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NEWER KNOWLEDGE OF CALCIUM METABOLISM IN HEALTH AND DISEASE, WITH SPECIAL CONSIDERATION OF CALCIFICATION AND DECALCIFICATION PROCESSES, INCLUDING FOCAL INFECTION PHENOMENA

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INTRODUCTION AND REVIEW

IN previous communications,[1] I have submitted evidence which I interpret to indicate that the difference in apparent tissue change about infected tooth roots is not necessarily an expression of difference in the quantity of infection but rather an expression of the type and extent of reaction on the part of the host; that decalcification with the production of a granuloma is a protective process, the granuloma being, in purpose and in effect, when functioning, a quarantine station placed by Nature between the infection and the host; that there may be, therefore, a condensing osteitis as the expression of a reaction rather than a rarefying osteitis, in which latter case there may be quite the opposite of a chamber about the infected tooth, and, further, that a zone of abnormally dense bone may surround a chamber of rarefaction and partially or quite completely hide it from view; that these qualities of reaction on the part of the patient are such that they may be divided into three groups on each of two bases: first, the type and nature of the local reaction, and, second, the presence or absence of a tendency to systemic involvement from focal infection and other so-called rheumatic group diseases in general.

I have demonstrated in the foregoing communications that one of the most important effects of focal infection is expressed in the blood changes, particularly the calcium of the blood; that the calcium of the blood is in different states, some of which is interpreted to be ionized because it is diffusible. Some associated with the thrombin in the circulating blood is released in the process of clotting, and a portion is easily available for chemical and physiologic reaction.

I have shown that the administration

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1. Price, W. A.: Dental Infections, Oral and Systemic (Vol. 1); Dental Infections and the Degenerative Diseases (Vol. 2), Cleveland, Penton Publishing Co., 1923; Dental Infections and Related Degenerative Diseases, Some Structural and Biochemical Factors, J.A.M.A., 84:254-259 (Jan. 24) 1925; Fundamentals Suggested by Recent Researches for Diagnosis, Prognosis, and Treatment of Dental Focal Infections, J.A.D.A., 12:641 June, 1925.

of cod-liver oil and calcium lactate, and particularly an activated cod-liver oil, has direct bearing and influence on the general symptoms and physical well-being and the reducing of susceptibility to dental caries.

The evidence presented also strongly indicated that the manner in which the body utilizes its calcium not only becomes a basis for classification of individuals into three particular groups, but also seems to have a direct bearing on the type of affections to which that individual will be susceptible or against which he will make a poor fight.

TABLE 1.—100 CONSECUTIVE FAMILIES*

	No. of Cases in Families	Rheumatic Group Affections					
		Severe		Mild		Absent	
		No.	%	No.	%	No.	%
Tuberculosis	51	6	12	7	14	38	75
Diabetes	15	1	7	3	20	11	73
Anemia	15	6	40	1	7	8	53
Stroke	72	8	11	25	35	39	54
Cancer	45	2	4	11	24	32	71

*Study of association of nonrheumatic group affections with presence or absence of rheumatic group susceptibilities.

This paper is not designed primarily further to support the evidence previously submitted, though I have much additional available evidence for doing so, but is designed to give a bird's-eye view of a new outlook on healing science in general, and dental and medical practice, and the prevention of dental caries in particular, in the light of the important new knowledge regarding the normal and abnormal uses, distribution and wastage of calcium.

That the calcium of the body is not only one of the most important and indispensable factors, but one of the most exacting and far-reaching in its influence on defense and susceptibility, is more and more abundantly demonstrated with the accumulation of new data. I have previously presented evidence indicating not only that the rheumatic group lesion susceptibilities are related to calcium metabolism and tend to be characterized by a lower than normal level of certain of its phases, but also that certain affections, such as diabetes, tuberculosis and cancer, show indications of a relationship to calcium in that they seem to be associated with certain high levels, as regards total calcium, as a characteristic of the individual before being broken by disease, this level characterizing the individuals who tend to decalcification in the presence of irritants; and that, apparently, it is not the levels of the calcium compounds, but chiefly the mechanisms that control these levels, with which we are concerned.

These studies have seemed to indicate that the calcification or decalcification of a lung tubercle would largely determine the progress of the affection, if not the fate of the individual. Similarly, it was shown that hyperglycemia tends to be associated with extensive peridental decalcifications, such as pyorrhea alveolaris, and that the infection of this disease tends to increase the hyperglycemia, and hence the necessity that diabetics be treated accordingly with regard to their predominant dental infections.

A further detailed study of this aspect of this problem has brought additional evidence which I am presenting in part in Tables 1 and 2. These show the results of careful tabulation on 100 consecutive families, where they have been studied with regard to the presence or absence in the family of tuberculosis, anemia, diabetes, stroke and cancer, in

order to determine the association of nonrheumatic group affections with the presence or absence of rheumatic group susceptibilities.

In these families, we study the individual, his or her brothers and sisters, the brothers and sisters of each parent, and the four grandparents, making, on an average, sixteen individuals per family. This, therefore, is a study of 1,600 individuals from this standpoint. As previously stated, records are discarded when the information is considered too incomplete to justify deductions.

TABLE 2.—STUDY OF ASSOCIATION OF NONRHEUMATIC GROUP AFFECTIONS WITH PRESENCE OR ABSENCE OF RHEUMATIC GROUP SUSCEPTIBILITIES (100 CONSECUTIVE FAMILIES)

	No. of Cases in Families	Rheumatic Group Affections			
		Severe		Mild or Absent	
		No.	%	No.	%
Cancer	45	2	*4*	43	*96*
Tuberculosis	51	6	*12*	45	*88*
Diabetes	15	1	7	14	*93*
Stroke	72	8	*11*	64	*89*
Anemia	15	6	*40*	9	*60*

We have divided these 100 individuals into three groups on the basis of my recent classification with regard to the rheumatic group affections; namely, severe, mild or absent susceptibility, and we find that when tuberculosis has appeared, in 75 per cent of the cases it has been in the group with absent susceptibility, as compared with 14 per cent mild, and 12 per cent severe; diabetes, 73 per cent in the absent group, 20 per cent mild, and 7 per cent severe; anemia, 53 per cent absent, 7 per cent mild, and 40 per cent severe; stroke, 54 per cent absent, 35 per cent mild, and 11 per cent severe; cancer, 71 per cent absent, 24 per cent mild, and 4 per cent severe. When we have been in doubt regarding classification, we have placed the individual in the more severe grouping of the two classifications in question.

If, now, we determine these percentages by combining the mild and absent groups into one, and compare these with the severe, we find that we have cancer, 96 per cent, as compared with 4 per cent; tuberculosis, 88 per cent, as compared with 12 per cent; diabetes, 93 per cent, as compared with 7 per cent; stroke, 89 per cent, as compared with 11 per cent, and anemia, 60 per cent, as compared with 40 per cent.

This seems strongly to emphasize again what I have brought out in my previous communications to the effect that, when cancer appears, it tends to be in a group of individuals with high defense for the rheumatic group diseases, people who quite routinely say either that they have never been sick a day in their life or have not had any rheumatic group disturbances; which, as I have repeatedly shown, is the group in which we find the high level of calcium.

It must not, however, be concluded or presumed that the matter is so simple as one of threshold or level of any calcium factor, total, active, diffusible, nondiffusible or otherwise. It is in all probability related not only to certain high levels but also to mechanisms of control of calcium levels, mechanisms which themselves become definitely disturbed, and regarding which we have apparently quite definite evidence.

It is of interest in this connection to quote from a communication that has

recently appeared[2] in which Dr. Ludwig M. Wolff, sanitary councillor and German cancer specialist and research worker, is reported, from Paris, to have discussed recent cancer etiology theories. The title of the article is "German Cancer Expert Denies Cancer Germ Theory." After stating why he feels justified in saying, "There is no such thing as a cancer germ. There can be none. How do I know that? Very simply," he goes on to outline how cancer appears only after thirty and forty years of age, while no organisms are known to be selective of age. His statement is so clearly to the point that the next three paragraphs are quoted directly from him.

> The last report of the Middlesex Hospital in London supports this view by recording the significant fact that cases of cancer there have been known to recover spontaneously. It is on this and similar facts that Prof. Barton Scammell, the president of the Radium Institute at Dover, England, bases his idea, for which there is a good deal to be said, that owing to certain defects in the diet and the preparation of modern food, the civilized human being of today suffers from lack of potassium in the body and that this is one of the factors, if not the main factor, in the occurrence of cancer. It is, of course, a well known fact that the primitive races do not suffer from cancer.
>
> The Dover idea of treatment involves the use of radio-phosphate of potash. This oxidizes the blood and prevents an excess of calcium, that usual phenomenon of middle age, just about the time when cancer begins to rear its head. The solutions of the radioactive alkali tend to clear out of the body the calcium accumulations.
>
> While the treatment and the avenue of research on which my own work and that of those with whom I am associated is based, starts from the same general conception as that of the Dover workers, we adopt somewhat different methods.

2. Science News-Letter, Vol. 7, No. 230, Sept. 5, 1925.

The line on which Dr. Wolff and his associates are working has to do chiefly with the roentgen ray and radium, both for treatment and prevention, and involves, as you will note, a conception of disturbance of the mechanisms of control of calcium. It is of more than ordinary interest that my researches from a clinical and blood chemical standpoint should have indicated the need for the same general point of view that these German and English workers have obtained from direct contact with the clinical and research aspect of the cancer problem.

RECENT ADVANCES

The space available for this communication does not permit of an abstract or review of the recent important communications bearing on calcium metabolism. A few are of such outstanding importance that I will refer to them both in this paragraph and later.

It has been known for years that the complete removal of the parathyroid glands of most animals, including human beings, will result in death preceded by tetany, and that this change is accompanied by a marked fall in blood calcium. Collip[3] has recently presented a method for extracting an active principle from parathyroid glands, with which he has been able to cure the tetany of parathyroidectomy and apparently return an animal to normal when it seemed to be dying from that condition.

Cameron[4] has done important work on the comparison of the total calcium

3. Collip, J. B.: J. Biol. Chem., 63:395 (March) 1925.

4. Cameron, A. T., and Moorhouse, V. H. K.: The Tetany of Parathyroid Deficiency and the Calcium of the Blood and Cerebrospinal Fluid, J. Biol. Chem., 63:687 (April) 1925.

of the blood and of spinal fluid in dogs, and has shown that in that animal, under the conditions of his experiments, the average of twenty-two determinations on 20 dogs gave 11.1 mg. total serum calcium and 5.8 total cerebrospinal fluid calcium, the latter averaging 53 per cent of the total calcium of the blood serum, with variations from 42 to 73.

Hess[5] has shown that, just as cod-liver oil will cure or prevent rickets, so cholesterol or phytosterol that has been exposed to irradiation will do so, while the nonirradiated products will not.

Steenbock[6] and his associates have shown that the exposure of the dry meal of a deficient diet, capable of producing a deficiency disturbance, will cure the deficiency if it is exposed to suitable irradiation.

Holt[7] has presented important evidence indicating that the ion product of calcium and phosphorus is more significant than is the product of inorganic phosphorus and total calcium.

OUTLINE OF TASKS UNDERTAKEN IN THESE STUDIES

Before outlining in detail the various determinations that have been made, I shall state briefly the objects to be sought. While our own and other studies have abundantly demonstrated both the importance of calcium in general, and particularly of the level of the active calcium, there are available no data adequately indicating the interrelationships between these, and their relative importance when disturbed. There has been much evidence that individuals may starve to death for calcium on a diet amply supplying it. We have therefore had no means of adequately interpreting the nature and rôle of activators.

While it has been abundantly demonstrated that the parathyroids largely control the total calcium of the blood, as evidenced by the death from tetany following the removal of the parathyroids, there has been practically no information as to the influence of the parathyroids on the active and diffusible calcium. The carrying on of investigations intended to determine the effect of parathyroid, which we have undertaken several times, has been entirely unsatisfactory, owing to the irregular results obtained, strongly indicating differences in efficiency of the experimental product. The influence of parathyroid extract and of activators has not been studied, or at least data are not available, demonstrating the rôle of these products in connection with deficiency diets or in connection with irradiation. I have had these various factors under intensive study during the past year.

THE ROLE OF PARATHYROID IN CALCIUM METABOLISM

The rôle of parathyroid in calcium metabolism, while known to be exceedingly important, has been but little understood. We have been continually embarrassed in our investigations on this problem during several years to find that we could not with any certainty duplicate our results. We readily discovered that the difference related to a variation in the product with which we were experimenting and that this lack

5. Hess, Alfred F., and Weinstock, Mildred: Antirachitic Value of Irradiated Cholesterol and Phytosterol, J. Biol Chem., 64:193 (May) 1925.

6. Steenbock, H., and Daniels, A. L.: J.A.M.A., 84:1093 (April 11) 1925.

7. Holt, L. Emmett, Jr.: Studies in Calcification. III. A Quantitative Study of the Equilibria Concerned with the Calcification of Bone, J. Biol. Chem. 64:579 (July) 1925.

of constancy obtained with practically all the available brands used.

With the announcement by Collip[3] of his success in concentrating an active principle from this gland by means of dilute hydrochloric acid, we began to use that method for making the extracts and again, three hours, six hours and twenty-four hours later. It will be noted that, in all of the products secured from drug stores, the level of the total blood calcium went progressively down; whereas, with the products that we prepared ourselves in each case, it

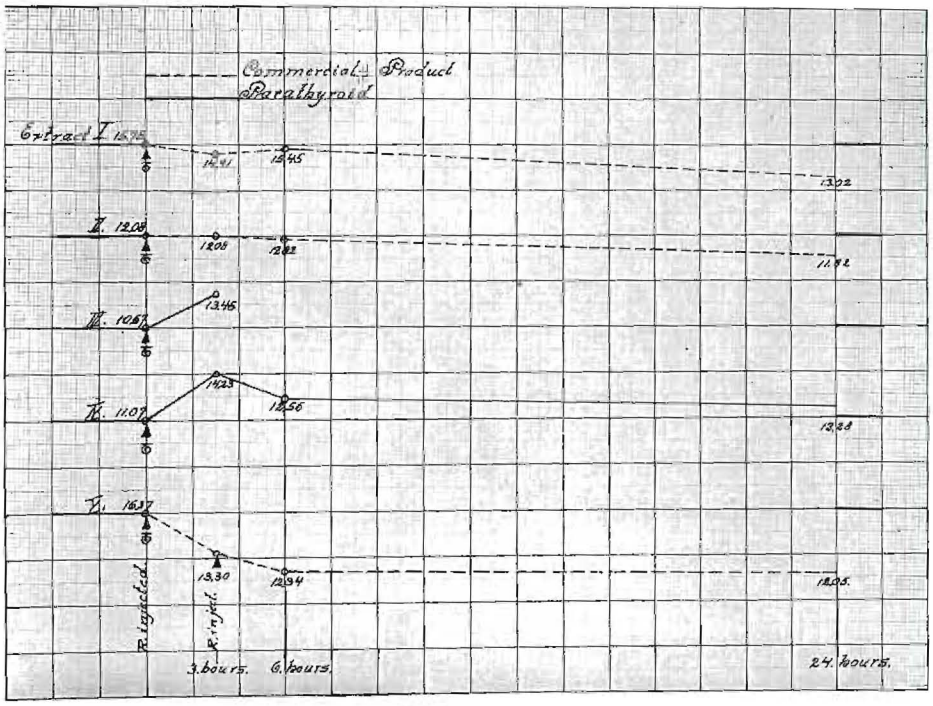


Fig. 1.—Variations between commercial products and those prepared in the author's laboratory. Dotted lines: commercial products. Solid line: laboratory products.

directly. Figure 1 indicates the difference between the commercial and our own products. In it, extracts Nos. I, II and V (shown by dotted lines) are from commercial products purchased at the drug stores; III and IV (shown by solid line) are products that we made ourselves.

In each case, one injection was made. The blood was taken before the injection and the total calcium determined, went up at three hours, dropped back part way at six hours, and in twenty-four hours was still above the normal level at which it started. It was, therefore, a continued and not a transient effect. The amount injected in each case was, as nearly as we could judge, the same.

That this result is not without exception is shown in Figure 2, a comparison of a commercial preparation

and our own preparation, in which it will be seen that, with the commercial preparation, two injections of 0.3 c.c. were used (Rabbit 1364). There was a slight increase from 11.34 to 11.6 in the total calcium and then a decline to 11.17, a little below the starting point, when four more injections were given and the total calcium rose to 11.8, an increase of 5.6 per cent, or 4 per cent above the starting level, and in twenty-four hours decreased to 11.33, just a little below the starting point.

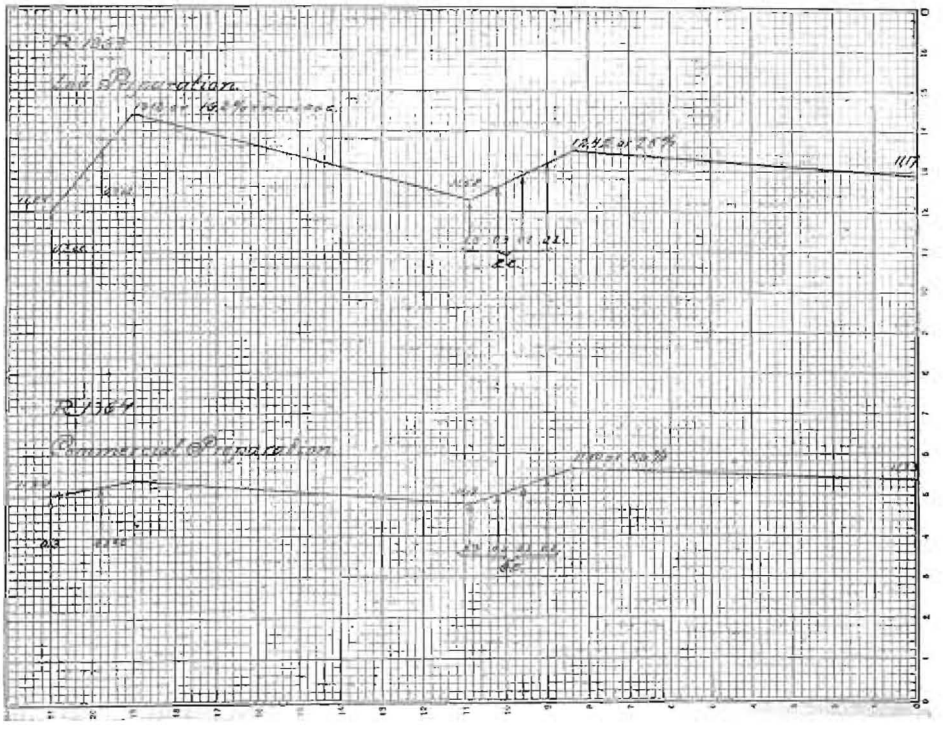


Fig. 2.—Comparison of commercial preparation and a preparation from the laboratory of the author.

At the same time (in Rabbit 1363), the same injections were made with one of our laboratory preparations, and in the same period there was an increase from 11.29 to 13.1, or 16 per cent, then a drop to 11.58, still above the original (whereas, in this time, the commercial product came below the starting point) then, after the four injections, increased again to 12.45, an increase of 7.5 per cent, and in twenty-four hours had come down to 11.1.

We have accordingly tried the effect of larger doses of parathyroid for comparison. Figure 3 shows results in two rabbits injected with fresh extract of parathyroid. The first (1362) received 0.2 c.c. of our preparation and in an hour a second injection of 0.2 c.c., with the effect that, in three hours, the total calcium had increased to 14.12

mg. from a starting point of 11.70, a total increase of 20 per cent. In three hours, this fell to 13.06 mg., and in twenty-four hours to 12.97, an amount still 11 per cent above the starting point.

Rabbit 1360 had a starting calcium of 11.51 mg. and received 2.5. c.c. at

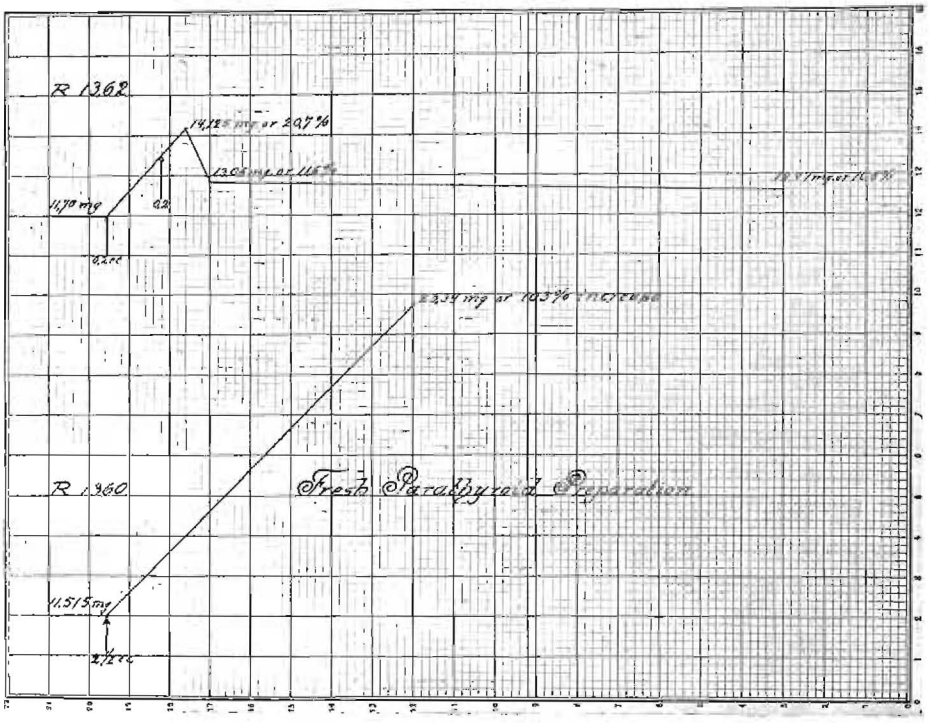


Fig. 3.—Results in two rabbits injected with fresh extract of parathyroid. In one, the total calcium doubled in six hours.

once, with the result that, in six hours, the calcium increased to 23.39 mg., a total increase of 103 per cent, soon after which the rabbit died.

This marked difference in the efficiency of the commercial and our own make of parathyroid extract is of such great importance that I gave the matter considerable study, going directly to the abattoir and ascertaining the nature of the products that were submitted by the slaughter houses, presumably for the purpose of making parathyroid products.

On being given material that was supposed to correspond with that supplied for the purpose of making the product, we made careful histologic sections, which indicated that a considerable part, amounting in some samples to as high as 50 per cent of the total gland material, consisted of other gland materials, including mucous, lymph, salivary and thyroid. It cannot easily be understood or appreciated what extreme difficulties are encountered in dissecting out these glands. The parathyroid glands in an ox are only about the size

of a small bean and are enclosed in a fibrous capsule, which is largely enmeshed in thyroid tissue. Each gland must, therefore, be dissected out with great difficulty, even if it is located, and its location is a particularly difficult procedure since so many other gland structures are encountered. The neck tissue in koshered animals is so mutilated that it is often impossible to locate these glands.

We have here two separate and important problems. One is the necessity for getting parathyroid product and the other is the necessity for not getting other gland product, which may have effects entirely different from those desired. Our studies in this matter will be reported later. We have enough facts to indicate that the effect of some of these other gland products is directly to depress the calcium, and they are accordingly antagonistic to parathyroid.

STUDY OF BLOOD TO DETERMINE THE CHANGES PRODUCED IN ITS CHEMICAL FACTORS BY THE PRESENCE OF FOCAL INFECTIONS, SUCH AS DENTAL INFECTION, WITH SPECIAL CONSIDERATION OF SPECIAL FORMS OF CALCIUM IN THE BLOOD

In previous communications, I have demonstrated important variations not only in total calcium of the blood, but also in a factor that we have, for want of better nomenclature, referred to as active or ionized. Normal circulating blood has, according to Vines, approximately from 10 to 11 mg. of total calcium, of which approximately 4 mg. will be combined with thrombin, and which is released in the process of clotting and will appear in the blood serum as an amount that will be active in the biologic test of producing normal clotting in a control serum in an amount approximately equivalent to that of the total calcium determined by incineration or colorimetric methods. In several reports by Vines, as in our own, it is demonstrated that a portion of the blood calcium does not appear as an active factor in certain pathologic states, and with removal of the pathologic state this factor tends to disappear. We have accordingly undertaken to study the factors that are influenced most, both by pathologic states and by medication.

As in the results of Collip, we have been able to raise the normal calcium of animals by injection of freshly made parathyroid extract, as indicated, for example, in Figure 3, in which it will be seen that the blood calcium has been more than doubled in a rabbit by intravenous injection in the short space of three hours, the actual increase being from 11.51 to 23.39 mg. It is of particular importance and interest to note that this increase in total calcium in this healthy rabbit of more than 100 per cent in three hours was not accompanied by an increase of the active calcium, which decreased slightly. This is of paramount importance as will be presently demonstrated.

While the knowledge of calcium metabolism has been enlarging rapidly, data have not been provided, to my knowledge, which establish the relation of the various factors, total, active, diffusible and nondiffusible, in each normal and pathologic state. This has seemed to be one of the paramount problems demanding solution before

proper progress can be made in interpreting the relative and actual importance of these various factors when made as single determinations. I have already reported large numbers of cases of tests on animals, both normal and pathologic, in which active and total calcium have been presented, though we did not, at that time, determine the diffusible and nondiffusible.

While several methods are available for making calcium phosphorus, fat and other determinations, the following have been used chiefly in these studies: total calcium by the Kramer-Tisdall method, and as modified by Tisdall, Clark, and Collip;[8] diffusible and nondiffusible calcium by the methods of Cushny, Cruickshank, Rona and Takahashi;[9] inorganic phosphorus by the method of Bell and Doisy;[10] active calcium by a combination of the methods of Vines, and that of West;[11] fat and lipoids by the method of Bloor.[12]

Table 3 presents, and Figure 4 illustrates, the important changes in these various factors which have been tested at the same time in two rabbits, whose normal health had been affected by placing an infected tooth beneath the skin. As will be noted from the weights, these animals were strong healthy stock; they had been in our pens for months, and they were fully accustomed to the environment and to the diet, which was not changed.

As previously reported, the effect of placing an infected tooth beneath the skin of an animal, such as a rabbit, is to start in progress a series of physical changes that are expressed in the blood picture as changes in blood cells and their proportions, particularly in the blood chemical constituents. It is practically a universal rule that animals so treated live or die within a few days or weeks in proportion as they have the ability to build about the involved tooth a fibrous encapsulation strongly resembling the dental granuloma and functioning, as I have shown, as a quarantine station. This protection may delay death for weeks or months, though, in time, these animals tend to break (even though they have encapsulated the tooth), with nephritis or pneumonia. As the active calcium goes down to or below 6, the animals become very lethargic, and death is usually a matter of only a few days or hours after the active calcium gets down to 5.5, since

8. Tisdall, F. F.: Kramer-Tisdall Method for Determination of Calcium in Small Amounts of Serum, J. Biol. Chem., 56:439 (June) 1923. Clark, E. P., and Collip, J. B.: Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem., 63:461 (March) 1925.

9. Cruickshank, E. W. H.: Studies in Experimental Tetany: I. Distribution of Calcium. II. Colloidal and Ionic Calcium, Brit. J. Exper. Path., 4:213 (Aug.) 1923; Cushny, A. R.: The Colloid-Free Filtrate of Serum, J. Physiol., 53:391 (May) 1920; Rona, P., and Takahashi, D.: Ueber das Verhalten des Calciums im serum and über den Gehalt der Blutkorperchen an Calcium, Biochem. Ztschr., 31:336, 1911.

10. Bell, R. D., and Doisy, E. A.: Rapid Colorimetric Methods for the Determination of Phosphorus in Urine and Blood, J. Biol. Chem., 44:55-61 (Oct.) 1920.

11. Vines, H. W. C.: J. Physiol., 55:86 (May) 1921. West, Fred; Bauer, J., and Barnickol, K.: A New Method for the Determination of Calcium and Thrombin in Serum, J.A.M.A., 78:1042 (April 8) 1922.

12. Bloor, W. R.: A Method for the Determination of Fat in Small Amounts of Blood, J. Biol. Chem., 17:377, 1914; A Method for the Determination of "Lecithin" in Small Amounts of Blood, ibid., 20:133, 1915.

TABLE 3.—CHANGES IN BLOOD CONSTITUENTS FROM PLACING AN INFECTED TOOTH BENEATH THE SKIN OF A RABBIT

Days Rabbit 1356	First Day*	5th Day	7th Day‡	7th Day 6 hrs. later	8th Day	9th Day‡	11th Day	12th Day	14th Day**	17th Day	22nd Day	33rd Day
Total calcium (1)	13.96	12.57	12.21	14.42	13.41	10.67	9.57	9 38	10.97	9 81	10.18	15.39
Active calcium (2)	10.52	6.29	6.12	8.29	10.23	9 96	8.23	7.44	8.80	7.18	9.35	10.02
Inorganic phosphorus (3)	4 57	3 40	2 93	3.53	3 12	2.13	4.54	3.79	2.83	3.15	6.36	3.07
Nondiffusible calcium (4)	8.45	7 81	7.43	7.42	8.56	4.95	3.74	5.92	3 06	4.23	4.40	10 35
Diffusible calcium (5)	4.90	4.61	4.78	7.00	4.85	5.72	5.77	3.46	7 91	5.58	5.78	5.04
Total calcium balance (7)	+21.19	+2 74	−4.23	+10.90	+1 84	−17 27	+3.17	−5.29	−8.96	−9 10	+24.75	+7.25
Active calcium balance (8)	+8.08	−18.61	−22.07	−10.74	−8 08	−18.79	−2 04	−12.47	−15.10	−17 38	+18.47	−9.24
Weight (9) (grams)	2,233	2,269	2,319		2,242	2,272	2,229	2,276	2,267	2,345	2,345	2,229
Leukocyte count (10)	7,200	9,600	7,500			9,400	8,800	8,200	9,600	10,200	28,600	10,800

*Tooth implanted beneath the skin. ‡Parathyroid administered.
†Cod-liver oil and calcium administered (Also ultraviolet ray, 30 minutes). **Ultraviolet ray for 30 minutes.

in that state they are rapidly overwhelmed.

This becomes, then, a simple and an efficient means for producing a pathologic state which is, as I have abundantly shown in my previous communications, comparable to that of patients suffering from chronic dental infections with regard to levels of calcium, ratio of polymorphonuclears to small lymphocytes and lassitude.

I have accordingly used rabbits prepared in this way on which to make determinations as to the effect of various procedures on calcium levels. These have included the use of parathyroid extract, the administration of calcium lactate and cod-liver oil, and irradiation with ultraviolet. Table 3 and Figure 4 present the data regarding Rabbit 1356. (We have the parallel data for another rabbit run at the same time, the report of which we have deleted because of the length of this paper.) These two rabbits each had a tooth planted beneath the skin. Rabbit 1356 started with a total calcium of 13.39, an active calcium of 10.52, a diffusible calcium of 4.9, a nondiffusible calcium of 8.45 and an inorganic phosphorus of 4.54. In four days, the total calcium had fallen to 12.57, or 6 per cent, the active calcium to 6.29 or 40 per cent (reduction), the diffusible calcium to 4.7, or 4 per cent, the nondiffusible calcium to 7.8, or 7.5 per cent, and the inorganic phosphorus to 3.4, or 24.5 per cent. For the next two days the active calcium and the diffusible calcium remained about constant, while the total calcium went down to 12.21 and the nondiffusible to 7.4, and the inorganic phosphorus to 2.93.

At this point, the animal was injected with parathyroid extract, 0.5 c.c.,

hourly, until three injections were given. Six hours after the first injection, the total calcium had increased to 14.92 mg., an increase of 19 per cent, and in twelve hours, it dropped to 13.4 mg. The active calcium rose abruptly from 6.12 to 10.23, a remarkable increase; the nondiffusible rose from 7.43 to 8.56; and the diffusible fell from 7.00 to 4.8, after a temporary rise, during the first eight hours, from 4.7. The inorganic phosphorus first rose from 2.9 to 3.5 and then dropped to 3.12.

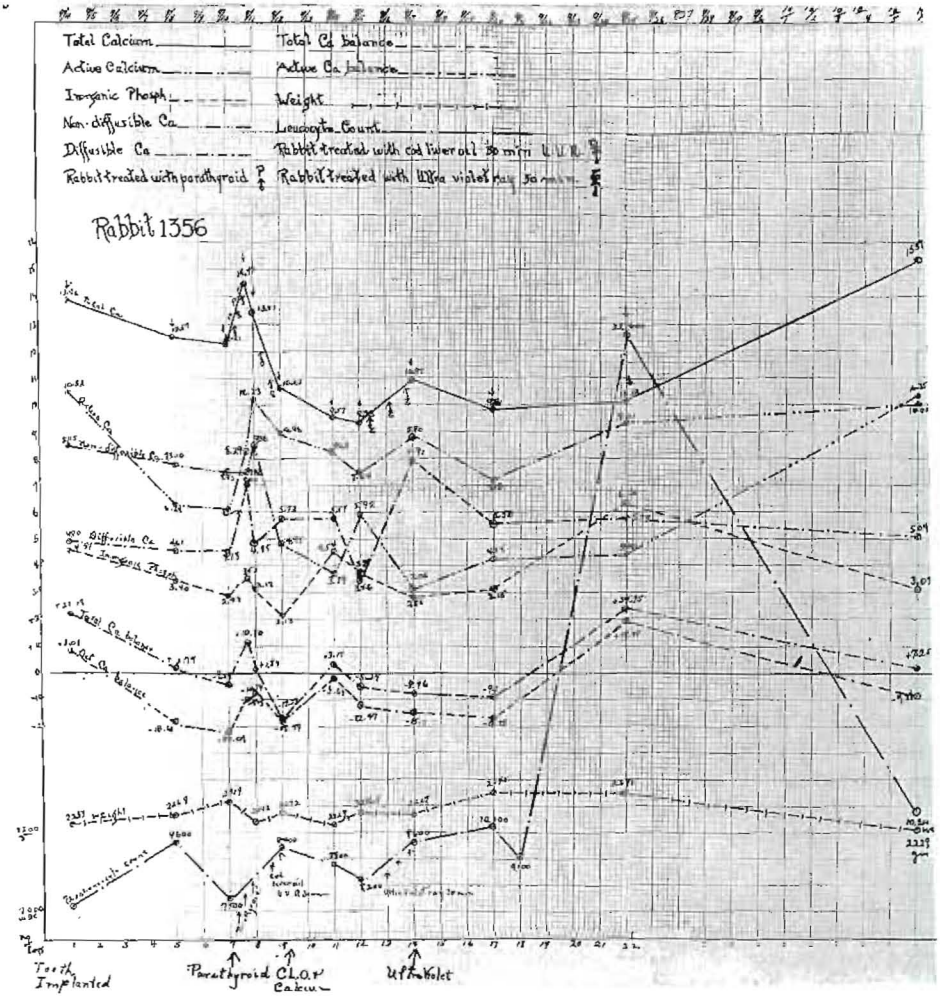


Fig. 4.—Changes in total and active and diffusible and nondiffusible calcium in a rabbit under the skin of which an infected tooth had been placed.

It is of especial interest to note, first, that the administration of parathyroid

extract was able temporarily to snatch this rabbit from a crisis, such as regularly results from a depression of the active calcium to or near 5, and that not only was the total calcium raised but also all the other forms.

This immediately raises the question as to where this calcium came from, for it is not at all probable that it came from the food. Light is thrown on this by the change in the animal's weight, which fell 77 gm. The parathyroid extract apparently made it possible for the blood stream to take calcium from the natural depots, the skeleton, but simply changing the location of calcium would not change the total body weight. This phase is being investigated.

During the next twenty-four hours, the animal was twice given 5 gm. of calcium lactate and 5 gm. of activated cod-liver oil by stomach tube, with the combined effect in three days of checking the rapid decline of the inorganic phosphorus, which, while it dropped at first to 2.1, rose to its starting normal level of 4.57. The total calcium dropped at first more rapidly than the active, but the nondiffusible made a considerable reduction from 8.5 to 3.7, then rose to 5.9 on the fourth day, with the total calcium at 9.3 and the active at 7.4.

At this time, the rabbit was given three treatments with ultraviolet rays from an air-cooled quartz mercury vapor lamp. This was followed by a rise of the total calcium to 10.9, the active from 7.4 to 8.8, and the nondiffusible from 5.9 to 7.9, the diffusible going down, and the inorganic phosphorus down to 2.85.

As more and more evidence accumulates, it emphasizes the great importance of the calcium balance as an expression of defense. By one method of determining it, total calcium is multiplied by total inorganic phosphorus, which should give a product of 40 or above. The amount above 40 is spoken of as a positive calcium balance, and below 40 as a negative calcium balance.

In Table 3, the calcium balance on the basis of these two methods of determination is presented, and it will be noted that, on a basis of the total calcium, there was a positive balance of 21, and for the active calcium, a positive balance of +8 on the first day of the experiment. On the fourth day of the experiment, that is, four days after the tooth was planted, the total calcium balance had dropped to a +2 and the active calcium balance to a —18. The active calcium balance remained negative throughout the entire course until the twenty-first day of the experiment, when it rose to +19; whereas, the total calcium balance went to a negative of —17 on the eighth day and rose finally to +24 on the twenty-first day. These two curves are shown in Figure 4. The tooth was removed surgically, and the rabbit returned rapidly to normal.

INVESTIGATIONS OF THE NATURE AND SOURCE OF ACTIVATORS FOR CALCIUM METABOLISM

That human beings, animals and birds may die with calcium metabolism disturbances on diets adequate in calcium but deficient in other factors has been abundantly demonstrated. Prominent among the accessory factors is phosphorus, but even an ample supply of phosphorus and calcium will not completely relieve serious and often fatal results in the absence of certain other accessory food factors, among

which are chiefly fat-soluble substances. I have found no terminology which seems so well suited to the conditions involved as the term "activators," for, in our investigations on animals and human beings, they seem clearly to be of that nature. We surely cannot speak correctly of parathyroid hormone as an accessory food factor and yet parathyroid is distinctly an activator.

I have already referred to the work of Hess and his co-workers with relation to the rôle of cholesterol in serving as an activator after it has been exposed to irradiation, though inadequate without that exposure, and of the effect of exposing to ultraviolet radiation the dried cereals which produced the pathologic states and thereby curing the same affection which they have produced, as so clearly brought out by Steenbock.

The information as to the nature, type and method of action of these activators has been exceedingly meager, and I have undertaken an extended series of investigations to throw light on this point. Owing to the rapidity of growth and ease of handling large numbers, I have chosen white rats and chickens as most suitable for these particular studies.

The first group of chickens consisted of 150 white Plymouth Rocks. These were divided into twenty-five groups of six each. All had the same diet and conditions of housing, the diet being No. 3143 of McCollum, which is ample in calcium and low in phosphorus and activators. The temperature of the room was maintained at 95 F. for the first week and 90 F. the second week, in accordance with the best care of young chickens. Table 4 gives the data on this series.

The controls, which were given sunshine in connection with this diet, consisted of two lots, one of nine and the other of six chicks, the former exposed for six hours a day and the latter, three hours a day, to sunshine. There were no deaths in either group in the fourteen days of the experiment. All were lively and well feathered. These controls were put in the same darkened room for the balance of the time that they were not in the sunshine. All chicks had the same basic diet, and were kept in darkness and subjected to ruby light.

Group 2 had darkness and an hour of ruby lamp twice a day for feeding. All of these chicks died by the tenth day. Their death was preceded by marked weakness, particularly of the legs.

Group 3 had, in addition, thirty minutes daily exposure to ultraviolet light from a mercury quartz lamp. Three died. The three that lived were lively and well feathered. Feathering is much affected by some diets, and is not a measure of growth or "pep."

Group 4 were given ultraviolet irradiation through a special filter. Three died, and three lived, and were lively and well feathered.

Group 5 were subjected to the same conditions as Group 4, except that window glass intervened. All died. Weakness of the legs was one symptom shown.

Group 6 were given raw cod-liver oil. Four died. Three lived, but growth was retarded.

Group 7 were given 0.1 per cent cod-liver oil. All died.

Group 8 were given 0.1 per cent cod-liver oil, activated in the sunshine. Four died. The two that lived showed medium growth.

Group 9 were given cod-liver oil,

TABLE 4—NATURE AND EFFECT OF ACTIVATORS (SIX CHICKS IN EACH GROUP, ALL OF WHICH HAD THE SAME ADEQUATE DIET AND TEMPERATURE)

Lot No.	Variable Condition	Deaths During Days of Experiment														No. Dead	No. Living	Lot No.	Condition
		1	2	3	4	5	6	7	8	9	10	11	12	13	14				
1	Controls															0	9	1	Peppy; well feathered
2	Darkness and ruby lamp				1	2		1		1	1					6	0	2	All dead; weak legs
3	Same as 2 plus ultraviolet daily for 30 min			1				2								3	3	3	Peppy; well feathered
4	Same as 3 plus blue filter			2						1						3	3	4	Peppy; well feathered
5	Same as 3 plus heavy window glass					3	2	1								6	0	5	All dead; weak legs
6	Same as 2 plus CLO 1%					2	1		1							4	2	6	Retarded growth
7	Same as 6 but 0.1%		1		1	2		1		1						6	0	7	All dead; weak legs
8	Activated CLO sunshine; 0.1%		1			2							1			4	2	8	Medium growth
9	Same as 8 but 1%			2			2								1	5	1	9	Medium growth
10	CLO activated 15 min.; 0.1%				1	1	2									4	2	10	Medium growth
11	Same as 10 but 1%		1				1	1								3	3	11	Peppy; medium growth
12	CLO activated 6 hr. sunshine; 0.1%						1		1							2	4	12	Peppy, well feathered
13	Same as 12 but 1%								1							1	5	13	Peppy; well feathered
14	Same as 12 but 5%		1	2		2							1			6	0	14	All dead
15	CLO activated ultraviolet 3 hr.; 0.1%		1	2			1									4	2	15	Retarded growth
16	Same as 15 but 1%			1	1		2	1								5	1	16	Retarded growth
17	Same as 15 but 5%							1								1	5	17	Peppy; well feathered
18	Raw cod liver oil 5%				1	3	1									5	1	18	Well feathered; moderate pep
19	CLO activated sun 30 minutes; rubbed on neck						1	2								3	3	19	Peppy; delayed feathering
20	Same as 19; raw cod liver oil					1	2							1		4	2	20	Delayed growth; poor pep
21	Cholesterol activated ultraviolet, 1%						1					1		1		3	3	21	Medium feathered; peppy
22	Same as 21 uot activated. 1%				1		4		1							6	0	22	All dead
23	1% parathyroid extract				1											1	5	23	Medium feathered; fair pep
24	Food exposed to ultraviolet daily			2	1	1										4	2	24	Delayed growth
25	Exposed 3 hr. daily to sunshine															0	6	25	Peppy; well feathered

activated in sunshine. Five died, and one lived. Growth was medium.

Group 10 were given 0.1 per cent cod-liver oil activated in sunshine for fifteen minutes. Four died, and the two that lived showed medium growth.

Group 11 were given 0.1 per cent cod-liver oil activated in sunshine for fifteen minutes.

Group 12 were given 0.1 per cent cod-liver oil, activated for six hours in sunshine. Two died, and the four that lived were lively and well feathered.

Group 13 were given the same treatment as Group 12, but with 1 per cent cod liver oil. One died and the five that lived were lively and well feathered.

Group 14 were given the same treatment as Group 12, but with 5 per cent cod-liver oil. Six died.

Group 15 were given 0.1 per cent cod-liver oil activated in ultraviolet light for three hours. Four died, and the two that lived showed retarded growth.

Group 16 were given the same treatment as Group 15, but with 0.1 per cent cod-liver oil. Five died, and in the one living, growth was retarded.

Group 17 were given the same treatment as Group 15, but with 1 per cent cod-liver oil. One died. Five lived and were lively and well feathered.

Group 18 were given cod-liver oil, 5 per cent. Five died. One lived and was well feathered and moderately lively.

Group 19 were given cod-liver oil activated in sunshine for thirty minutes the oil being rubbed on the neck. Three lived and were lively but feathering was delayed.

Group 20 were given the same treatment as Group 19, but with raw cod-liver oil. Four died, and the two that lived showed delayed growth and little spirit.

Group 21 were given 1 per cent cholesterol, activated by ultraviolet rays. Three died. The three that lived were moderately well feathered and lively.

Group 22 were given the same treatment as Group 21, but the cod-liver oil was not activated. All died.

Group 23 were given 1 per cent parathyroid extract. One died and the five that lived were moderately well feathered and fairly lively.

Group 24 were given food exposed to ultraviolet rays daily for thirty minutes. Four died, and the two that lived showed delayed growth.

No. 25 was the other control referred to at first.

Blood chemical determinations were made on these various groups, with special consideration for calcium, total and active, and inorganic phosphorus.

It will readily be seen, from the data herewith presented, that these chickens were very largely dependent on the various forms of activation, employing ultraviolet rays, raw and activated cod-liver oil, and raw and activated cholesterol, and that the raw cod-liver oil had a quite different effect from that activated for fifteen minutes, and that activated a short time as compared with that activated for a long time. The products did not save the chickens if exposed to either sunshine or ultraviolet overlong, but, on the contrary, hastened their death. All the chicks receiving an overactivated product in all the groups died. This is particularly important because of the harm that will be done by ignorance in undertaking to activate preparations for practical use. I will refer to this in further detail later.

In order further to check these problems, a second group of 100 chicks was divided into five groups. Group 1, controls, received the sunshine again; Group 2, ruby light; Group 3, ruby light and raw cod-liver oil; Group 4, ruby light and activated cod-liver oil; Group 5, ruby light and ultraviolet rays. As in the previous series, the chicks were kept in a room from which all light was excluded except from a ruby lamp, which was left burning night and day. This was a much brighter ruby light than the one in the preceding experiment.

Several facts are of interest: The highest percentage of gain in weight occurred in the group receiving the ultraviolet radiation. The total calcium was higher in the two groups receiving cod-liver oil, one raw and the other activated, and also in the group exposed to ultraviolet irradiation, than in the controls, for part of which there were two groups. The active calcium was higher in the controls receiving sunshine than in any of those receiving treatment. The diffusible calcium was lowest in the group receiving the raw cod-liver oil. The most striking difference was in the nondiffusible or colloidal form, probably as calcium proteinate, the group receiving the raw cod-liver oil being much the highest. The organic phosphorus of the whole blood was highest in the group receiving the raw cod-liver oil. This is of importance. The product of the total calcium and inorganic phosphorus was highest in the group with the raw cod-liver oil and the ultraviolet irradiation. The product of the active calcium and inorganic phosphorus was highest in the group with the raw cod-liver oil. Table 5 gives these data, from which it will readily be seen that many factors are involved other than simply the administration of calcium, cod-liver oil or ultraviolet rays. I therefore carried through another series (Table 6), in which 250 chicks were used, being divided into twenty-six groups, and in which it was undertaken to establish more definitely the changes produced in the various levels of the calcium in its various forms in the blood.

TABLE 5.—EXPERIMENTAL DATA

		Calcium						Phosphorus							Ca×P			
									W'le Blood		Plasma		Cell					
	% Gain	Total	Active	Diffusible	% Diffusible	Non-diffusible	% Non-diffusible	In. Phosph. P	Org. Phosph. P	Org. Phosph. PO_4	Org. Phosph. P	Org Phosph. PO_4	Org. Phosph. P	Org. Phosph. PO_4	Total Calcium × In. P.	Act. Ca. × In. P.	Diff. Ca. × In. P.	Ca++ −Log Product $(\times PO_4)_2$ Ph=7.35
Controls	520 193 2	8 61 10 92	6.08	6 35 4 94	73.70 54 75	2.26 5 97	26.30 45.25	3.24	78 0	250	18.7	60.0	1,155	370	27.89	19.69	20 57	24.38
Ruby light	256 9	10 37	5.18	5.99	57.70	4.38	42.30	3.31	71.3	228	10.8	37.8	1,015	325	34 32	17 14	19 82	24 10
Ruby light + raw cod liver oil	165.3	13.59	5 60	3.92	28.80	9.67	71.20	5 0	78.0	250	18 7	60.0	1,155	370	67.95	28.00	19.60	23.41
Ruby light and act. cod liver oil	226.9	13.41	5.60	5.31	39.50	8.10	60.50	2.87	106 0	340	18 7	60 0	125	400	38.48	16.07	15.23	23.90
Ruby light + ultra violet ray	266.9	14.79	5.25	6.18	41.70	8.61	58.30	3.05	60 2	192	17.36	55.6	1,215	389	45 10	16 01	18 84	23.73
		Diet 3143																

It should be noted in passing, in order that some slight idea may be had of the prodigious task of making chemical analyses of so many animals, that it takes several hours to make these various determinations on a single bird or animal, and exceeding care has to be taken with every step of the procedure.

Table 6 gives the results of the blood chemical studies on the third set, consisting of 250 chickens. The percentage of gain of the controls was 63.8 per cent in the period involved. It is of interest to note that several of the groups outdistanced the controls in gain.

The average total calcium for the controls was 9.96; active calcium, 8.14; inorganic phosphorus, 4.52. Of those under treatment, several had a distinctly higher total calcium in the blood than did the controls. Again, 5 per cent cod-liver oil activated in the sun for fifteen minutes is high in calcium, this group having a total calcium of 13.13. Ten per cent cod-liver oil activated for fifteen minutes in the sun gave a total calcium, 10.07; 10 per cent cod-liver oil activated for one hour in the sun, 11.43; 1 per cent cod-liver oil activated for twenty-four hours in the sun, 11.37; raw cod-liver oil rubbed on the necks, 11.26; activated cod-liver oil (thirty minutes in the sun), rubbed on the necks, 15.04; 5 per cent cholesterol, activated for thirty minutes, 10.2, in contrast with 5 per cent cholesterol, not activated, 9.3.

The active calcium, which in the controls averaged 8.14, was 10.02 in the group receiving 5 per cent cod-liver oil activated for fifteen minutes in the sun and 10.2 in the group receiving 10 per cent cod-liver oil activated in the sun. The cod-liver oil activated for thirty minutes in the sun, rubbed on the necks, gave an active calcium of 10.2. We have here, then, distinct evidence of the influence of the oil activated in the sun.

The inorganic phosphorus also gives important information. For the controls, it was 4.52; for the group receiving 5 per cent raw cod-liver oil added to the food (Diet No. 2966, Steenbock and Nelson) it was 5.26; for the 5 per cent cholesterol activated for thirty minutes in the sun, 4.77; 5 per cent cholesterol not activated, 2.24; 5 per cent cod-liver oil activated for fifteen minutes in the sun, 2.93, distinctly lower than the 5 per cent raw in this group.

Another item of great importance has developed in this research. Several of the chickens that were having cod-liver oil rubbed on the neck, in each group given raw and activated oil, developed large cystic sacs filled with a serous fluid. This fluid was aspirated, pooled together for each group, and from Group 20 bad the remarkably high level of 18.97 for total calcium, and 14.19 for active, and from the group of chickens with the activated cod-liver oil, 27.14 per cent for total calcium and 18.09 for active.

We seem here to have evidence that the application of activated cod-liver oil or even raw to the surface has a local action that is very distinct, and it is significant in this connection that the calcium of the blood of the group that had the activated cod-liver oil rubbed on the necks was 15.04 as compared with 9.96 for the controls. This point is being given further study.

There are many factors which are both intentionally and unintentionally varied and thereby modify the results.

One of these has been the intensity and source of the ultraviolet ray. Another has been the source of the cod-liver oil. For these reasons, the results of two different sets of investigations should not be expected to check. There is also an important difference in the stock, for we cannot always get the kind of chicks we desire.

TABLE 6.—EXPERIMENTAL DATA

	Chicks Diet 2966	Calcium			In. Phosphorus	Ca×P Total Ca × In. Phos.
		% Gain	Total	Active		
1	Controls Sunshine	63.80	9.96	8.14	4.52	45.00
2	Ruby light	154.70	10.28	8.30	4.83	49.65
3	U. Vi. R. 20 min. daily	111.60	9.25	8.30	4.10	37.92
4	U. Vi. R. 2 hr. daily	95.70	8.53	8.13	4.10	34.97
5	1% raw C. L. oil	176.60	9.73	6.60	6.33	61.59
6	5% raw C. L. oil	57.70	8.95	8.33	5.26	47.19
7	10% raw C. L. oil	74.30	9.45	8.13	2.90	27.40
8	1% C. L. oil 15 min. sun.	69.20	10.90	8.82	3.17	34.55
9	5% C. L. oil 15 min. sun.	78.03	13.13	10.02	2.93	38.48
10	10% C. L. oil 15 min. sun.	55.05	10.07	10.22	2.10	22.48
11	1% C. L. oil 1 hr. sun.	85.20	20.21		2.22	46.82
12	5% C. L. oil 1 hr. sun.	77.30	9.66	7.64	3.90	37.67
13	10% C. L. oil 1 hr. sun.	70.60	11.43	8.32	2.77	31.62
14	1% C. L. oil 24 hr. sun.	72.90	11.37	8.66	3.71	42.18
15	5% C. L. oil 24 hr. sun.	76.60	10.25	8.52	3.62	37.20
16	10% C. L. oil 24 hr. sun.	67.20	9.72	8.82	3.51	34.10
17	1% C. L. oil 24 hr. U. Vi.	133.10	10.84	5.84	5.45	59.07
18	5% C. L. oil 24 hr. U. Vi.	89.04	10.96	6.60	4.85	53.16
19	10% C. L. oil 24 hr. U. Vi.	36.80	10.42	8.32	1.94	20.20
20	Raw C. L. oil on necks	6.30	11.26			
20	Fluid from necks of 20		18.97	14.19		
21	C. L. oil 30 min. on necks	56.07	15.04	10.22	2.15	32.35
21	Fluid from neck 21		27.14	18.09		
22	5% raw cholesterol	1.40	9.35	8.02	2.24	20.91
23	5% cholest. 30 min. sun.	26.10	10.25		4.77	48.90
24	10% raw butter	62.20	11.69	7.25	5.40	63.13
25	19% butter 24 hrs. U. V.	50.80	8.95	6.75	5.20	46.54

RESULTS IN MORE THAN 1,100 BLOOD CHEMISTRY STUDIES OF PATIENTS

The purpose of this investigation has been to determine the systemic expressions that obtain as chemical changes in the blood as the result of focal infections, particularly dental infections. The procedure includes some or all of the following: a microscopic study of

the blood cells, differential count, hemoglobin, color index, Arneth index, Walker index, calcium in different forms, alkalinity index, blood sugar, inorganic phosphorus, total organic phosphates, plasma phosphates, blood cell phosphates, nonprotein nitrogen, total proteins, total albumin, total globulin, euglobulins a, b and c, calcium—inorganic phosphorus product—the product of the calcium ions and phosphate ions, with other factors in special cases. A large percentage of the patients have pathologic states as a reason for the examination. A considerable number are approximately normal.

I am presenting herewith typical cases representing three distinct groups: the first, those with a high total calcium, accompanied by a high active calcium; the second, a high total calcium, accompanied by a low active calcium; and the third group, a low total calcium and low active calcium. These groups are presented in Tables 7-9.

It is of special interest to note that those individuals in Group I, Table 7, are largely individuals who would be classified as having an absent susceptihility, on the basis of classification previously presented hy me, for the rheumatic group affections. Group II is made up largely of individuals who would be grouped on the hasis of rheumatic susceptibility as having acquired susceptibility; and Group III is made up largely of individuals who would be in the classification I have previously given of inherited susceptibility.

Several factors are of exceeding importance. In the clinical study of these individuals, we are continually finding a predominance of decalcification in the presence of apical and gingival irritation in Group I, the group with high calcium. In previous papers, I have stressed the apparent significance of this quality of decalcification in the presence of an irritant in its relation to the poor fight that the people of this class make in case of a serious tuberculous infection. The same type of dental infection, such as a putrescent pulp, will, with this group, produce large periapical areas, usually readily disclosed in radiograms; whereas, a similar typical dental infection produces a very different local tissue change and radiographic appearance because of the tendency to a condensing osteitis about the rarefying, which hides or obstructs the view of the zone of rarefaction.

By referring to Table 7, it will be noted that Group I, with high total and high active calcium, are well above the averages that are usually published for total calcium. It will also be noted that, on the the basis of both total and active calcium, the calcium balance is either positive or but slightly negative. It will also be noted that the polymorphonuclears, except in the first two cases, are high in proportion to the small lymphocytes. Except for the first two individuals, these patients have been conspicuously free from disturbances of the rheumatic group. The inorganic phosphorus, in all the cases of this group except the first one, will be noted to be above 3.

In an analysis of the cases in Group 2, Table 8, those with a high total and low active calcium, it is interesting to note the prevalence of disturbances of the nervous system. In our experience, a marked difference, exceeding 1 mg., between active and total calcium is suggestive, and, if more than 2 mg., distinctly abnormal. Further, individuals

with an active calcium below 9 are practically always in a state of reduced vitality and energy, frequently referred to by the patients as lassitude or lack of pep. Six of the thirteen individuals in this group have an inorganic phosphorus below 3, and nine of the thirteen show a negative active calcium balance of more than 10. My interpretation of the suggestiveness of the blood pictures of the individuals in this group would be that they are practically all suffering from overloads, an important factor of which may be dental. When they return to normal, the blood pictures will be much more like those of the preceding group, Group 1.

An analysis of Group 3, Table 9, indicates a low total calcium and a low active calcium as characteristic throughout, and frequently associated with low inorganic phosphorus. Seven of the thirteen have an inorganic phosphorus below 3 and three below 2. A striking feature is the quite general negative calcium balance of both total and active calcium. When a calcium balance is in negative phase more than 10 points, for children it is interpreted to be suggestive, if not diagnostically significant, of rickets. In adults, when the developmental processes are completed, it takes quite different expressions. I would expect the people of this group

TABLE 7.—CALCIUM METABOLISM (GROUP 1) *High* TOTAL. *High* ACTIVE.

Case	Alkalinity Index	Total Calcium	Active Calcium	Inorganic Phos.	Total Organic Phos.	Total Ca Balance	Active Ca Balance	Sugar	N. P. Nitrogen	Cholesterol	Total Fats	Fatty Acids	% Polymorphonuclears	% Small Lymphocytes
1346 MrKn	33.8	11.42	10.32	2.3	58.5	−13.0	−15.6	105	31	143	951	808	51.2	41.1
1545 MrHs	33.0	12 13	11.62	3.9		+ 8.2	+ 6.2	100	27				52.5	37.0
1549 MsNh	32.4	11.42	10.96	3.1		− 4.6	− 6 1	132	25				70.6	21.5
1560 MrWn	30.5	11.44	10.20	3.2		− 2.9	− 6.9	122	56				63.8	28.4
1565 MrFr	29.1	13.12	11.05	3.8		+10.0	+ 2.5	131	18				79.0	13.8
1569 DrMy	41.3	12.54	10.57	3.1		− 0.9	− 7.1	97	34				60.5	29.0
1572 MrBn	39.0	11.33	11.00	3.1		− 4.4	− 5.5	86	22	114	474	360	66.0	33.2
1575 MrRh	34 2	11.28	10.06	3.6		+ 1.4	− 3.1	102	27	129	464	335	65.0	26.6
1612 MrHn	31.0	12.70	10.06	3.1	36.7	− 0.4	− 8.6	105	34	190	740	554	65.3	20.0
1620 MrGs	35.4	12.55	10.52	3.2	31.4	+ 0.9	− 5.8	98	27	124	900	775	65.4	25.9
1624 J.Kn	38.0	11.62	10.18	3.5	39.5	+ 1.5	− 3.6	101	26	134	470	236	63.0	28.5

to be dragging considerably and with many serious breaks.

I shall refer to the individuals in these various tables again as I discuss the matter of treatment, for many of them, particularly in the third group, can be helped a great deal by systemic treatment for the raising of their calcium in addition to the removal of dental infections, where such exist, together with the removal of all possible overloads, including other infections.

TABLE 8.—CALCIUM METABOLISM (GROUP 2: *High* TOTAL; *Low* ACTIVE)

Case	Alkalinity Index	Total Calcium	Active Calcium	Inorganic Phos.	Total Organic Phos.	Total Ca Balance	Active Ca Balance	Sugar	N. P. Nitrogen	Cholesterol	Total Fats	Fatty Acids	% Polymorphonuclears	% Small Lymphocytes
798 MrCy	34.4	11.20	8.80	2.2	58.0	−15.0	−20.2	97	29	89	713	624		
1268 MrGu	32.4	11.36	9.78	3.4		− 0.6	− 6.1	500	67	448	878	430	61.2	26.4
1414 MsKn	39.5	11.06	9.87	2.8	52.0	− 8.0	−11.5	125	34	98	1025	912	55.0	37.0
1484 MsMe	37.0	10.37	8.27	3.5		− 3.0	− 9.7	107	22	72	662	590	68.8	26.6
1573 MrHk	36.7	11.05	9.46	4.1	37.2	+ 5.1	− 0.6	81	30	111	800	689	55.8	29.4
1580 MrKr	28.6	11.43	8.70	4.2	39.1	+18.1	− 3.4	109	33	84	320	236	58.6	33.0
1583 MrHs	28.5	10.60	9.08	5.1	57.3	+14.6	+ 0.6	93	35	176	509	334	48.3	45.4
1585 MrLe	30.1	11.41	8.80	2.0	34.4	−16.9	−22.2	127	31	89	833	744	53.0	41.0
1586 MrDy	32.1	11.73	9.24	2.3	33.1	−12.6	−18.5	138	32	111	463	352	61.8	30.8
1617 DrDt	34.5	11.12	9.02	1.9	13.6	−18.7	−22.7	104	27	128	696	565	68.3	24.0
1619 MrBr	34.0	11.58	9.42	1.3	33.2	−26.7	−27.3	149	28	128	600	472	65.6	27.9
1621 DrSy	39.5	10.42	8.49	3.3	31.8	− 5.6	− 12.0	108	22	258	740	488	60.2	31.4
1623 CbMn	34.7	12.53	8.17	3.3	33.2	+ 2.1	−12.5	107	22	93	687	584	64.1	26.2
1623 CbMn	36.4	11.12	9.17	2.6	51.1	−10.9	−16.0	98	26				60.0	30.0

PHOTOGRAPHIC PLATE EFFECTS

These various investigations have strongly emphasized not only the important part played by calcium in various physiologic processes, particularly as a factor in immunity and defensive capacity of the organism, but also the necessity that, in addition to a source of calcium for the needs of the body, there should be a source of activator. The nature of these activators is understood only in a very general way and their

methods of action is but slightly comprehended.

This particular aspect of this investigation has been carried on to determine somewhat of the nature of the action of the activators. In previous communications, I have reported,[13] in connection with the important rôle of calcium, the significant fact that, if the blood serum of an animal whose calcium is low, particularly the active calcium, shall be exposed to ultraviolet radiation for from fifteen to twenty minutes, and then injected into the circulation of the animal, there is an elevation of the active calcium within an hour or two which, in the presence of the continued drain on the system, tends again to decline within twenty-four hours.

I have further demonstrated that this blood serum will make an impression on a suitably sensitive photographic plate, and, further, that such photographic plate reaction is changed by the exposure of that blood serum through

TABLE 9.—CALCIUM METABOLISM (GROUP 3; *Low* TOTAL; *Low* ACTIVE)

Case	Alkalinity Index	Total Calcium	Active Calcium	Inorganic Phos.	Total Organic Phos.	Total Ca Balance	Active Ca Balance	Sugar	N. P. Nitrogen	Cholesterol	Total Fats	Fatty Acids	% Polymorphonuclears	% Small Lymphocytes
492 MsEn	37.1	9.57	8.28	1.8	28.5	−22.1	−24.6	116	33	129	733	604	64.2	26.6
589 MrBn	39.0	9.66	9.30	1.8	29.3	−22.4	−23.0	98	28	85	710	624	50.0	42.5
945 MrHk	33.4	9.73	8.52	3.5		− 4.3	− 9.6	92	40	148	1090	842	63.7	28.6
1124 MsMr	35.9	9.27	8.85	3.7		− 5.3	− 6.9	105	38				50.0	41.4
1522 MsBr	38.1	8.81	8.78	3.8		− 6.0	− 6.1	67	26				71.0	19.9
1553 MrFr	37 1	9 51	9.23	2.3		−17.8	−18.5	98	26				76.3	12.8
1554 MrJn	38.2	9 69	8.84	3.1		− 9.1	−11.9	100	27				68.6	24.4
1561 MsKs	33.6	9.81	8.92	2.6		−13.9	−16.2	108	28				51.0	39.3
1589 MrFr	31.0	10.13	8.92	1.9	32.5	−20.0	−22.4	125	27	89	600	511	50.0	40.0
1601 MrSd	41.3	10.09	8.79	2.4	58.6	−15.4	−18.6	84	26	112	752	640	50.7	32.2
1622 MsMs	42.3	9.83	8.96	2.6		−14.1	−16.4	115	39				07.7	25.1
1624 J.Kn	38.5	8.58	8.78	3.8		− 7.0	− 6.2	112	26				70.6	19.5
1625 MsSp	36.9	9.84	8.80	3.4	144.2	− 6.4	−10.0	102	37	111	281	179	58.2	32.4

13. Footnote 1, last reference.

the action of the ultraviolet ray, and that an overexposure of the blood serum causes the active calcium to decrease instead of increase.

For three years, I have been studying intensively the phenomena involved in this reaction, and also those involved in the exposure of cod-liver oil to the ultraviolet ray, and the fact that this substance makes a strong impression on a photographic plate, largely in proportion to the type and extent of the irradiation with the ultraviolet ray. This has been demonstrated at length in my lectures during the last three years.

I wish, at this time, to present a quantity of new data which throw a vast new light on the mechanism of this whole process. That cod-liver oil will impress a photographic plate is so easily and strikingly demonstrated that anyone may readily reproduce the evidence. The simple placing of a photographic plate over a dish containing the cod-liver oil, without an intervening protection, will produce fogging in proportion to both time and temperature. It is therefore exceedingly easy to produce a very active preparation.

Figure 5 shows a series of exposures produced as follows: 1 is cod-liver oil, raw and unexposed; 2, a similar quantity of the same oil that had been exposed to sunshine for five minutes; 3, oil exposed to sunshine for ten minutes; and, similarly, 4, 5 and 6, thirty, forty and sixty minutes. It will be noted that the blackening of the plate has been progressive, as shown in the illustration reversed as a positive, directly in proportion with the time of exposure to irradiation. This is a specimen of Newfoundland cod-liver oil. The right hand series of this same figure shows the same results with another excellent oil.

Kindly have in mind the relation of this radiant energy to the ultraviolet irradiation which stimulates it. I have made an extensive study to ascertain, if possible, the nature and type of this energy, a part of which data will be presented herewith, and, because of the length of this paper, a part will be made a separate communication.

When cod-liver oil, whether irradiated or not, is placed in a refrigerator with a photographic plate over it, the effect is entirely different from that which obtains if it is placed in an incubator. Figure 6 shows two specimens made with the same oil. These differences of temperature constituted the difference in causative factors.

The science of radiotherapy, which is so rapidly developing, is calling for many applications which are not as yet built upon an adequate experimental basis.

I have previously presented evidence[1] (Vol. I, chap. 27) illustrating that ultraviolet irradiation, when administered to both healthy and diseased rabbits, produces at first a rise in the number of leukocytes, or positive phase, which is always followed by a more or less severe and more or less prolonged negative phase, the latter of which may more than offset in its depression the stimulation of the positive phase, provided the dosage has not been adequately measured and administered.

I have also shown previously, in this paper, that the chicks in Series I, which received cod-liver oil that had been exposed to ultraviolet radiation for too long a time, died, and that the same thing happened with too extended radiation to sunshine. Similarly, the evi-

dence brought out in the second series of chicks illustrates the importance of the dosage of the irradiation.

In Series 3, we have fed chicks on butter that had been exposed to ultraviolet rays for twenty-four hours. It has been shown by others that an extract of the toxic material from butter, injury that would be occasioned from exposing food overlong to ultraviolet light, whether from the sun or from an artificial generator, because of the production of substances distinctly deleterious to health. I have learned much from experimenting on myself, and one of the early safeguards that came from

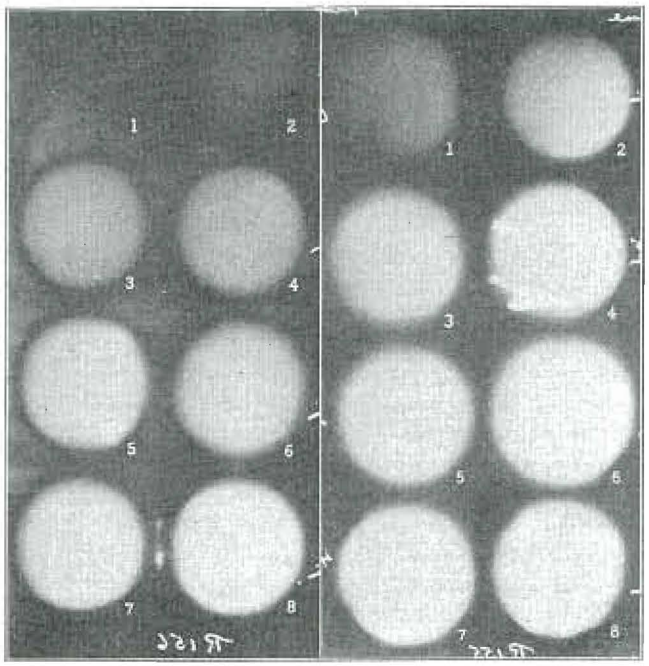


Fig. 5.—Series of exposures of panchromatic plate film which was placed over (left) Newfoundland cod liver oil and (right) Squibb's cod liver oil, which had been exposed to the ultraviolet ray for various intervals. The film was left over the oil for sixteen hours, and then developed for five minutes. *1*, oil not exposed to the ultraviolet ray; *2*, exposed to ray for five minutes; *3*, for ten minutes; *4*, fifteen minutes; *5*, twenty minutes; *6*, thirty minutes; *7*, forty minutes; *8*, sixty minutes.

placed on bread, killed mice in eight days, where the controls lived fifty days and died then for want of a growth promoting activator.

In this connection, it is important to raise a note of warning for those who would advise or in any way be responsible for the abuse and possible serious that source was secured as the result of severe headaches produced by taking cod-liver oil that had been exposed to ultraviolet rays from a mercury quartz vapor lamp for one half hour, even though the dosage was only a few drops.

Other important changes than these which take place in the cod-liver oil

when it is exposed to sunshine, thereby enabling it to produce fogging effects, are those changes which are produced in various organic and inorganic substances and in organ extracts as the result of irradiation. I have studied in this way most of the glands of internal secretion.

It has been known for some time that, when exposed to light, certain resins, oils, varnishes, paints, etc., give off hydrogen dioxid in sufficient quantity to blacken a photographic plate, a quality which they retain for a long time. We have demonstrated that this

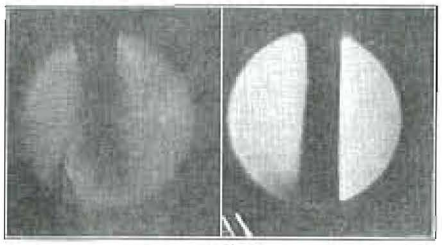


Fig. 6.—Exposure on panchromatic film of cod liver oil, not exposed to the ultraviolet ray. Left: Oil kept in ice box. Right: Oil kept in incubator.

is what takes place with cod-liver oil by placing it in a vacuum, in which condition it ceases to produce this effect, the water vapor, of course, heing extracted with reduced pressure. These substances will not produce these effects in the absence of water vapor. It is also possible to transfer the effect to other substances; for example, if the tissue containing tbis material is put in a box and then the material is removed, the box will continue, for a period, to produce some of the effect.

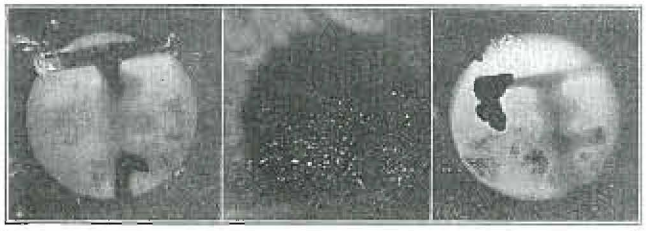
That it is not radiant energy is also demonstrated by the following experiment of putting a photographic plate over a dish containing the material and sliding it to a new position every five minutes. The effect is progressive with time, in accordance with the accumulation of the hydrogen dioxid in the water vapor of the air contained. I have also made very extensive studies with very sensitive electroscopes and have not been able to establish the presence of an energy carrying a charge.

The various kinds of radiant energy do not all carry charges, and, for this reason, we should distinguish between true photochemical effects, which are due to radiant energy producing chemical action, and photographic effects, which may be due to a gas reacting on a photographic plate. We are accordingly concerned here not with a radiant energy that is given off from blood serum, cod-liver oil, or organ and tissue extracts, but with a chemical reaction which takes place through space or some intervening fluids. These chemical compounds, which react on a photographic plate, are changed not only in quantity hut also in quality, as judged by their different effects as the result of exposing the medium in question to radiant energy of different types.

We have quite different effects with many compounds whether the radiant energy comes from the sun or a quartz lamp. The suhstances, therefore, show evidence of difference in reaction to different lengths of rays. For example, Figure 7 shows the difference in effect in studying desiccated total pancreas. *A* shows the photographic reaction in the presence of an obstructing guide of the raw material; *B*, the same exposed to ultraviolet rays for thirty minutes; and *C*, the same exposed to sunlight for one hour. The marked difference between the effect of sunlight and of ultraviolet light may he noted. Limit of space

requires that this phase of this problem must be made the subject of a more extended individual report.

Typical illustrations will be found in such as the following: Solutions of various gland substances have been exposed to ultraviolet radiation from a mercury vapor lamp and to sunshine, in comparison with the same product without exposure. That there is much significance in the fact that these various organ substances produce fogging reaction even at a distance from the plate has been demonstrated by such means as the experiment previously reported of placing back in the circulation the blood serum that had been irradiated and noting its direct effect on calcium of the blood. It is a most interesting phenomenon that various organ substances do not behave similarly in effect on a photographic plate.



A B C

Fig. 7.—*A*, panchromatic film placed over desiccated total pancreas, 5 per cent, in physiologic sodium chlorid solution, which had not been exposed to the ultraviolet ray. The film was exposed for sixteen hours and developed for two minutes. *B*, film exposed as in *A*, but after the pancreas in solution had been exposed to the ultraviolet ray for thirty minutes. *C*, film exposed as in *A*, after the pancreas in solution had been exposed to sunlight for one hour.

Before referring further to these results, it should be noted that there is to be taken into consideration the change that is produced in a photographic plate, particularly a sensitive panchromatic plate, when all or part of it is exposed to water vapor for a period of time before its development. If, for example, an exposed plate is placed over a small dish of water for an hour or a few hours, the fogging will be reduced at that point which is directly over the water. If the plate has not been fogged and is similarly placed over a dish of water for one or several hours and then developed, it will be found that the plate is lighter in color where it was over the vessel of water than in the area surrounding the vessel. I have not been able to find an explanation of the physical chemistry involved. However, this is not the effect that is to he observed in the following illustrations, though evidence of it will often be an accompaniment.

When a photographic plate is placed over a vessel of water so that the water vapor comes in contact with it for an hour or two, and that surface is then put in contact with a piece of glass on which writing has been made with a wax pencil, and left in contact for five minutes, there will be a further whitening where the wax letters came in contact, as shown in Figure 8. When with the same procedure a solution of

certain organ substances is used instead of water, instead of there being a further whitening of the plate where it comes in contact with the wax lettering, there is a strong darkening of the plate, as shown in *B*, Figure 8.

When cod-liver oil that had been exposed to radiation is shaken with a solution of one of the gland products, say suprarenal, and each is in contact with the other by this emulsification for a short period, it is then separated by centrifuging, and then photographic plates are exposed to them and to other portions of these substances, which did

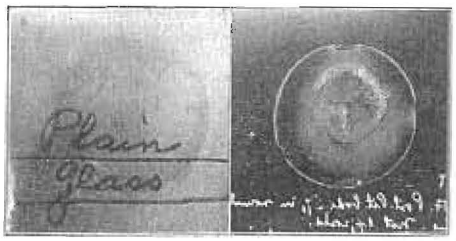


Fig. 8.—Left: Panchromatic plate placed over distilled water for sixteen hours, and developed for five minutes. Plain glass with wax writing was placed against the film side of the plate for five minutes before development. Right: Panchromatic plate placed over a solution of posterior pituitary body (not exposed) for sixteen hours, and developed for two minutes. Writing from another was transferred by contact for about five minutes before development. Note reversal.

not have this contact each with the other, it will be noted that there is a reduction in the activity of both the cod-liver oil and the gland product. It will also be noted that the plate fogging reaction of cod-liver oil on the one hand and of the various gland products on the other are entirely different in their nature. In certain cases, there is much evidence of a quite opposite type of action.

When cod-liver oil which is activated is brought in contact with calcium lactate, there is a rapid neutralizing of its fogging effect, as in Figure 9, which shows progressively the effect of increasing the proportion of calcium.

When blood is used as the test material, there is a distinct difference in the effect on the plate whether the blood has been oxalated, citrated, defibrinated or clotted, and in each of these conditions, blood reacts differently when exposed to the ultraviolet radiation from the sun, and still differently when exposed to the ultraviolet radiation from a mercury quartz vapor lamp.

When this blood has been allowed to stand for twenty-four hours, that part which has been oxalated makes a most striking reaction on a photographic plate, while of the other three preparations of blood, only the citrated blood exposed to ultraviolet continues to do so.

One cannot refrain from associating these various phenomena with the clinical effect that is produced in our animals as the result of medication with irradiated products and with results on our patients who have been suitably treated with calcium activators. May it not be possible that we have an approach here to the mystery of the hormones, whose illusive method of action and interaction has so completely eluded investigation; and, further, do we not here get a suggestion as to the nature of bacterial toxins and also to enzyme action? For some, this is a fancy; for others, there will be associated with these data a realization of a great systemic change that has come about in their own bodies as the result of stabilizing and improving their calcium metabolism through the proper

selection and usage of calcium associated with a suitable activator. There is much evidence, which the space available for this paper does not permit a review of, that a negative calcium balance is one of the fundamental, if not the most important, factors involved in dental caries.

TREATMENT AND PROCEDURE

This brings us to a consideration of the treatment of pathologic states that

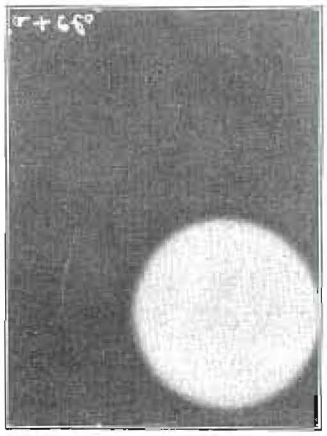


Fig. 9.—Above: Panchromatic plate placed over 50 per cent cod liver oil, exposed to the ultraviolet ray for thirty minutes, and 50 per cent calcium lactate. The plate was allowed to remain for sixteen hours, and then developed for five minutes. Below: Plate cod liver oil alone exposed to the ultraviolet ray for thirty minutes.

are related to calcium metabolism disturbances. In cases of pregnancy in various stages of advancement, we will see that the individuals have a markedly depressed calcium. This is not a universal accompaniment though the exceptions are few in the later stages of this physiologic process. The expectant mother has not only the continued demands of her own system, which will require approximately 0.6 gm. of calcium per day, but, in addition, now has the even greater demand of the new being which is developing, so that there is need for a greatly increased calcium in available form.

There are probably not only thousands but even millions of expectant mothers in the world who are not capable of readily paying this double bill, and, accordingly, Nature proceeds to borrow from the storehouses of the maternal body; namely, the teeth and bones.

If one will observe a herd of dairy cattle that is being intensively drained of its milk throughout the summer, it will be noted that, with the long-continued draft, particularly if the pasture has been poor, there is a settling of the rump bones so that the tail does not drop straight nor the pelvic bones maintain the square configuration of the rump. During the period of lactation, these animals have been borrowing from the storehouses of calcium to furnish it to the milk. They have been largely in negative calcium balance, and during the winter, when they do not have the stress of lactation and have an abundance of good fodder, they will more or less completely pay back this calcium borrowed from the bones.

Few of the tragedies of Nature have been more unrelenting and death dealing than has this overdraft on motherhood. I think no experience of my life has been more gratifying than to see how simple and easy it is to pay this bill for the expectant mother by the simple administration of calcium in a suitable form and quantity and an activator in suitable form and quantity.

The dosage for both calcium and activator is largely indicated by the

chemical analysis of the blood, though one cannot be far amiss in a routine program on a minimum basis. Extreme conditions will not only justify but also demand a more comprehensive program.

This is similarly true of the caries of childhood; for these individuals, on chemical analysis of the blood, prove to be also in negative calcium balance and are in need of virtually the same type of treatment.

The addition to diet that I recommended for negative calcium balance in general is as follows: from 1 to 1½ 5-grain tablets of calcium lactate taken with each meal, and with it a 00 capsule containing approximately 10 drops of cod-liver oil of good grade, which has been exposed to the sunshine for from one to fifteen minutes in order to activate it—one minute on bright summer days, to fifteen minutes on dull winter days. During this exposure, it should be in a shallow dish, preferably not more than an eighth inch in depth, and should be stirred meanwhile. Or raw cod-liver oil, 20 drops in a capsule, may be given.

Too much emphasis cannot be placed on the urgent necessity that the mistake shall not be made of putting this in the hands of indifferent or careless persons who will not watch the time carefully. Exposure for one hour to the noonday summer sun or to a mercury vapor quartz lamp produces a product which is distinctly harmful, and it would be better to use the raw cod-liver oil unactivated than to use this product. Different types of calcium disturbance require different treatments. Space does not here permit of further discussion. I will discuss this whole problem in a much more detailed manner, in an extended communication and in other papers.[14]

14. Price, W. A.: Some Systemic Expressions of Dental Infections, Ann. Clin. Med., 4 (May) 1926; Relation of Light to Life and Health, Ind. and Eng. Chem., 18:679 (July) 1926; Calcium Metabolism Studies. (a) Raising of Serum Calcium by Tropical Applications of Raw and Activated Cod Liver Oil. (b) Calcium Metabolism Disturbances, Associated with the Active Dental Caries of Childhood and Pregnancy, Am. J. Dis. Child., 32 (Nov.) 1926.

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