CALCIUM METABOLISM STUDIES

A. THE RAISING OF SERUM CALCIUM BY TOPICAL APPLICATIONS OF RAW AND ACTIVATED COD LIVER OIL

B. DISTURBANCES ASSOCIATED WITH THE ACTIVE DENTAL CARIES OF CHILDHOOD AND PREGNANCY

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That sunshine and cod liver oil will markedly affect calcium metabolism is altogether likely. The processes by which these effects are produced are but little understood. The studies presented here are part of a series being made to obtain data to throw light on the nature of the forces at work, and the mechanisms involved in the utilization of calcium by the body with special considerations of disturbances in calcium metabolism, particularly those which relate to tooth and bone formation, and degenerative changes in those structures after their development.

It has been demonstrated by many workers, especially by Alfred F. Hess,[1] Mildred Weinstock [2] and H. Steenbock,[3] that when animals are placed on a diet deficient in either phosphorus or calcium in the absence of sunlight, disturbances of the hard structures tend to appear, and that these may be prevented or corrected in large part by the addition of small amounts of cod liver oil to the diet, or the application of ultraviolet irradiation from artificial source to the surface of the animal.

Figure 1 shows typical progressive stages in the production of leg weakness in chickens, produced by placing them in restricted light on a diet low in phosphorus and low in fat soluble vitamins. This condition can be largely prevented by the administration of cod liver oil with the diet, also by the application of ultraviolet light from the quartz mercury vapor lamp. Figure 2 shows (*A*) a chick that was down practically as flat as the most extreme one shown in figure 1, and when cod liver oil was added to its food got up, as shown in *B*.

In order to demonstrate the nature of the action of cod liver oil and of ultraviolet light, chicks have been subjected to varying conditions. Table 1 shows in condensed form the result of placing twenty-five groups of chicks with six in each group, except the control group which con-

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* Read before the National Academy of Sciences at Washington, D. C., April 27, 1926.

1. Hess, A. F.: The Ultraviolet Rays of the Sun, J. A. M. A. **84**:1033 (April 4) 1925.
2. Hess, A. F., and Weinstock, Mildred: Lancet **1**:12 (Jan. 2) 1926.
3. Steenbock, H.; Hart, E. B.; Sell, M. T., and Jones, J. H.: J. Biol. Chem. **56**:375 (June) 1923.

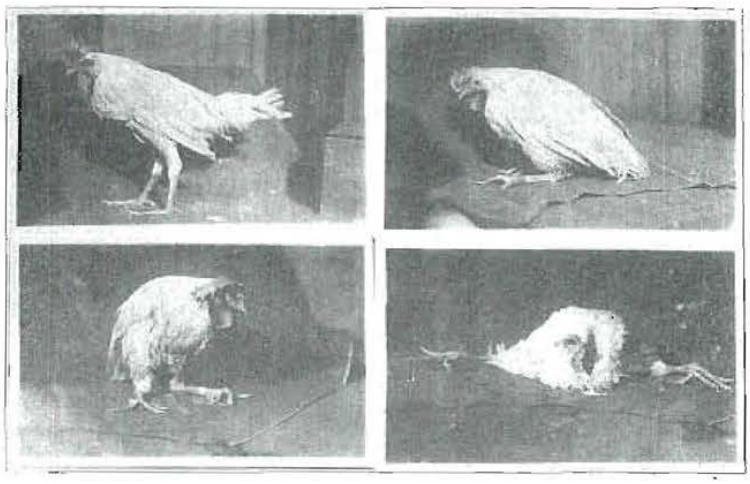

Fig. 1.—Progressive weakening of the legs of a chick deprived of radiant energy, and on a diet low in phosphorus and low in antirachitic factor. Control, upper left, had same diet but occasional sunshine.

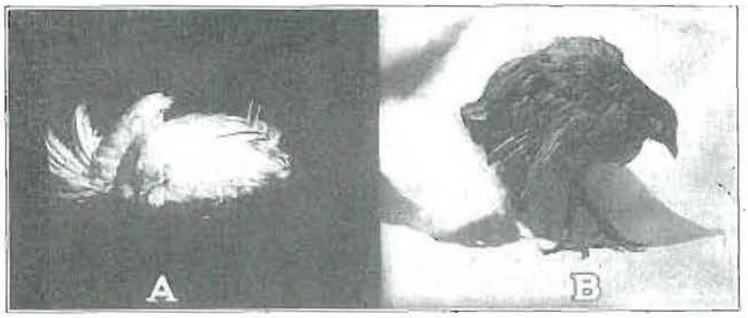

Fig. 2.—Two views of the same chick on a diet low in phosphorus and deprived of ultraviolet irradiation. *A*, completely prostrated with typical weak legs. *B*, same chick a few weeks later, after cod liver oil was added to the food. The leg deformity should be noted.

tained fifteen, namely, nine in lot 1, and 6 in lot 25. The first control lot had as much sunshine as could be given during the day, and the last had three hours daily. All of these chicks were on the same basic diet (McCollum's, 3143), the variation being entirely in activation or light source. All except the two control groups were kept in darkness except for the turning on of ruby light twice daily for two hours for feeding.

TABLE 1.—*Comparative Studies of Different Methods for Modifying Treatment of Chicks on Low Phosphorus Diet* *

Lot No.	Variable Condition	Deaths During Days of Experiment 2	3	4	5	6	7	8	9	10	11	12	13	14	Number Dead	Number Living	Condition
1	Controls														0	9	Active; well feathered
2	Darkness and ruby lamp			1	2		1		1	1					6	0	All dead; weak legs
3	Same as 2 plus ultraviolet daily for 30 minutes		1				2								3	3	Active; well feathered
4	Same as 3 plus blue filter		2						1						3	3	Active; well feathered
5	Same as 3 plus heavy window glass				3	2	1								6	0	All dead; weak legs
6	Same as 2 plus cod liver oil 1 per cent				2	1		1							4	2	Retarded growth
7	Same as 6 but 0.1 per cent	1		1	2		1		1						6	0	All dead; weak legs
8	Activated cod liver oil sunshine, 0.1 per cent	1			2							1			4	2	Medium growth
9	Same as 8 but 1 per cent		2			2								1	5	1	Medium growth
10	Cod liver oil activated 15 minutes. 0.1 per cent			1	1	2									4	2	Medium growth
11	Same as 10 but 1 per cent	1				1	1								3	3	Active; medium growth
12	Cod liver oil activated 6 hours sunshine, 0.1 per cent					1		1							2	4	Active; well feathered
13	Same as 12 but 1 per cent								1						1	5	Active; well feathered
14	Same as 12 but 5 per cent	1	2		2							1			6	0	All dead
15	Cod liver oil activated, ultraviolet 3 hours, 0.1 per cent	1	2			1									4	2	Retarded growth
16	Same as 15 but 1 per cent		1	1		2	1								5	1	Retarded growth
17	Same as 15 but 5 per cent						1								1	5	Active; well feathered
18	Raw cod liver oil 5 per cent			1	3	1									5	1	Well feathered; medium activity
19	Cod liver oil activated, sunshine 30 minutes, rubbed on neck					1	2								3	3	Active; delayed feathers
20	Same as 19; raw cod liver oil				1	2							1		4	2	Delayed growth; poor activity
21	Cholesterol activated ultraviolet, 1 per cent					1					1		1		3	3	Medium feathered; active
22	Same as 21 not activated, 1 per cent			1		4		1							6	0	All dead
23	1 per cent parathyroid extract			1											1	5	Medium feathered; fair activity
24	Food exposed to ultraviolet daily	2	1	1											4	2	Delayed growth
25	Exposed 3 hours daily to sunshine														0	6	Active; well feathered

* Nature and effect of activators. Six chicks in each group. All had same adequate diet and temperature.

OUTLINE OF PLAN

Group 1, control sunshine. All lived.

Group 2, darkness and ruby light, plus the basic diet. All of these died.

Group 3, the same, plus ultraviolet rays, for thirty minutes daily; three are living and three are dead. Those alive are active and well feathered.

Group 4, the same as 3, plus blue filter. Three are dead, and three living, active and well feathered.

Group 5, the same as 3, namely, ultraviolet rays for thirty minutes daily, plus heavy window glass. All died. They had weak legs.

Group 6, the same as 2, plus 1 per cent cod liver oil. Four are dead, two are living, but their growth was retarded.

Group 7, the same as 6, with 0.1 of 1 per cent of cod liver oil. All died.

Group 8, 0.1 of 1 per cent of cod liver oil aetivated in sunshine. Four are dead, two living, with medium growth.

Group 9, the same as 8, but with 1 per cent of activated cod liver oil. Five are dead, one is living, with medium growth.

Group 10, 0.1 of 1 per cent eod liver oil activated for fifteen minutes with ultraviolet rays. Three are dead and three living, with active and medium growth.

Group 11, the same as 10, but with 1 per eent activated cod liver oil. Three are dead and three living, with active aud medium growth.

Group 12, 0.1 of 1 per cent cod liver oil activated six hours in sunshine. Two are dead; four living are active aud well feathered.

Group 13, same as 12, but with 1 per cent cod liver oil. One died; five living are active and well feathered.

Group 14, same as 12, but with 5 per cent of cod liver oil. All are dead.

Group 15, 0.1 of 1 per cent cod liver oil, activated for three hours. Four are dead; two living, with retarded growth.

Group 16, the same as 15, but with 1 per cent of cod liver oil. Five are dead; one is living, with retarded growth.

Group 17, the same as 15, but with 5 per cent cod liver oil. One is dead; five are living, and are active and well feathered.

Group 18, 5 per cent of raw cod liver oil. Five are dead; one is living, well feathered and with medium activity.

Group 19, cod liver oil, activated in sunshine for thirty minutes, rubbed on the neck. Three are dead; three living, are active, with delayed growth of feathers.

Group 20, raw cod liver oil rubbed on neck. Four are dead; two are living, with delayed growth and poor activity.

Group 21, cholesterol activated with ultraviolet ray, 1 per cent in food. Three are dead; three living are medium feathered and active.

Group 22, 1 per cent nonactivated cod liver oil added to food. All died.

Group 23, 1 per cent parathyroid extract. One is dead; five are living, medium feathered and fairly active.

Group 24, the food was exposed to ultraviolet rays daily. Four are dead; two living, with delayed growth.

Group 25, sunshine three hours daily. All lived.

It will be noted from these data that with nonactivated cholesterol added to the food, all chickens died; with the activated cholesterol, three lived. Further, that with 5 per cent of cod liver oil, activated in the sunshine for six hours, added to the food, all died; further, that by placing of heavy window glass in front of the ultraviolet to obstruct the rays, all chicks died. It should further be noted that cod liver oil, activated thirty minutes in the sunshine, rubbed on the necks of the chicks, saved three out of six and raw cod liver oil used the same way saved two out of six. One per cent of freshly made extract of parathyroid added to the food saved five out of six.

In order to study further the nature of these processes, chemical analyses were made of the blood to determine changes in certain of the calcium factors. This is shown in table 2. For these Steenbock

and Nelson's diet 2966 was used. In this series, 216 chicks were used. I will here call attention particularly to the following:

TABLE 2.—*Blood and Lymph Chemical Studies of Chicks by Groups*

Chicks	Diet 2966	Gain, per Cent	Calcium		Inorganic Phosphorus	Total Calcium × Inorganic Phosphorus
			Total of Serum	Active		
1	Controls, sunshine	63.8	9.96	8.14	4.52	45.00
2	Ruby light	154.7	10.28	8.30	4.83	49.65
3	Ultraviolet ray, 20 minutes daily	111.6	9.25	8.30	4.10	37.92
4	Ultraviolet ray, 2 hours daily	95.7	8.53	8.13	4.10	34.97
5	1% raw cod liver oil	176.6	9.73	6 60	6.33	61.59
6	5% raw cod liver oil	57.7	8.95	8.33	5.26	47.19
7	10% raw cod liver oil	74.3	9.45	8.13	2.90	27.40
8	1% cod liver oil, 15 minutes sunshine	69.2	10.90	8.82	3.17	34.55
9	5% cod liver oil, 15 minutes sunshine	78.03	13.13	10.02	2.93	38.48
10	10% cod liver oil, 15 minutes sunshine	55.05	10.07	10.22	2.10	22.48
11	1% cod liver oil, 1 hour sunshine	85.2	20.21	.....	2.22	46.82
12	5% cod liver oil, 1 hour sunshine	77.3	9.63	7.64	3.90	37.67
13	10% cod liver oil, 1 hour sunshine	70.6	11.43	8.32	2.77	31.62
14	1% cod liver oil, 24 hours sunshine	72.9	11.37	8.66	3.71	42.18
15	5% cod liver oil, 24 hours sunshine	76.6	10.25	8.52	3.62	37.20
16	10% cod liver oil, 24 hours sunshine	67.2	9.72	8.82	3.51	34.10
17	1% cod liver oil, 24 hours ultraviolet	133.1	10.84	6.84	5.45	59.07
18	5% cod liver oil, 24 hours ultraviolet	89.04	10.96	6.60	4.85	53.16
19	10% cod liver oil, 24 hours ultraviolet	36.8	10.42	8.32	1.94	20.20
20	Raw cod liver oil on necks	6.3	11.25	.....	....	.....
20	Fluid from necks of 20	....	18.97	14.19	....	.....
21	Cod liver oil 30 minutes on necks	56.07	15.04	10.22	2.15	32.35
21	Fluid from neck of 21	....	27.14	18.69	....	.....
22	5% raw cholesterol	1.4	9.35	8.92	2.24	20.91
23	5% cholesterol, 30 minutes sunshine	26.1	10.25	....	4.77	48.90
24	10% raw butter	62.2	11.69	7.25	5.40	63.13
25	10% butter, 24 hours ultraviolet	50.8	8.95	6.75	5.20	46.54

CHEMICAL ANALYSIS

The average total calcium of the controls was 9.9, the active 8.1, and the inorganic phosphorus 4.5. Of the chicks under treatment, several have had distinctly higher total calcium than the controls. For example, those receiving 5 per cent cod liver oil activated in the sun for fifteen minutes had a total calcium of 13.1. One of the methods of investigation of the influence of cod liver oil was to rub it on a limited portion of the chicken's body, as, for example, the neck. This had a very marked effect on the level of the calcium of the blood and on the general physical condition of the chicks. The average total calcium of the blood of this group was 11.2, whereas the average total calcium of the controls was 9.9. The chicks of another group were treated similarly with the cod liver oil on the neck, except that it had been activated in the sun for thirty minutes. The average total calcium of the blood of the chicks of this group was 15.

The inorganic phosphorus was also influenced by the various methods of the utilization of cod liver oil. The average in the control groups was 4.5, and of the group receiving 5 per cent raw cod liver oil in the food the average was 5.2. The group receiving activated cod liver oil on the necks had an inorganic phosphorus of 2.1.

Similar studies were made by making topical applications of cholesterol. The average total calcium of the group receiving applications of 5 per cent nonactivated cholesterol was 9.3, whereas another group receiving the same method of treatment and material, except that it was activated in the sun for thirty minutes, had an average total calcium of 10.2.

Several of the chicks that were having cod liver oil rubbed on their necks in each of the different groups developed large cystic sacs filled with serous fluid. This fluid was aspirated, pooled together for each group, and calcium determinations were made. As the circulating lymph, spinal, pleuritic and ascitic fluids have total calcium levels from 40 to 60 per cent of that of the total calcium of the blood, and since the total calcium of these serums has corresponded approximately in amount with the diffusible calcium of the blood, it has been suggested that the differences in level of calcium in these serums and the blood are controlled by the diffusion through the tissues, the colloidal calcium being held back by the tissues. I have already stated that the total calcium of the blood of these serums was higher than that of the control, namely, 11.2 and 15, while the control was 9.9. If now one would anticipate the same general relationships between blood calcium and cystic fluid, as in ascites and lymph, he would have factors approximately half of 11 and 15. Contrary to expectations, the average total calcium of the fluid from the neck of the group receiving raw cod liver oil applied topically was 18.9. instead of 5 or 6, and for the group having the activated cod liver oil applied locally the average was 27, instead of 7 or 8. In other words, in the second group the total calcium level of the fluid in the neck was nearly twice that of the total calcium of the blood, instead of half.

MECHANISM OF ACTIVATION

This seems to throw an important new light on the mechanism of activation. Had a calcium salt been applied with cod liver oil, raw or activated, one might think that the calcium was absorbed by the tissue being treated. Since, however, in this case, the calcium of the aspirated fluid was higher than that of the blood stream, and since no calcium could reach this fluid except through the blood stream, there must have been established in the chicks a condition of increased solubility for calcium in this fluid, which in turn influenced the blood to bring the total blood calcium higher than that of the controls. This also indicates that this fluid had a solubility factor higher than that of the blood to take calcium from the blood to it.

From the foregoing, it will be noted that exposing the cod liver oil and cholesterol to radiant energy, sunshine or ultraviolet rays, changes in a marked degree the effect produced by the use of the oil or cholesterol.

and, further, that overexposure produced deleterious effects. Evidence has been presented to the effect that butter exposed to ultraviolet irradiation for several hours was made distinctly poisonous for mice, though this observation would indicate that it was not poisonous for chicks.

In order to study further the effect of ultraviolet irradiation, cod liver oil, so exposed, has been further studied as follows: When ordinary raw cod liver oil is placed in a dish, and a photographic plate is placed over the dish, the chemical action produces fogging of the emulsion, which is decreased by decreasing temperature, and increased by increasing temperature, as shown in figure 3. *A* was placed in the icebox, but *B* in the incubator for an equal period of time. *A* had an obstruction made of tissue paper in varying thicknesses, progressing

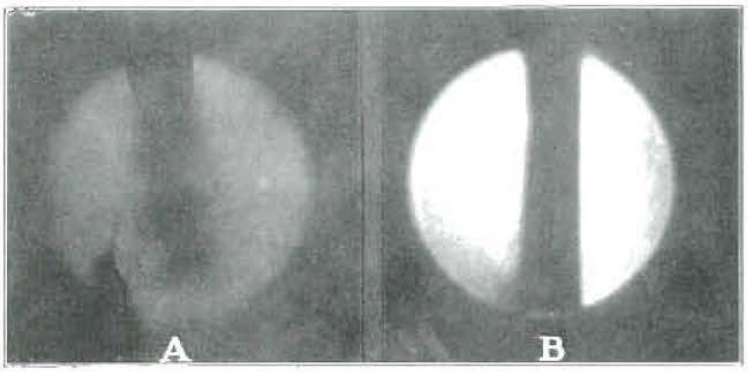

Fig. 3.—Clouding of a photographic plate produced by cod liver oil from hydrogen dioxide formation.

from 1 to 20 layers. These twenty layers obstructed completely the gaseous substance which produced the chemical action. In *B* the obstruction was a piece of card. This photographic effect is not produced by radiant energy given off by the oil, but by gases, the chief of which is hydrogen dioxide. When cod liver oil is exposed to ultraviolet light or sunshine, this capacity for clouding a photographic plate is very markedly increased, as shown in figure 4. Two different brands (*A* and *B*) of cod liver oil were used, and the figures 1 to 8 show progressively the exposures for the following units of time:

1. Not exposed to ultraviolet ray.
2. Exposed to ultraviolet ray for five minutes.
3. Exposed to ultraviolet ray for ten minutes.
4. Exposed to ultraviolet ray for fifteen minutes.
5. Exposed to ultraviolet ray for twenty minutes.
6. Exposed to ultraviolet ray for thirty minutes.
7. Exposed to ultraviolet ray for forty minutes.
8. Exposed to ultraviolet ray for sixty minutes.

In a subsequent communication will be reported studies made of a large number of organic compounds, chiefly tissue extracts, only one of which is included here. In figure 5 is shown the effect of exposing an extract of pancreas in "B" to ultraviolet rays form a mercury vapor lamp for thirty minutes, and in "C" to sunshine for one hour, in comparison with the same shown in "A" without exposure. It is important to note the marked difference in effect of the ultraviolet rays from the quartz

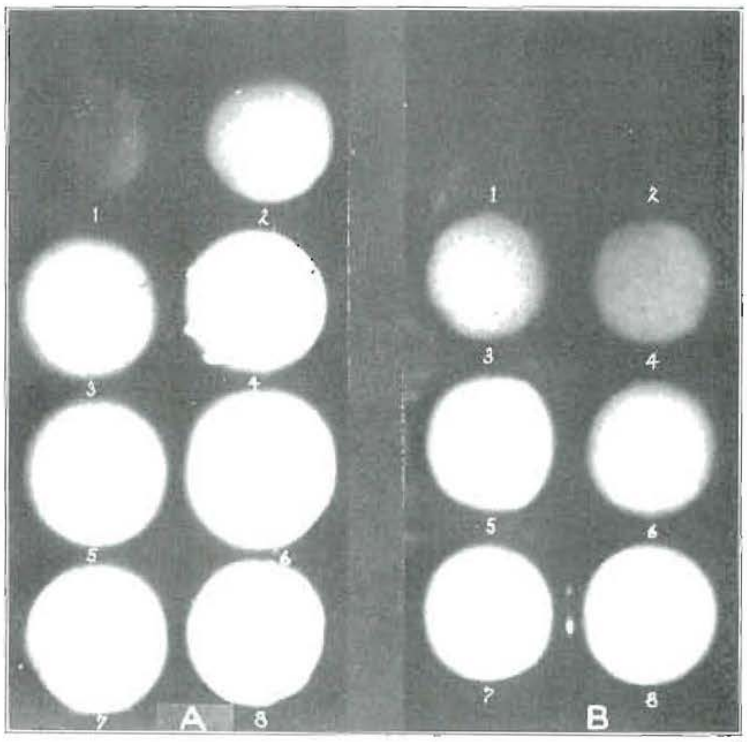

Fig. 4.—Progressive increase in capacity of cod liver oil to cloud a photographic plate, with increase of time of exposure of oil to sunshine or ultraviolet irradiation.

vapor lamp and that of sunshine. The administration of calcium lactate with cod liver oil produces entirely different effects, both clinically and as expressed in chemical constituents of the blood from the administration of either of these substances alone.

I have made observations to determine the effect on the ability of cod liver oil to cloud a photographic plate, with and without the addition of calcium lactate. In figure 6 three views are shown: *A*, cod liver oil

alone with its brilliant reaction; *B*, 90 per cent cod liver oil, and 10 per cent calcium lactate, and *C* shows 50 per cent cod liver oil, and 50 per cent calcium lactate. It will be observed that in the last proportion, the capacity of the cod liver oil to produce clouding has been completely destroyed, and indeed on close observation of the negative one can see a distinctly opposite affect, which on first consideration might be thought to be a true reversal, but which on testing is not the reversal of overexposure.

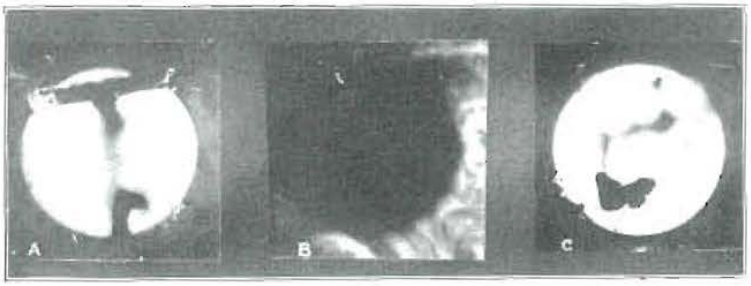

Fig. 5.—The marked difference in effect on a photographic plate, with exposure to sunlight in mercury vapor lamp.

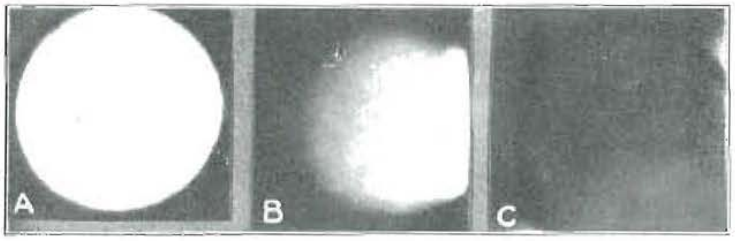

Fig. 6.—The change in effect of cod liver oil on the addition of calcium lactate.

A typical result of applying these processes in an experimental case. is shown in the following experiment:

Since the various forces operating to maintain normal balance are in equilibrium in health, the effects of treatment in changing relative levels will be essentially different in normal and in pathologic states. In the latter state, depletion or exhaustion may become determining factors, unless reinforcement is provided. This the physician has undertaken to do by producing a pathologic state, then undertaking to modify the developing abnormalities through the means of treatment. Some idea of these general effects can be obtained from a review of the progressive changes produced by placing an infected tooth beneath the skin, as shown in figure 7, which

shows a graph of the consolidated story of the inoculation of rabbit 1356 by putting an infected tooth beneath its skin, at which time the total calcium (1) stood at 13.9 mg.; the active calcium (2) at 10.5 mg.; non-diffusible (4) at 8.4 mg.; diffusible (5) at 4.9 mg.; inorganic phosphorus (3) at 4.5 mg.; total calcium balance (7) at plus 21 mg. (the product of inorganic phosphorus and total calcium, minus 40); the active calcium balance (8) at plus 8 mg. (the product of active calcium and inorganic phosphorus, miuus 40). The horizontal line on the chart represents 40, and the figures above and below this liue represent positive or negative calcium balance. The weight line, 2,200 Gm., which is represented by increase or decrease above or below the starting point, is shown in (9) and the leukocytic count, starting at 7,000 in the graph (10). The heavier penpendicular lines of the squares represent the number of days, and tbe heavier horizontal lines milligrams per hundred. It will be noted that in the first five days, after the infected tooth was placed under the skin of the animal, the total calcium decreased from 13.9 to 12.5, during which time tbe active calcium decreased from 10.5 to 6.2; the inorganic phosphorus decreased from 4.5 to 3.4, and the calcium balance for both total and active accordingly dropped rapidly. All animals and all subjects whose calcium balance lines are below the base line are presumably in a pathologic state. In more than 200 rabbits studied by placing an infected tooth beneath the skin, 75 per cent have died, as I have stated when the active calcium decreased to the vicinity of 5 mg. This rabbit, at the end of seven days, was therefore in grave danger. The active calcium balance stood at minus 22. According to the history of previous cases, the animal would soon have been dead. At this point, an injection of parathyroid extract was made, at which time the leukocytic count, which had gone up during the first four days, was receding. It will be noted that with the three injections of our own preparation of parathyroid by the method of Collip, which increased the solubility factor of the blood for calcium, all of the graphs rapidly moved upward, the total going from 12.2 to 14.4, the active from 6.1 to 8.2; the calcium balances both changed. The leukocytic count improved, but this improvement was temporary, and the rabbit soon began to decline. With this temporary improvement, at which time calcium was being taken from the bones through the increase in the solubility factor of the blood for calcium, there was a marked loss in weight of the animal, coincident with the improvement in the clinical picture. The fuel for the defense was secured at the expense of the body tissues. At this point, to check the further decline, and in order to pay the calcium bill from without, activated cod liver oil and calcium lactate, on two days in succession, were placed in the rabbit's stomach by tube, as shown at the point of the arrow on the ninth day. Again there was a marked improvement in the calcium balance, largely through the reenforcement of the metabolism of inorganic phosphorus.

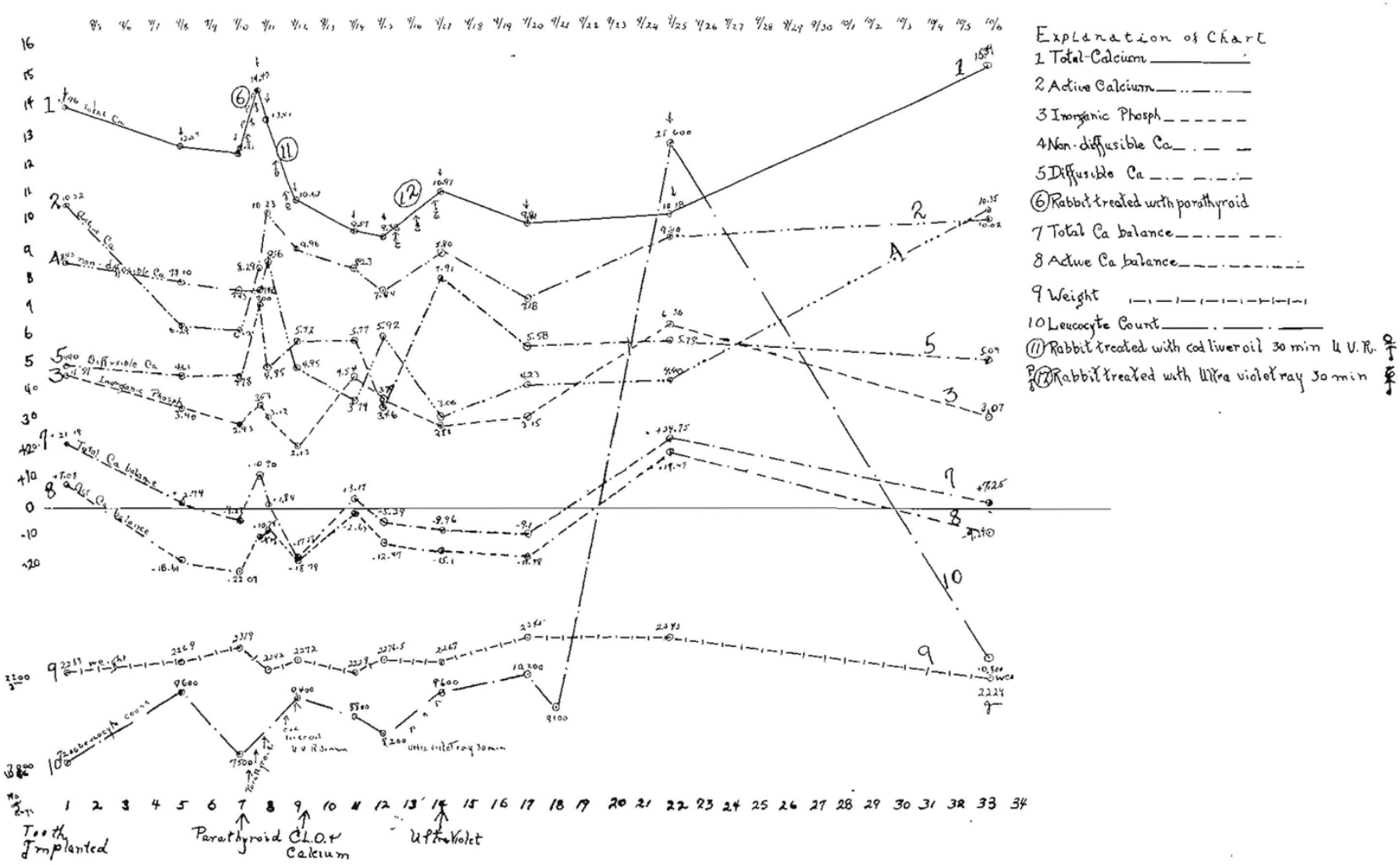

Fig. 7.—Changes produced in various blood factors by placing infected tooth beneath the skin of rabbit 1356.

This improvement was again temporary. It should be noted that the total calcium came down progressively (at the figure marked 11) following the administration of parathyroid, but with the administration of the activated cod liver oil and calcium lactate, the active calcium came up rapidly to 10.2, approximately its starting point. The rabbit was still carrying the infection, and a quantity of pus, making an abscess about as large as a hen's egg, had accumulated around the tooth. Ultraviolet irradiation, thirty minutes daily, was given on three successive days, at the time marked (12) on the total calcium line. One should note the increase shortly after this in the leukocytic count, which jumped from 9,000 to 28,000. With this splendid defensive reaction, the size of the accumulation around the tooth decreased from the size of a hen's egg to about the size of a hickory nut, so that the pus was no longer palpable. It should be noted that the calcium balance for both total and active calcium passed well above the zero line; the total calcium again mounted to and above its original normal, 15.3; the tissue over the tooth broke down, the tooth was exfoliated and the animal was out of danger. At the time of this writing, six months after the foregoing experiment, the animal is apparently still in good health. Space does not permit the inclusion in the graph of extensions of the lines to the time of the exfoliation of the tooth.

The negative calcium balance produced in this experiment by the placing of an infected tooth beneath the skin of the animal resulted from exhaustion of the easily available calcium supply of the circulation, and the depression of function of the factors involved in maintaining the defensive warfare. In other words, a pathologic state has been produced which creates an abnormal stress on the mechanisms of immunity and defense, a part of which involves the calcium and phosphorus metabolism.

In previous communications,[4] I have presented data which related calcium metabolism disturbances both to focal infections and to various degenerative diseases. These data throw light on some of the mechanisms involved in these processes.

PHYSICAL DISTURBANCES AND DENTAL CARIES

Physiologic stresses may produce very unusual demands on the same factors. This is well illustrated in the conditions of the stress of growing childhood and of motherhood. It is a matter of universal knowledge that both childhood and maternity constitute periods of an unusual susceptibility to dental caries. The old saying, "A tooth for every child" is familiar to all. The period of lactation is known to be quite as susceptible a period as that of pregnancy. Oral hygiene and prophy-

4. Price, Weston A.: Dental Infections, Oral and Systemic, Cleveland, Penton Publishing Company; Dental Infections and the Degenerative Diseases, Cleveland, Penton Publishing Company; Ann. Clin. Med. 4:943 (May) 1926.

laxis have tended to reduce dental caries in both these groups. They have not, however, proved adequate to prevent dental caries in conditions of marked susceptibility.

These studies have involved investigations along many lines to throw light on the mechanisms whereby calcium is taken from the food and made available to the body for growth and nutrition, and the forces which disturb their normal progress.

During growth, there is an abnormal demand for calcium for tooth and skeleton building. During pregnancy and lactation, there is an increased demand on the mother for the fetus and for the growing infant. When the nutrition cannot supply ample calcium for the immediate demands, the mother takes the essential constituents from her own system to meet the needs. The laws of supply and demand operate in favor of the fetus in preference to the mother. In case of a deficient supply, the mother is in negative calcium balance, that is, she is using calcium faster than she is assimilating it, with the result that the storage depots in the calcified structures are being depleted.

Since the body is not able to utilize calcium, except through the aid of certain accessory food factors and radiant energy factors, the expectant mother may be in marked negative calcium balance on a diet actnally containing adequate calcium, but unavailable for her use. These studies indicate that in the rapid caries of childhood and in pregnancy and lactation, there is a state of marked negative calcium balance, and that this condition is an important contributing factor to the process in conjunction with bacterial processes.

The administration of calcium lactate and cod liver oil, raw or activated, to the growing child at the period of active caries, and to the expectant mother as well as during her period of lactation, not only benefits their well-being, but in a very marked degree reduces the tendency to dental caries. Their change in susceptibility to caries is directly associated with their change from a negative to a positive calcium balance.

The average number of cavities per pregnancy has been estimated as five, with an average of one tooth completely lost. These factors will vary greatly in different communities. Under the treatment mentioned in the foregoing, in my experience, this has been reduced to an average of approximately one cavity per pregnancy. In the rapid caries of childhood, mouths that would have a dozen or more new cavities per year, have had the same very greatly reduced, in some nearly to zero. Delayed development of permanent teeth in childhood, associated with delayed shedding of deciduous teeth, and the eruption of permanent teeth, has changed to a condition in which exfoliation, root-formation and eruption have been greatly hastened under this treatment. In some cases there has been as much progress in a few months after starting treatment as in the few years preceding it.

A practical application is shown in the following case. Figure 8 shows the teeth of a boy at 7 years of age (A), and again at 11 (B), during which time the deciduous teeth had not been normally exfoliated or the permanent teeth erupted, which should have taken place at 9 or 10 years of age. The roots of the permanent teeth were not forming properly, nor were the bones surrounding them of normal radiopacity. In one month's time, after placing this boy on the treatment of activated cod liver oil and calcium lactate, the deciduous teeth were shed, and in three months' time the permanent teeth showed marked advance in their calcification and eruption. During this period of three months the boy grew 1 inch in height. Table 3 shows his changed physical state in two months' time, during which he grew $^{1}\!/_{16}$ of an inch, gained 4 pounds in weight, and physically was markedly better. Sufficient improvement in calcium and phosphorus levels was produced in these two months to change his negative calcium balance of minus 16 to a positive calcium balance of plus 33 (*C*).

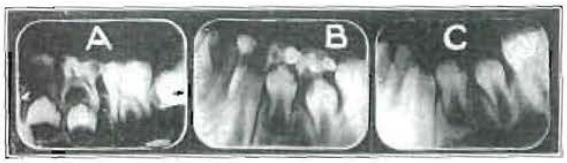

Fig. 8.—Comparison of progress of calcification between the first two pictures (*A* and *B*), three years and eleven months apart, and between the last two pictures, three months apart (*C*). The retained deciduous teeth were shed in one month after starting treatment.

TABLE 3.—*Change Produced in a Boy with Delayed Dentition by Sixty Days' Treatment to Improve Calcium Metabolism*

	Conditions or Symptoms		
	Before Treatment	Time Elapsed	After Treatment
Total weight	70 pounds	2 mo.	4 pounds gain; 74 pounds
Height	4 ft. 5½ in.		4 ft. $6^{9}\!/_{16}$ in. (gain $^{11}\!/_{16}$ in.)
Physical state	Poorly nourished		Looks better nourished
Nervous state	Listless; irritable		Very anxious to go to school.
Digestive condition	Poor appetite; shunning fruits and vegetables		Good appetite; now likes vegetables
Serum calcium	9.06		9.56
Inorganic phosphorus	2.65		7.71
Calcium balance	−16 (negative)		+33.7 (positive)

A disturbance of the mechanisms of calcification occurs very frequently in children of delayed development. This has its physical expression in lack of density of the bone around the teeth, and in delayed development of the tooth structure, particularly a delay in the reduction of the size of the pulp chambers of permanent teeth. This condition frequently happens in children with marked susceptibility to dental caries.

Such a case is shown in figure 9. This boy, at 14 years of age had a large number of cavities, some of which nearly entered the pulp chambers, partly because the pulps were abnormally large. He was placed on calcium lactate and activated cod liver oil. In the upper illustration it will be seen that the pulp chamber is abnormally large, and in the lower one, taken a year later, the same condition is shown, showing that the pulp chamber has reduced approximately to normal size for that age. During this period of a year, only one very small new cavity has developed, which is a most important improvement. Physically, he has changed from a nervous, irritable, easily frightened child, in which state

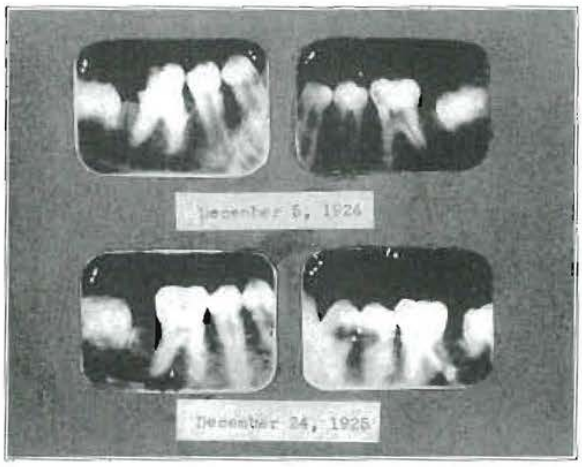

Fig. 9.—Change in calcification of permanent teeth in one year's time by treatment to improve calcium metabolism. Previous active caries completely checked.

it was almost impossible at first to render professional service, to a condition of marked lessening of this abnormal state.

An illustration of the change in the condition of expectant motherhood is shown in table 4. The change in physical state is shown by comparison in the two columns. The negative calcium balance was reduced almost to zero. The abnormal demand was now supplied from external sources and the stress of maintaining body equilibrium was thereby reduced. The patient's physical state was so greatly improved that she was able to perform her duties practically all day, whereas with her first pregnancy she was dragging, and almost bedridden through the entire period.

Another and striking illustration of improvement following treatment in the calcium factors in a case of pregnancy is shown in table 5. It will be seen that in twenty-five days the calcium balance changed from a negative one of minus 28 to minus 7. The diffusible calcium, which was at 3.8, increased to 5.2. The total serum calcium per hundred cubic centimeters of serum (not of blood) increased from 9.1 to 12.2, an increase of 33.1 per cent. With these changes there was marked improvement in the patient's general physical condition. An important

TABLE 4.—*Change in a Case of Pregnancy After Six Weeks' Treatment to Improve Calcium Metabolism*

	Conditions or Symptoms		
	Before Treatment*	Time Elapsed	After Treatment
Disturbance	Many boils	6 weeks	Complete absence
Physical state	Fatigue		Exhilaration
Nervous state	Depression		Animation
Digestive condition	Poor appetite and nausea		Excellent appetite; no nausea
Serum calcium	10.06	24 days	10.28
Inorganic phosphorus	3.32		3.87
Total proteins	5.91		7.12
Total globulin	2.41		4.02
Calcium balance	—6.7		—0.3

Second pregnancy. Aged 30.
* Treatment began third month.

TABLE 5.—*Calcium Stress of Pregnancy*

			May 28, 1926	June 22, 1926
Calcium per 100 cc. of whole blood			7.39	9.29
	Before	After		
Calcium of serum of 100 cc. of whole blood	6.89	8.28		
Calcium of cells and clot of 100 cc. of whole blood	0.50	1.01		
	7.39	9.29		
Calcium of 100 cc. of serum			9.12	12.22
Calcium of 100 cc. of cells and clot			1.99	3.16
Cellular calcium per cent of total			6.71	8.29
Calcium of 100 cc. of plasma (citrated)			8.00	10.42
Diffusible calcium			3.89	5.20
Nondiffusible calcium (colloidal)			5.25	7.02
Cell volume			25.40	22.50
Inorganic phosphorus			1.25	2.63
Sugar			91.80	.....
Nonprotein nitrogen			23.00	.....
Total calcium balance (negative)			—28.60	—7.8

Second pregnancy, eighth month. First lost at seventh month.

factor in her condition was the tendency to anemia. The red blood count was 3,800,000; Arneth index 51, and white blood cell count 13,800. There was marked central pallor in the red cells, but no anisocytosis or poikilocytosis, and in both cases normoblasts were seen.

In another paper I will discuss data which relate to the distribution of the calcium in the blood plasma and cells in anemia. This patient has completed her term, has had a normal birth, and both she and the child are in excellent condition.

COMMENT

The evidence strongly indicates that the marked susceptibility to dental caries of both childhood and motherhood is, in part, due to a state of stress, in which the subjects are in a condition of negative calcium balance, and that a correction of this phase can often be improved generally by the administration of small quantities of activated cod liver oil, together with calcium lactate. The cod liver oil is given in capsules 0 or 00. In the 00 capsules 10 drops of the activated oil are placed with a dropper, and sufficient is made up to last two weeks. The oil becomes rancid much more quickly after being activated. It should be kept on ice in the meantime. The oil is given simultaneously with the calcium lactate, 1 to 10 grains, according to the overload. These are taken together during the meal, with 3 meals a day in accordance with the conditions. In a few cases, 2 capsules and 20 grains will be taken to advantage with each meal. Usually this will be too large a dose. Increasing the cod liver oil over this amount is a distinct disadvantage, as is also increasing of the calcium lactate over this amount in most cases.

Cod liver oil is activated by placing it in an open dinner plate, in a layer not over one eighth of an inch deep, and exposed to the bright noonday sunshine for from three to five minutes in the summer, and from five to fifteen minutes in the winter. It should be stirred while being exposed. Exposure for longer periods, say an hour or two, will produce a change in the oil so that very undesirable symptoms such as headache may develop. When, for example, butter is exposed to the ultraviolet light for several hours, it is so poisonous as to produce the death of mice, and, as I have indicated before, all of the chicks died after being fed on cod liver oil that had been exposed to six hours' sunshine. In our experience, cod liver oil should not be activated with ultraviolet light from the mercury vapor lamp, since it produces changes in the oil which are distinctly harmful.

I am reporting here only a limited phase of the studies on this problem. Intensive studies also are being made on the relation of focal infection, particularly dental infection, to calcium metabolism disturbances, and with particular consideration of the correction of these disturbances, or betterment of pathologic conditions thereby created, both by the removal of the focal infections, and by treatment with a view to reinforcing disturbed calcium and phosphorus metabolism. Among these disturbances are the anemias and various degenerative diseases of special tissues.

SUMMARY

1. Data have been presented indicating that certain calcium factors of the blood are influenced by activators which may be applied either through the normal route by the stomach, or externally to the surface

of the body. In the former, they may be related directly to the utilization of the calcium from the food. When applied externally, however, they must act on the food by first acting on the circulating fluids of the body.

2. A specific action of the activators on fluids of the body for the increasing of their capacity to carry calcium is shown by the raising of calcium in tissue fluid to a concentration which is higher than the concentration of the blood from which it must be obtained directly or indirectly, notwithstanding the fact that the level of calcium tissue fluid is normally of approximately one-half that of the total calcium of the plasma.

3. Data are presented indicating that the dental caries of both childhood and pregnancy are influenced directly by the administration of activators for calcium metabolism.

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