FECES *

	N gm.	CaO gm.	MgO gm.	S gm.	P ₂ O ₅ gm.
Urine total.....	99.68	3.344	1.151	7.112	19.112
Feces total	11.72	18.80	3.40	1.024	15.57
Total outgo	111.4	22.14	4.55	8.14	34.68
Total intake (food)	121.4	21.17	4.69	10.03	35.55
Retention	10.0	0.14	1.89	0.87
Loss	0.97
Per cent. retained.	+8.3%	—4.6%	+3.0%	+18.8%	+2.4%

* The food and feces analyses were made in triplicate.

DISCUSSION

For a correct interpretation of the figures, the percentage accuracy of the results should be known. It is not necessary to give the weights of all the final precipitates with a discussion of the accuracy of each since the approximate accuracy of the methods can be judged by anyone familiar with them. The last figures in each case in the reported balances are probably correct to within a few figures—that is, the retention of nitrogen lies between 9.98 and 10.02 gm.; the loss of calcium oxid between 0.93 and 1.01 gm., etc.⁷

4. McCrudden, F.: The Quantitative Separation of Calcium and Magnesium, etc., Jour. Biol. Chem., 1910, vii, 83.

5. Folin, O.: Sulphate and Sulphur Determinations, Jour. Biol. Chem., 1905, i, 131.

6. Neumann, A.: Einfache verraschungs Methode, etc., Ztschr. f. physiol. Chem., 1902, xxxvii, 131; Nachträge zur Säuregemisch-Verraschung, Ztschr. f. physiol. Chem., 1904, xliii, 35.

7. The probable limits of experimental error are about as follows:

	N.	S.	CaO	MgO	P ₂ O ₅
Total urine	±0.2	±0.03	±0.01	±0.01	±0.05
Feces	±0.02	±0.01	±0.03	±0.02	±0.07

Taking the larger of these two sets as the possible error for the total outgo, we get:

Total outgo	±0.2	±0.03	±0.03	±0.02	±0.07
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For food the figures are about as follows:

Food	±0.2	±0.05	±0.04	±0.02	±0.07
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Taking the larger of each of these two sets for the error in the balance, we get

Balance	±0.2	±0.05	±0.04	±0.02	±0.07
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It is plain that there was a definite loss of calcium accompanied by a retention of all other elements and that the amounts lost and retained were outside the limits of experimental error. The question arises: Is the amount lost a significant amount? The significance of the loss depends partly on the amount metabolized, partly on the relative loss of other substances. The amount of calcium oxid lost in twelve days was about 1.0 gm., nearly 5 per cent. of the amount in the food, and over three times the average daily amount in the urine, and is probably lost chiefly through the urine for the amount in the urine is nearly double the normal.⁸ Furthermore, everything else was being retained, the retention running from 3 per cent. in the case of magnesium to 19 per cent. in the case of sulphur. These relations cannot be normal. Towle⁹ has pointed out that there is a parallelism in the metabolism of nitrogen and calcium in health and in disease unless very large quantities of calcium are especially given. And this has been found to be true for other elements. The balance given in Table 4 was found in the case of a healthy boy.

TABLE 4.—METABOLISM OF A HEALTHY BOY

	N.	S.	CaO	MgO
Total intake	86.10	6.138	14.99	3.26
Total outgo	71.46	5.222	12.42	2.53
Balance	+14.64	+ .916	+ 2.57	+ 0.73
Per cent.	+17.0	+14.9	+17.1	+22.4

The results of Hoffström,¹⁰ who studied the metabolism of a pregnant woman for a long period, showed similar parallelism in retention between nitrogen and mineral salts.

The retention of sulphur and magnesium is greater in proportion than that of nitrogen and corresponds to a growth of tissue richer in sulphur and magnesium than any of the soft tissues—such a tissue as bone. This condition is in accord with McCrudden's conception regarding the process going on, namely, that bony tissue is being catabolized and that the new bone laid down to replace it is poorer in calcium

8. The loss of calcium and retention of magnesium and sulphur are not so great in this experiment as in the experiment on which my conception of the etiology and process was based. In one of those experiments there was an average daily loss of nearly 1 gm. of CaO (*Am. Jour. Physiol.*, 1906, xvii, 211), and Berger (*Presse méd.*, 1905, xiii, 249), speaks of a case in which he analyzed the urine only and found 9.0 gm. CaO per day. The patient was in relatively good condition at the time of the present investigation, probably as a result of the good hygienic environment. If we could have studied her condition when the process was more active, greater losses might have been expected.

9. Towle, C.: Calcium Metabolism with Special Reference to Exophthalmic Goiter, *Am. Jour. Med. Sc.*, 1910, cxi, 100.

10. Hoffström, K.: Eine Stoffwechseluntersuchung während der Schwangerschaft, *Skandin. Arch. f. Physiol.*, 1910, xxiii, 326.

but richer in sulphur and magnesium than normal bone, similar to osteoid tissue plus magnesium salts.

The clinical course of this case of osteomalacia is in accord with McCrudden's conception of the etiology. The various bony tumors need lime salts for their growth and, as already pointed out in earlier papers, the bones act as a reservoir of lime salts from which the body may draw in time of need.¹¹

The tendency of the body to overproduction, to the continuation of an activity once started after the need for activity has ceased to exist, is shown in this case. The hard tumors which were probably responsible for starting the increased catabolism of bone were no longer actively and rapidly growing, yet the flux of calcium salts from the bones continued and, as shown by the metabolism experiment, the calcium was simply excreted. There are many analogies for this process. Under the name of "functional inertia," Harris¹² points out that it is as fundamental and important an attribute of living matter as irritability itself. He defines functional inertia as "that property of protoplasm whereby living matter contrives to remain in a functional *status quo ante* notwithstanding that it has received a stimulus, or, having responded to the stimulus, it contrives to exhibit its functional activity for a certain time after the stimulus as a form of energy has ceased." The condition may be compared with that of a heavy door which, when at rest, requires a certain time to get into full swing after it has been pushed and, when moving, takes time to stop if held. Of examples of latent period in starting activity, there is the latent period of muscular contraction, that occurring after glands are stimulated through their nerves and before they begin to secrete, and that occurring before the heart-beat begins to accelerate its rate when the augmentor or accelerator nerves are stimulated. Of examples of continued activity after the original stimulus has ceased

11. Further evidence to this effect has recently appeared: King, Bigelow, and Pearce (Experimental Obstructive Jaundice, Jour. Exper. Med., 1911, xiv, 148) have shown that the calcium content of the bones decreases in cases of obstructive jaundice in which calcium is needed to neutralize the toxic effects of the bile acids. Schmidt (Verhandl. d. deutsch. path. Gesellsch., 1909, xiii, 3) has pointed out that the decrease of calcium in the bony system in rickets is accompanied by an increase of this element in the soft tissues such as muscle and liver, and Higbee and Ellis, in a recent paper on osteitis deformans (Jour. med. Research, 1911, xxiv, 43)—a condition which is recognized as one of localized osteomalacia—state that calcification of the arteries is so common in these cases that it has been mentioned as a possible etiological factor.

Dr. Charles F. Painter of Boston has called McCrudden's attention to the occurrence of a late variety of non-rachitic bow-legs occurring in children about the time the epiphyses begin to harden. Is it not possible that a flux of calcium might be started by the demand for this element by the hardening epiphyses analogous, in a way, to the physiologic osteomalacia noted by Hanau and Wild in the pelvic bones of pregnant women?

12. Harris, D.: The Functional Inertia of Living Matter, London, 1908.

may be mentioned the continuation of accelerated heart action for a time after stimulation of the augmentor nervous apparatus has ceased, the continued overproduction of free receptors which, according to Ehrlich's theory, is the explanation of acquired immunity and the overproduction which Weigert has pointed out is characteristic of all tissue repair. These examples are analogous to the continued catabolism of the lime salts of bone after the original stimulus for this process has ceased.¹³ It is not improbable that overproduction may be another example of the factors of safety with which, as Meltzer¹⁴ has pointed out, the body is so well endowed.

The recurrence of attacks of osteomalacia earlier and earlier in succeeding pregnancies, and the increasing severity of subsequent attacks, make one think of the more severe and rapid production of symptoms of certain diseases: e. g., serum disease and others after a previous inoculation — a kind of allergy,¹⁵ or, to put it still more broadly, "a cell stimulated to perform a certain act not only continues to perform that act for some little time after the stimulus has ceased, but, what is more, on a second occasion a slighter stimulus will induce the like series."¹⁶

It ought to be emphasized that the conception regarding the etiology and process in osteomalacia outlined here is, of course, based *not on these theories* of functional inertia and allergy, *but on the facts* observed in chemical, clinical and anatomical investigations. The analogies are cited merely to show that, in all probability, the process in osteomalacia is but a special example of certain more general laws governing the *modus operandi* of living matter.

SUMMARY

The findings in the present case of osteomalacia are, then, in accord with the views outlined in this and previous papers² regarding the process and etiology of osteomalacia and give further support to these views. The loss of calcium and retention of magnesium and sulphur are in accord with the conception of the process in osteomalacia, as one in which the bone is undergoing metabolism but in which the new bone laid down is an osteoid tissue poor in lime salts but richer than normally in magnesium. The presence of bony tumors preceding the osteomalacia is in accord with the conception that the starting point in osteomalacia can

13. It is not improbable that another example of such overproduction or functional inertia is the change in the metabolism brought about by morphinism which enables the body to destroy increasing amounts of morphin but which continues and has a damaging effect on the organism itself if the drug is suddenly withdrawn.

14. Meltzer, S. J.: *The Factors of Safety in the Animal Structure and Economy*, Harvey Society Lectures, 1906-1907.

15. v. Pirquet, C.: Allergy, *THE ARCHIVES INT. MED.*, 1911, vii, 259 and 382.

16. Adami: *The Principle of Pathology*, 1910, i, 195.

usually, if not always, be traced to a demand for calcium salts. And the continued excretion of an excess of calcium when the bones really need this element is in accord with the conception regarding the importance of overproduction in bringing about the softening of the bone.

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