CARBOHYDRATE IN THE TREATMENT OF POSTOPERATIVE TETANY, WITH SPECIAL REFERENCE TO LACTOSE

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The usual methods of treatment of postoperative tetany are not entirely satisfactory. To any who have experienced the difficulties in the management of this condition, the need of simpler effective measures is apparent. The oral administration of calcium, even in large doses, is not always sufficient to control the symptoms, and repeated injections of it over long periods is undesirable or impossible. Injections of parathyroid extract alone or in addition to calcium may be effectual, but are inconvenient and expensive. Methods are reported here for the control of phosphate metabolism to an extent that will afford distinct benefit to patients suffering from this disease.

Serum Calcium

The best-known and perhaps the most satisfactory single criterion by which the severity of parathyroid tetany may be judged is the degree of depression of the level of total serum calcium. Examination of a large series of serum calcium levels in tetany makes the fact apparent, however, that the symptoms do not necessarily parallel the total calcium levels. This confirms the opinion of John.[1]

It is known that the total serum calcium can be raised and frequently brought to normal in tetany by the feeding of large doses of calcium. In some of our cases the symptoms were not controlled by these measures, and their severity was thought to be out of proportion to the calcium level. This was especially striking since a patient might be symptom-free with a certain calcium level on one day, while on another occasion, although the serum calcium was at the same height, symptoms might be present. Abnormally high levels of blood phosphates accompanied nearly normal calcium values in some of these cases.

Blood Inorganic Phosphates

Ver Ecke[2] in 1898 noted a lessened phosphate excretion in the urine in tetany. This has received ample confirmation by Salvasen,[3] Greenwald,[4] and others, and it is now recognized that one

of the constant features of parathyroid tetany is phosphate retention. Furthermore, tetany has been produced experimentally by feeding phosphates.[5] The phosphate retention in tetany usually is associated with a distinct rise of blood phosphates, the concentration of which partially governs the severity of the symptoms. This is definitely indicated by the observations reported here and by a review of the literature. Pronounced mitigation of symptoms accompanying a fall in blood phosphates has been observed, and simultaneously the neuromuscular electrical excitability approaches normal.

Calcium phosphate is a relatively insoluble compound. It has been stated that the blood is supersaturated with this salt.[6] This has been questioned,[7, 8] but it is certain that it approaches the saturation level. Under these conditions, it might be expected that a decrease in blood phosphates would result in an increase in serum calcium.[9] It has been observed more frequently in these studies, however, that there is a slight fall in total serum calcium accompanying the fall in blood phosphates. It is possible that the relief of symptoms associated with this fall in phosphates is the result of an increase in the percentage of calcium ionized. It is also possible that the decrease in phosphates independently decreases neuromuscular excitability.

Relation of Carbohydrates to Blood Phosphates

At the beginning of this century it was generally accepted that phosphate metabolism was not normal in diabetes mellitus.[10, 11, 12] Since that time intensive study has demonstrated an extraordinarily close relationship between carbohydrate and phosphate metabolism. Harrop and Benedict[13] showed that in normal glucose-tolerance curves, the level of blood phosphate fell, the low point of the phosphate curve being subsequent to the highest glucose level. They believed that phosphates are utilized temporarily during the transference of glucose from the blood. This has been corroborated by many writers.[14, 15, 16]

It has been shown that in dogs suffering from tetany, the symptoms are more pronounced on a meat than on a carbohydrate diet. Dragstedt[17] states that dogs with tetany lived longer when fed milk, white bread, and lactose than the usual survival period for thyroparathyroidectomized dogs. In spite of insufficient evidence, his conclusions appear to be correct. Blood studies were not made in his series, and the improvement was considered to be the result of changes in the gut. That the Dragstedt diet is beneficial in tetany has received confirmation. Inouye[18] and Frank, Haring and Kühnau[19] also contend that the beneficial effect of lactose is due to

changes in the intestinal tract, since parenteral administration is not effective. This conclusion is not completely justifiable for lactose is not absorbed as such, but is first hydrolized, with the formation of glucose and galactose. Hydrolysis takes place only to a small extent, however, if the lactose is given intravenously.[20]

Dragstedt believed that benefit was obtained in tetany by a diet of white bread, milk, and lactose because this diet prevented the absorption of toxic substances. Salvasen[3] criticizes Dragstedt's work, and in an excellent treatise presents evidence to prove that the entire benefit of milk is produced by its calcium content. He makes little comment on the effect of milk on blood phosphates. Although there is no question that calcium is essential, the studies herein reported make it apparent that the efficacy of this diet is partly attributable to its effect on phosphate metabolism.

In studying carbohydrate metabolism in parathyroidectomized dogs, Reed[21] found that not only ingestion but also injection of dextrose tends to alleviate symptoms of tetany, causing a decrease in inorganic phosphates and a less pronounced decrease in calcium.

The Object of the Study

From the preceding statements it is apparent that an increase in the level of inorganic phosphates in the blood may be closely associated with the production of symptoms in tetany. A fall in inorganic phosphates may cause alleviation of symptoms, even though it is not accompanied by a rise in serum calcium.

The object of this study was to find therapeutic measures which would lower the abnormally high level of blood phosphates, with the expectation that clinical improvement of the patient would result. Since there is such an intimate relationship between carbohydrate and phosphate metabolism, it seemed possible that the level of blood phosphates in tetany might be governed by the proper regulation of carbohydrate assimilation.

Effect of Glucose on Blood Phosphates in Normal Individuals

In Table I and Chart 1 are given results which confirm the finding that inorganic phosphate disappears from the blood after the administration of glucose in normal individuals.

The technic employed is as follows: A specimen of venous blood was obtained after the patient had been without food for twelve to fourteen hours. One hundred grams of glucose were fed, and samples of venous blood were obtained at intervals of half an hour and one, two, three, and four hours, respectively, after the ad-

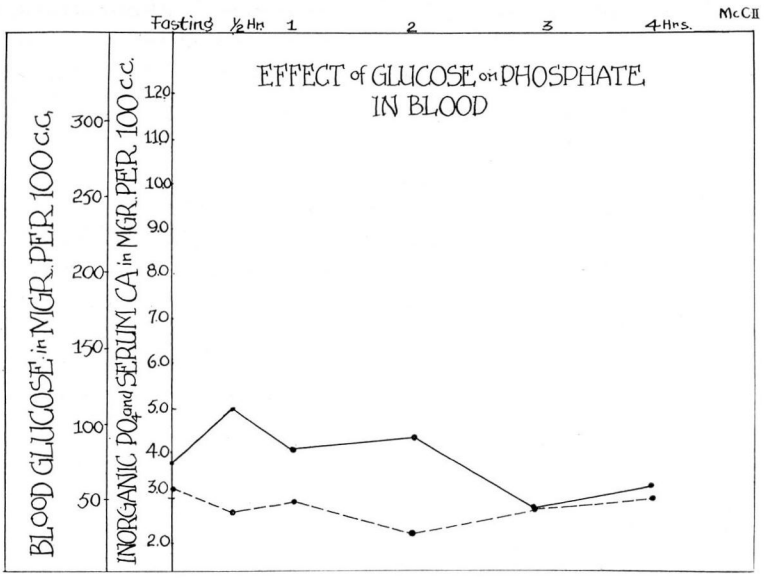

Chart 1

TABLE I

Effect of Glucose on Normal Individuals

Time in Hours	*Fasting*	½	1	2	3	4
Case 1 Sugar, mg. per 100 c.c. whole blood.	83	155	154	119	52	75
Phosphate, mg. per 100 c.c. whole blood.	3.22	2.77	3.09	2.40	2.21	3.25
Case 2 Sugar, mg. per 100 c.c. whole blood.	79	86	111	63	54	53
Phosphate, mg. per 100 c.c. whole blood.	3.64	3.07	3.31	2.58	2.31	2.78
Case 3 Sugar, mg. per 100 c.c. whole blood.	99	113	115	88	90	90
Phosphate, mg. per 100 c.c. whole blood.	3.28	2.23	2.57	2.25	2.34	2.50

ministration of the glucose. Blood sugar and phosphate estimations were made on each sample of blood. Blood sugar was estimated by the method of Hagedorn and Jensen.[22] Phosphates were measured by the colorimetric procedure of Kuttner and Cohen[23] (Table I, Chart 1).

An examination of these results demonstrates that the lowest point on the phosphate curve usually appears later than the highest point of the sugar curve. Not infrequently the phosphates return to the normal fasting level before the end of four hours.

Effect of Glucose on Blood Phosphate, Serum Calcium, and Neuromuscular Excitability in Chronic Parathyroid Tetany

The method used was the same as that described above, with the following additions:

Serum calcium determinations according to the Clark and Collip[24] modification of the Kramer and Tisdall method were made on the fasting specimen and on two of the other specimens. The electrical neuromuscular excitability (Erb's sign) was measured immediately before obtaining each specimen of blood. The procedure was as follows:

One of the patient's hands was placed on a large moist electrode connected to the anode of a circuit through which a variable direct current could be passed. The cathode consisted of a small metallic terminal covered with wet chamois. The skin over the median nerve at the wrist on the opposite side was moistened, and the electrode was applied. The circuit could be closed or opened by means of a small switch near the cathode. The amount of current running through the circuit was read from a milliammeter. In each case the current was gradually increased until a point was reached when, on closing the switch leading to the cathode, a contraction could be noted in the hand. The number of milliamperes necessary to produce the contraction was called the cathode closing contrac-

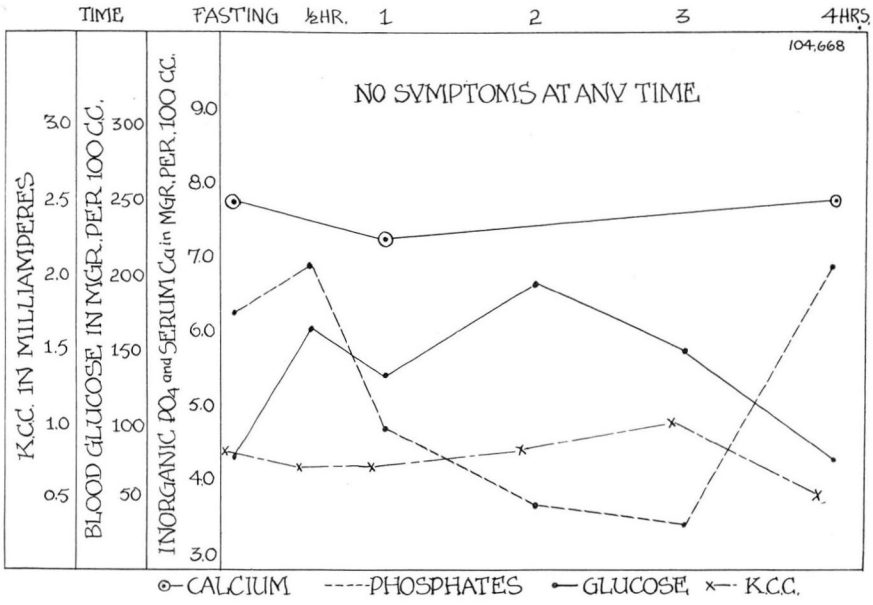

Chart 2

TABLE II

Effects of Glucose on Chronic Tetany

Time in Hours	*Sugar Mg. per 100 c.c. Whole Blood*	*Calcium Mg. per 100 c.c. Serum*	*Phosphate Mg. per 100 c.c. Whole Blood*	*Cathode Closing Contraction*	*Symptoms*
Case 1,					
Fasting	71	4.8	5.21	1.6	Present
½	133	—	4.74	1.6	Present
1	161	5.8	4.74	1.8	Improved
2	126	—	4.21	1.9	Improved
3	61	—	4.16	1.6	Present
4	59	4.8	4.87	1.4	Present
Case 2,					
Fasting	65	6.8	6.50	0.8	Present
½	120	—	4.05	0.8	Present
1	87	6.8	5.30	0.7	Improved
2	87	—	3.60	0.8	Improved
3	58	—	3.00	0.7	Present
4	52	6.8	4.70	0.6	Present
Case 3,					
Fasting	82	7.7	4.07	1.7	
½	142	—	3.30	1.9	
1	182	7.3	3.66	1.9	No definite symptoms
2	158	—	2.88	1.8	
3	117	—	2.42	1.8	
4	76	7.3	2.42	1.7	
Case 4,					
Fasting	79	8.2	4.70	0.7	Present
½	154	—	4.70	1.2	Present
1	134	9.2	4.00	0.8	Improved
2	109	—	4.10	0.7	Improved
3	70	—	4.40	0.7	Present
4	54	8.2	4.10	0.7	Present
Case 5,					
Fasting	83	7.8	5.50	1.6	Present
½	155	—	5.70	1.4	Symptoms better
1	129	7.3	4.80	1.1	
2	111	—	3.30	0.9	
3	68	—	3.45	1.1	Present
4	71	7.3	3.48	1.4	Present
Case 6,					
Fasting	67	6.3	4.80	0.6	Present
½	81	—	5.60	0.7	
1	98	6.8	4.00	—	Gradual
2	89	—	3.20	0.6	Improvement
3	70	—	3.75	0.5	
4	70	6.3	3.75	0.4	Present
Case 7 (Control, no	glucose given),	No. 223213			
Fasting	73	7.3	6.82	0.9	
½	75	—	6.40	1.0	
1	79	7.3	7.50	1.0	
2	77	—	6.40	0.6	
3	72	—	6.82	0.7	
4	70	7.3	6.40	0.6	

tion (K.C.C.). A decrease in this figure represents an increased irritability.

The patients on whom the following studies were made developed chronic parathyroid tetany following thyroidectomy. In each case Trousseau's, Erb's and Chvostek's signs were present, the latter only at times. Abnormally low blood calcium and high blood phosphate levels were always found, as shown in Table II. (Two cases which are not included in the tables are graphically depicted in Charts 2 and 3.) The blood sugar curves were essentially normal. The blood calcium changes were small and not constant. In four cases there was an increase, followed by a decrease. In two, there was a decrease which persisted until after the end of the experiment. In one case a decrease was followed by an increase, and in one

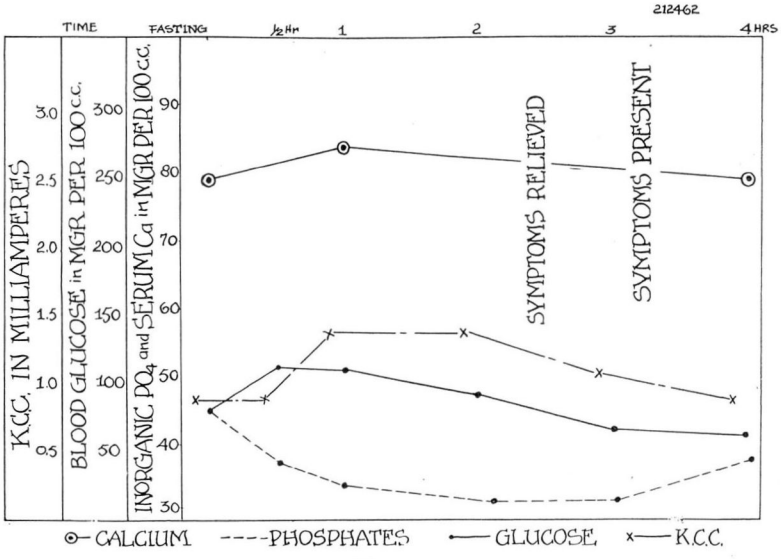

Chart 3

there was no change. The phosphates invariably were decreased. Only in Case 3 did the decrease continue for as much as four hours. This was associated with a more prolonged rise in the blood sugar than in any of the other cases. The neuromuscular excitability showed an almost constant tendency to decrease during the test. Only in Case 5 was there a definite increase in excitability. In all cases in which there were symptoms at the beginning of the test the symptoms were definitely improved during the test, but increased in severity at the end of the experiment when the phosphate level rose. Apparently the symptoms paralleled the phosphate curve more than that of the serum calcium.

In Case 7 no glucose was administered. The results were included to show that the changes recorded in the other tables were caused by the glucose.

Effect of Lactose on Blood Calcium and Phosphate in Normal Dogs

In one of the following sections it is shown that lactose is of great benefit in the treatment of tetany. The effect of feeding lactose to healthy dogs has been compared with the effect of feeding glucose to the same animals. The methods used were the same as those employed for glucose-tolerance tests. The results are shown in Table III. In this table, the blood sugar is expressed in terms of milligrams of glucose. The curve is very different after lactose

TABLE III

Effect of Lactose and Glucose in Normal Dogs

Dog No. 1, Weight 38, Experiment No. 1, Effect of Glucose, Dose 15 Grams

Time in Hours	*Fasting*	½	1	2	3	4	5
Sugar mg. per 100 c.c. whole blood	92	101	132	95	92	84	—
Phosphate mg. per 100 c.c. whole blood	2.39	2.27	—	2.12	2.32	2.39	—
Calcium mg. per 100 c.c. whole blood	11	—	—	—	—	10	—

Dog No. 1, Weight 38, Experiment No. 2, Effect of Lactose, Dose 15 Grams

Time in Hours	*Fasting*	½	1	2	3	4	5
Sugar mg. per 100 c.c. whole blood	77	74	117	75	66	75	—
Phosphate mg. per 100 c.c. whole blood	3.11	2.80	2.87	2.96	3.35	3.30	—
Calcium mg. per 100 c.c. whole blood	12.0	—	—	12.1	—	—	—

Dog. No. 2, Weight 55, Experiment No. 1, Effect of Glucose, Dose 20 Grams

Time in Hours	*Fasting*	½	1	2	3	4	5
Sugar mg. per 100 c.c. whole blood	77	90	119	77	74	72	—
Phosphate mg. per 100 c.c. whole blood	2.82	2.06	2.34	2.61	3.41	3.35	—
Calcium mg. per 100 c.c. whole blood	—	—	—	—	—	—	—

Dog No. 2, Weight 55, Experiment No. 2, Effect of Lactose, Dose 20 Grams

Time in Hours	*Fasting*	½	1	2	3	4	5
Sugar mg. per 100 c.c. whole blood	79	79	79	75	81	81	79
Phosphate mg. per 100 c.c. whole blood	3.30	2.77	2.84	2.69	2.84	3.03	3.27
Calcium mg. per 100 c.c. whole blood	8.7	—	8.4	—	8.8	—	—

feeding from that exhibited after glucose feeding. The glucose curves are similar to those in normal individuals; the lactose curves are very low, and indicate either a very high tolerance or very poor absorption. The serum calcium does not show a marked or regular change. There is no difference between the type of phosphate curve obtained with the two sugars, and no indication that lactose produces any prolonged depression of inorganic phosphate in the blood.

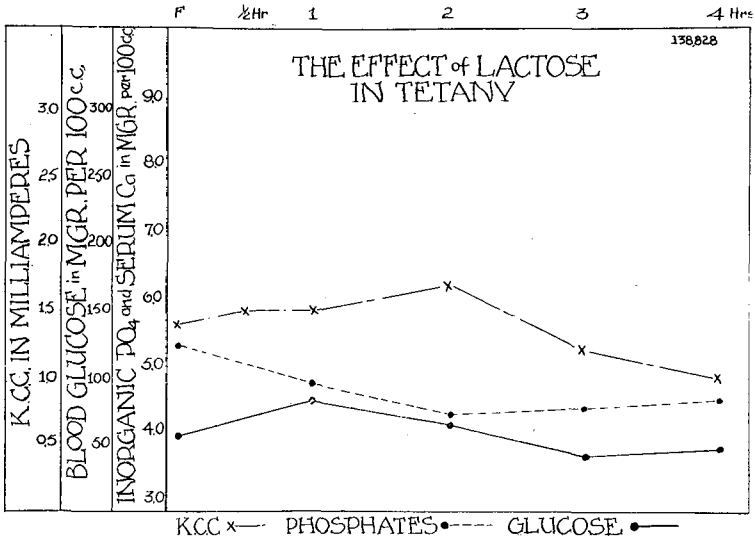

Chart 4

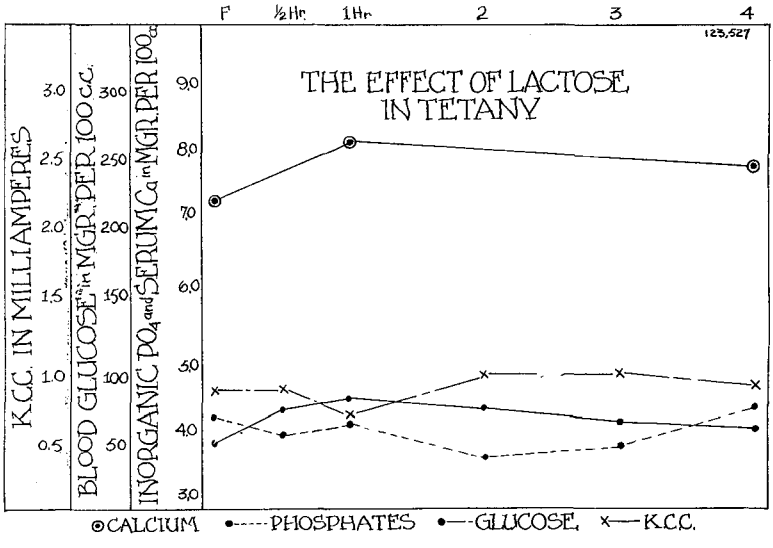

Chart 5

Effect of Lactose in Chronic Tetany

One hundred grams of lactose were administered to each of four patients suffering from chronic parathyroid tetany. The results are presented in Table IV and Charts 4 and 5. The blood glucose curves are of the same general type as those secured after the administration of glucose to normal individuals. The sugar values tend to be

TABLE IV

Effect of Lactose in Chronic Tetany

Time in Hours	*Sugar Mg. per 100 c.c. Whole Blood*	*Calcium Mg. per 100 c.c. Serum*	*Phosphate Mg. per 100 c.c. Whole Blood*	*Cathode Closing Contraction*	*Symptoms*
Case 8					
Fasting	77	7.7	5.00	0.7	Present
½	120	—	4.16	0.9	Present
1	117	7.2	4.16	0.7	Present
2	92	—	3.95	0.8	Improved
3	70	—	3.75	0.8	Improved
4	66	7.2	3.60	0.8	Improved
Case 9					
Fasting	65		3.85	1.0	Present
½	101		2.90	1.5	Present
1	77		3.56	1.4	Improved
2	77		3.56	1.8	Improved
3	48		3.82	1.1	Present
4	61		3.74	1.0	Present

low. Again there is no definite effect on the serum calcium. The depression of inorganic phosphate is about the same as after glucose administration. It appears probable that the lactose is readily digested, with the formation of glucose and galactose, and that absorption takes place rapidly.

EFFECT OF GALACTOSE ON BLOOD CALCIUM AND PHOSPHATE IN A NORMAL INDIVIDUAL

Since the glucose resulting from lactose digestion could account for all the changes in inorganic metabolism after lactose feeding, the effect of the galactose moiety was studied separately. The method was the same except that fifty grams of galactose were administered orally. It was considered advisable to use this smaller dose of galactose because of the low tolerance shown by most

TABLE V

Effect of Galactose in Chronic Tetany

Time in Hours	*Sugar Mg. per 100 c.c. Whole Blood*	*Calcium Mg. per 100 c.c. Serum*	*Phosphate Mg. per 100 c.c. Whole Blood*	*Cathode Closing Contraction*	*Symptoms*
Case 1					
Fasting	83	7.2	3.76	1.5	No definite change in symptoms
½	95	—	3.66	1.8	
1	104	6.2	3.59	1.8	
2	97	—	3.68	1.7	
3	90	—	3.68	1.8	
4	83	7.6	3.81	1.8	
Case 2					
Fasting	65	7.8	4.45	0.9	No definite change in symptoms
½	117	—	3.66	0.9	
1	95	7.9	3.55	1.0	
2	102	—	3.57	1.0	
3	83	—	3.64	0.9	
4	75	7.3	3.61	1.0	

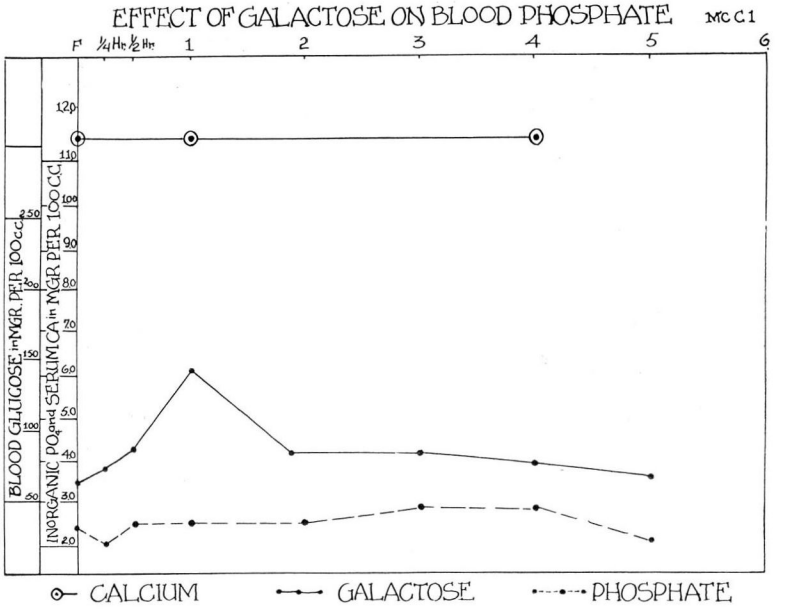

Chart 6

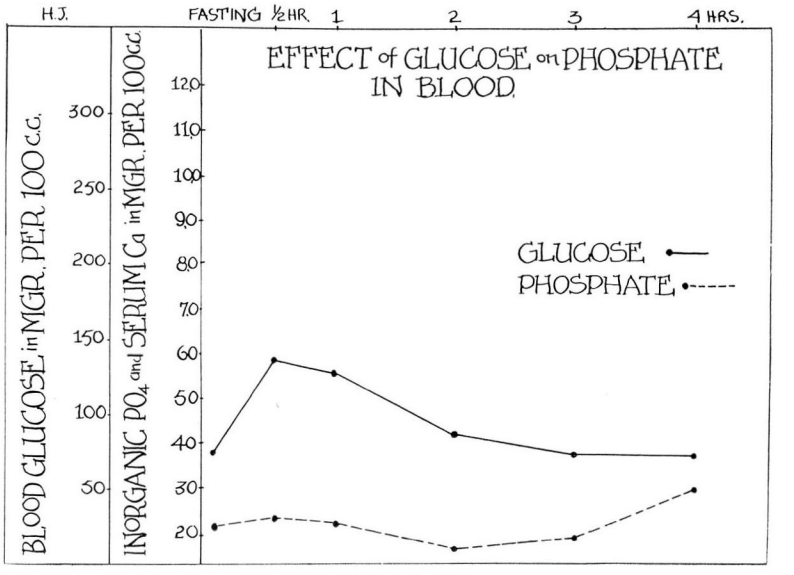

Chart 7

individuals to this sugar. In the following cases, sugar was excreted in the urine. The results are shown in Table V and Chart 6. As a control experiment, 100 grams of glucose were administered to the

same individual (Chart 7). The effect of galactose on blood phosphate is in sharp contrast to that of glucose. This is in accord with the results of Barrenscheen. Galactose does not produce a depression of the phosphate level in the blood.

Effect of Galactose in Chronic Tetany

Galactose was administered also to two patients suffering from chronic parathyroid tetany, with the result summarized in Table V. Evidently there is no difference between the reaction to galactose of normal individuals and of those with chronic tetany. No constant changes in inorganic metabolism appear following the administration of this sugar, the neuromuscular irritability does not show changes corresponding to those which occur after the administration of glucose, and the symptoms are not relieved during the test. Thus it seems improbable that it is the galactose moiety of the lactose molecule which results in depression of the blood phosphate. Further studies concerning the mechanism of the action of lactose on blood phosphate are in progress.

Effect of Glucose, Lactose, and Galactose on Urine Phosphate Excretion

The fate of the inorganic phosphate which disappears from the blood stream has been considered, and it has been demonstrated that this phosphate is not excreted in the urine. In fact, when the blood phosphate is depressed after glucose or lactose administration, the phosphate excretion in the urine diminishes. After the administration of galactose, no definite change develops in the

Table VI

Effect of Glucose, Lactose, and Galactose on Urine Phosphate Excretion

(a) In normal individuals

Case No.	*Dosage*	*1 Hour*	*2 Hours*	*3 Hours*	*4 Hours*
1	Glucose, 100 gm.	43.8	38.8	29.8	10.5
2	Glucose, 100 gm.	65.9	66.2	58.3	39.6
3	Glucose, 100 gm.	33.3	12.3	0.78	1.05
4	Glucose 100 gm.	32.1	1.16	1.65	0.95
5	Galactose, 50 gm.	33.2	12.9	27.3	21.0
b) In chronic tetany					
6	Lactose, 100 gm.	42.8	45.1	5.9	3.0
7	Lactose, 100 gm.	21.3	5.2	20.2	1.5
8	Lactose, 100 gm.	14.7	20.8	10.8	3.9
9	Lactose, 100 gm.	22.1	17.1	4.9	13.8
10	Galactose, 50 gm.	—	37.7	15.9	28.7
11	Galactose, 50 gm	5.2	5.7	4.0	5.4

rate of phosphate excretion. This is to be expected, since galactose does not affect the phosphates in the blood stream. There is no difference between the reaction of normal individuals and those with chronic tetany. The results are given in Table VI. Since the urine specimens were not taken with a catheter, the results given in this table are only approximations. The changes, however, are very marked and regular. It seems probable, from this work, that the phosphates which disappear from the blood are carried into the tissues.

Lactose in the Treatment of Chronic Parathyroid Tetany

In the following cases all calcium and phosphate estimations were made from samples of blood taken after the patient had fasted for approximately twelve hours.

Case 1. A young woman eighteen years of age underwent thyroidectony for adenoma of the thyroid in January, 1921. Two months after the operation she complained of paresthesia and stiffness of the fingers in attacks lasting from a few minutes to a few days. These symptoms persisted. She was treated by oral administration of calcium lactate at irregular intervals. On February 2, 1929, she complained of having had two severe tetanic convulsions. Examination showed the presence of Chvostek's and Trousseau's signs, and the serum calcium was 5.8 mg. per 100 c.c.

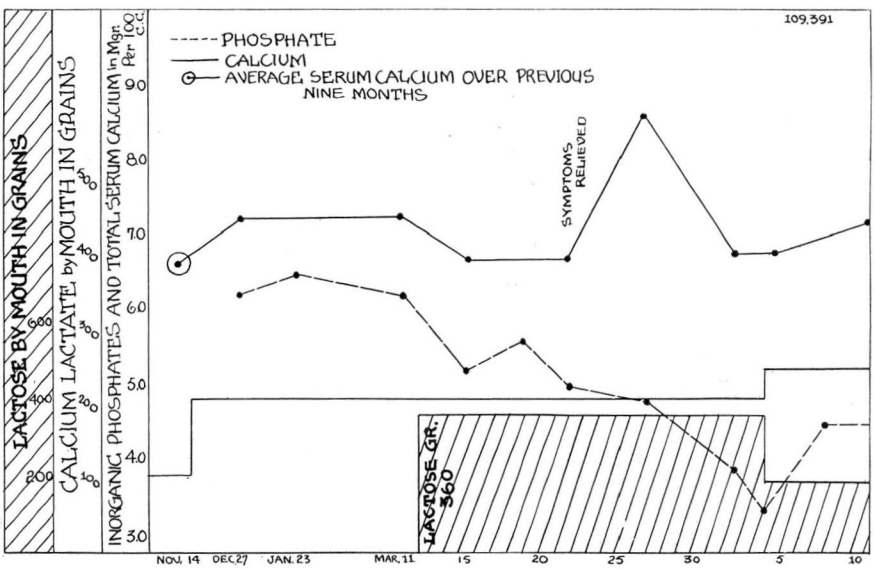

Chart 8

From this date, 100 grains of calcium lactate were given daily. The symptoms were partially relieved, but mild symptoms continued.

Chart 8 shows that the average serum calcium level, taken at monthly intervals for a period of nine months previous to November 14, 1929, was 6.6 mg. per 100 c.c. On November 14 the daily dose of calcium lactate was increased to 200 grains. The symptoms were improved slightly, and the serum calcium had risen to 7.2 mg. per 100 c.c. on December 27. On this date the inorganic phosphates were estimated for the first time, and were found to amount to 6.2 mg. per 100 c.c.

On January 23 the patient was placed on a high carbohydrate diet containing no meat, eggs, or cheese. In the hope of lowering the phosphate level, extra nourishment, consisting of candy, cake, biscuits, or fruit juices, was advised between meals and at bedtime. Between January 23 and March 11, she had five severe attacks of tetany, the symptoms always being more noticeable in the morning on wakening. Mild symptoms persisted between severe attacks, and the blood chemistry remained approximately the same.

On March 12, 1930, 360 grains of lactose per day were prescribed in addition to 200 grains of calcium lactate as before. These substances were divided into three doses, given before meals. The characteristic change in the chart consists in a persistent fall of the phosphate level. The symptoms were gradually alleviated and finally disappeared on March 27.

On April 4 the blood phosphates had fallen to a level which was lower than that considered necessary. The serum calcium was not normal, and therefore the dose of lactose was reduced to 180 grains and the calcium increased to 240 grains per day. The phosphate level rose, but remained within normal limits. The serum calcium also apparently rose somewhat. The temporary rise of serum calcium on March 27 is unexplained. The average serum calcium level was not greatly affected by the addition of lactose, and except for the one high value, there was a slight lowering of this figure until the calcium intake was increased on April 4. Since March 27 the patient has been completely symptom-free, with the exception of two days when she voluntarily discontinued treatment. On May 8 she stated that she was feeling better than she had for years.

Case 2. A woman, thirty-four years of age, underwent thyroidectomy for adenomata of the thyroid with tracheal compression on November 21, 1929. The basal metabolic rate before operation was minus 16 per cent. On the morning following operation she complained of tingling in the fingers. Her serum calcium on this day was 8.6 mg. per 100 c.c.

At first the patient received calcium gluconate one dram three times a day, and calcium lactate, 20 grains three times a day. Her symptoms demanded the administration of parathormone (parathyroid extract — Collip) on three occasions during the first thirteen days after operation, during which period the blood calcium fell to 7.7 mg. On December 4 the treatment was changed to one dram of calcium carbonate three times a day before meals. The symptoms were lessened in severity and the blood calcium rose from 7.7 mg. to 8.7 mg. on December 9, and to 9.2 mg. on December 12.

This treatment was continued, and the patient was not again observed until she returned on March 5, complaining that she had experienced almost daily stiffness and numbness of the fingers and

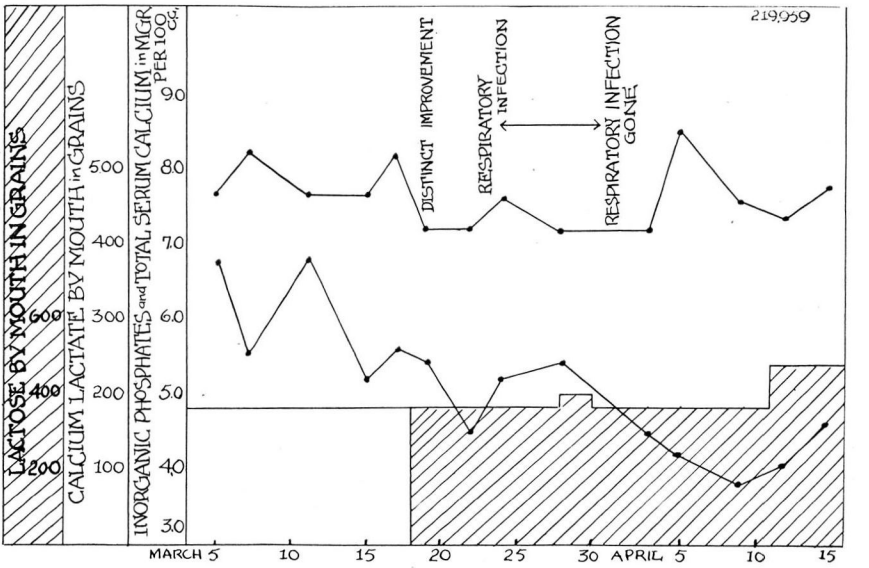

Chart 9

twitching of the facial muscles. The serum calcium was then 7.7 mg. per 100 c.c. and blood phosphates 6.8 mg. as shown at the beginning of Chart 9. The treatment was changed on this date to calcium lactate, 180 grains per day, given in three doses of one dram each before meals. The serum calcium changed very little and the blood phosphate varied between 6.8 mg. and 5.2 mg. per 100 c.c. There were mild symptoms daily.

On March 18 the administration of lactose was started in doses of two drams three times a day before each meal. On the first day there was no improvement. On the second day the symptoms had disappeared, and on March 22 the blood phosphate was 4.5 mg. and

the serum calcium 7.2 mg. On March 23 she developed a mild infection of the upper respiratory tract, associated with aching pains in the back and limbs. This lasted until March 30, and was accompanied by a slight rise in the blood phosphate level, but there was no paresthesia of fingers or toes and no stiffness of the fingers. Following March 23 the blood phosphate level continued to fall, and the patient felt entirely well.

It should be noted that while the patient's serum calcium varied slightly around the level of 8 mg. per 100 c.c., she had moderate symptoms of tetany associated with a high blood phosphate. Later when the average serum calcium level was lower, the symptoms were greatly improved, associated with a fall in blood phosphates. It might be mentioned again that the blood phosphate levels given were estimated while the patient was fasting. Probably they were lower during the day than those shown in the chart.

Case 3. A woman aged thirty-two underwent a thyroidectomy for hyperthyroidism on February 20, 1930. Her basal metabolism before operation was plus 49 per cent. About thirty-six hours after the operation she complained of twitching of the facial muscles and paresthesia and stiffness of the fingers. Both Chvostek's and Trousseau's signs were present. The serum calcium on February 22 was 7.2 and on February 24 was 6.7 mg. per 100 c.c. The blood phosphate on this date was 6.2 mg. per 100 c.c.

Treatment was begun February 22 in the form of calcium lac-

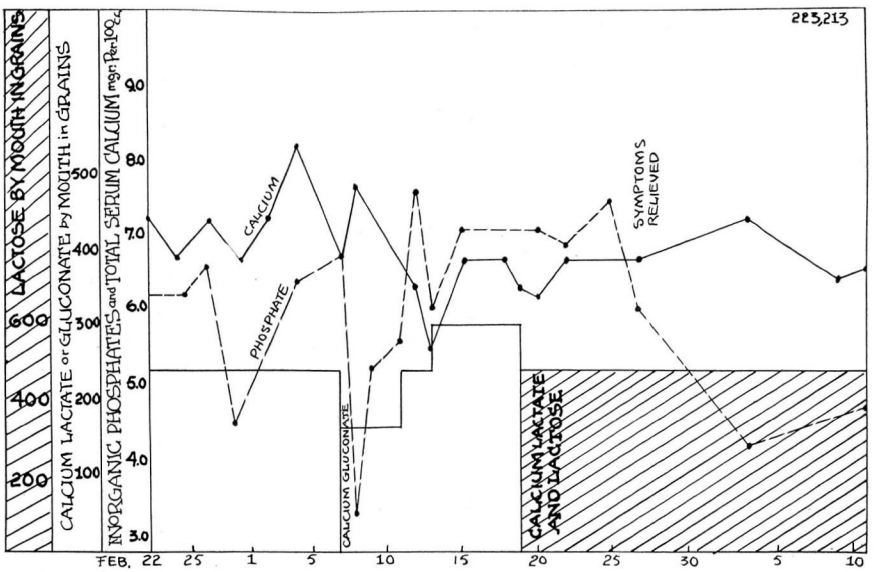

Chart 10

tate, 240 grains per day, 1 dram before meals and at bedtime, as shown in Chart 10. Symptoms were present daily, and the fasting serum calcium and blood phosphate varied as indicated.

On March 7, calcium lactate was discontinued and calcium gluconate was started, 180 grains per day in doses of 1 dram before each meal. The blood phosphate content fell markedly, but soon rose again to a higher level than before, in spite of the fact that the dose of calcium gluconate was raised first to 240 grains and later to 300 grains per day. The symptoms had disappeared on March 10, but on March 11 they reappeared and were more severe than before. Symptoms were present from the latter date until March 26.

On March 19 the treatment again was changed. The same amount of calcium lactate as was given previous to March 7 was prescribed. In addition to this, lactose was given in amounts of 480 grains per day, two drams being given with one dram of calcium lactate before each meal and at bedtime. For six days no distinct benefit was noted, but on March 27, the eighth day after the administration of lactose was started, there was definite improvement in the severity of the symptoms, accompanied by a fall in blood phosphates but without any rise in serum calcium. On this treatment the blood phosphates fell to a normal level, and symptoms disappeared entirely. The fasting blood phosphates are known to have remained normal for at least one month on this treatment, with the exception of two estimations done within one week following the extraction of an acutely abscessed tooth. On these occasions the phosphates were 6.4 and 6.0 mg., respectively. The patient was known to be symptom-free on May 8, 1930.

It is interesting to note again that the improvement in symptoms was associated with a fall in the level of blood phosphates but not with a distinct rise in the total serum calcium.

Case 4. A woman thirty-four years of age underwent thyroidectomy for adenoma of the thyroid in June, 1923. The second day following this operation tetany developed. She experienced tingling, numbness, and stiffness of the fingers daily, and on occasions had severe generalized convulsions which were thought to be epileptic in character, but as the convulsions have not recurred since she has had adequate treatment for tetany, it is probable that they were caused by this condition.

From June, 1923, to the present time the patient has required constant treatment. At first, when she was taking 10 grains of calcium lactate and 1/10 grain of parathyroid extract twice a day together with a mixture containing sodium bromide and tincture of hyoscyamus, she was not relieved, and continued to have symp-

toms daily and generalized convulsions occasionally. In May, 1925, when the calcium lactate was increased to 20 grains three times a day, she was somewhat relieved.

In June, 1926, injections of parathyroid extract (Collip) were begun, and a dose of 1 to 2 c.c. was administered subcutaneously every second or third day. In addition to this, she received parathyroid extract, grams 1/5, and calcium lactate, grains 10, three times daily, together with cod liver oil. In October, 1928, the intake of calcium lactate was raised to 120 grains per day. The patient felt better than she had since before the onset of the condition, but as moderately severe symptoms frequently were present, it was still necessary to give parathyroid extract (Collip) in doses of 20 to 40 units (1 to 2 c.c.) on alternate days.

This type of treatment was continued until January, 1930, when the dose of calcium lactate was raised to 360 grains per day. At this time the symptoms, though reduced, were persistent, and the patient began again to take about 2.5 c.c. of parathyroid extract daily. On March 11, 1930, lactose was added in amounts of 360 grains per day, with two drams each of lactose and calcium lactate before meals. The patient became symptom-free, and the parathyroid extract was reduced gradually.

Many important details have been necessarily omitted, but this outline conveys some idea of the severity of the disease in this case and of the type of treatment employed. Serum calcium and blood phosphate levels are not quoted in detail, but from January, 1925, to March, 1930, the serum calcium varied from 6.2 mg. to 9.7 mg. per 100 c.c., according to the treatment used. The most constant figure was between 7 and 8 mg. The blood phosphates in January, 1930, before beginning treatment with lactose, were 6 mg. per 100 c.c.

At the time indicated at the beginning of Chart 11 the patient was receiving 1 c.c. of parathyroid extract (Collip) per day, 300 grains of calcium lactate, and 360 grains of lactose. As she had been symptom-free since beginning the use of lactose, it was decided that the calcium lactate and lactose should be stopped entirely in order to see how much parathyroid extract (Collip) was necessary to relieve the symptoms completely. With the patient's permission and cooperation, on April 9 no calcium or lactose was taken at noon or in the evening, two drams of each being taken before breakfast as usual.

Early in the morning of April 10 symptoms appeared and therefore 2 c.c. of parathormone (parathyroid extract, Collip) were given subcutaneously at 8 a.m. and 4 c.c. at 5 p.m. On April 11 the severity

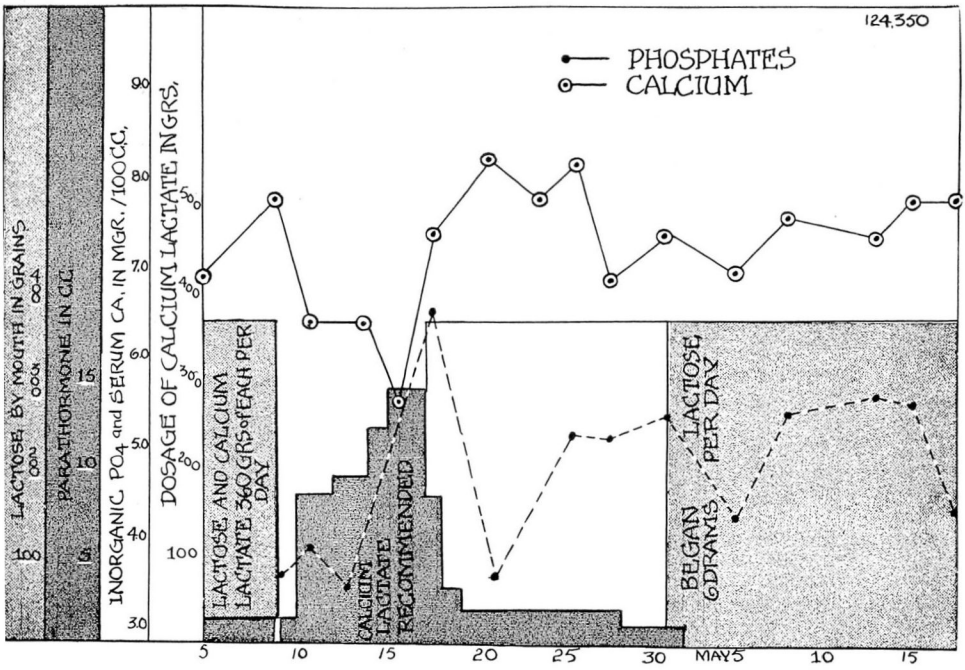

Chart 11

of the symptoms increased and 8 c.c. of parathormone were used, 4 c.c. at 8 a.m. and 4 c.c. at 5 p.m. The same dose was given on the following day. The blood calcium apparently was falling, but the phosphates were being held well in check. On April 13, despite the administration of 4 c.c. of parathormone at 8 a.m. and 5 c.c. at 5 p.m. the symptoms were becoming more severe. The fingers were stiff, the patient was nauseated all day and took only small amounts of food with difficulty, and she staggered markedly when she walked. On April 14, 6 c.c. of parathormone were given subcutaneously at 9 a.m. There was slight relief in half an hour, but at 4:30 p.m. the symptoms again became more severe. On April 15, 6 c.c. of parathormone were injected at 8 a.m. and 7 c.c. at 5 p.m. The patient was slightly better on this day, but still had some carpal spasm and nausea. On April 16, the symptoms were severe. The muscles of the arms and legs were becoming sore. Seven c.c. of parathormone were given at 8 a.m. and 6 c.c. at 5 p.m. The report on the blood chemistry showed that the serum calcium had fallen to 5.2 mg. and the phosphate had risen to 4.5 mg. per 100 c.c. Because of this and the severity of the symptoms, calcium lactate was given, 2 drams before dinner and 2 drams at bedtime.

The following day she again began to take calcium lactate, 360 grains per day. The serum calcium rose promptly and the symptoms were completely relieved. The parathormone was reduced to 2 c.c. per day. Since slight symptoms were present, the dosage of parathormone was not decreased until April 28. The symptoms from April 17 to May 1 were very slight, but not mild enough for the parathormone to be discontinued. On May 2, 360 grams of lactose were given, divided into three doses, before meals, in addition to the same dosage of calcium lactate as before. The patient was instructed to use parathormone as before, when required for the relief of symptoms. Up to May 8, she had not found it necessary to use any injections, as there had been no paresthesia or stiffness of the fingers since administration of lactose was started.

It was expected that the phosphate level would rise somewhat after the discontinuance of the parathormone, and this has occurred. The patient has noticed very mild symptoms on two days, but they have been so slight that up to the present time she has preferred not to use parathormone.

The patient was last seen on May 20, when she was practically symptom-free.

Discussion

In chronic tetany, definite improvement in symptoms apparently results from the feeding of lactose. This is associated with a fall in the level of inorganic phosphates in the blood. During glucose assimilation after the ingestion of glucose or other carbohydrates, there is always temporary improvement in symptoms, associated with a fall in the phosphate level. Nevertheless, even frequent carbohydrate feedings do not result in the permanent benefit which is observed after the administration of lactose. After single doses of glucose or lactose the blood phosphate returns to the previous level within four hours. It seems remarkable that when lactose is used therapeutically, low levels of inorganic phosphate can be demonstrated in the blood twelve to fourteen hours after the last dose of lactose is taken.

The complete mechanism of the action of lactose on blood phosphates is obscure. At first it was thought that the slow digestion of lactose, and the resulting slow absorption of glucose and galactose, might account for the prolonged depression in the phosphate level in the blood. After examination of the blood following the oral administration of one dose of lactose this seems unlikely. The blood sugar level rises sharply and falls again within four hours, indicating rapid absorption and assimilation. The inorganic phosphates also return to a normal level within this period. The feces have not been

examined quantitatively, but it has been shown that the phosphate depression is not the result of increased urinary excretion. On the contrary, there is a retention of urinary phosphates after the administration of single doses of lactose.

The possibility that galactose might have a specific effect was considered. It is known that glucose can be formed in the body from galactose which has been absorbed from the intestine. If the glucose, so formed, is assimilated in the same manner as ingested glucose, it was thought that an extended period of carbohydrate assimilation might result. This in turn would cause a prolonged depression of the phosphate level which would simulate the long, low phosphate curve noted after the administration of glucose to diabetics, when assimilation of the glucose is delayed.

At present, the data concerning this point are insufficient to warrant definite conclusions. Our results, however, and those of Barrenscheen[25] fail to demonstrate any connection between the metabolism of galactose and that of inorganic phosphate in the blood. The use of galactose over long periods may cause us to draw different conclusions. As yet, there is no definite evidence that the efficacy of lactose is due to changes in intermediary metabolic processes. It may be that there is a slowing of the absorption or an acceleration of the excretion of the phosphates.

Neither Dragstedt[17] nor his recent supporter, Hutton,[27] have associated the effect of lactose with mineral metabolism. Those who believed that parathyroid tetany was caused by changes in calcium metabolism were of the opinion that lactose produced an increased absorption of calcium by the production of acidity in the gut.[26] So far as we are aware, no one has demonstrated an increased blood calcium after lactose administration. Since calcium phosphate is very insoluble, it is possible that an increased absorption of calcium might result in a lowering of the phosphate level due to a deposition of calcium phosphate in the tissues. Hence, increased calcium absorption might not be apparent on examination of the blood.

Summary and Conclusions

1. The symptoms of chronic parathyroid tetany may be lessened in severity or completely controlled by lowering of the amount of inorganic phosphates in the blood without raising the total calcium content of the blood serum.

2. Glucose temporarily lowers the amount of inorganic phosphates in the blood of normal subjects and in individuals with chronic parathyroid tetany.

3. Lactose in single doses has the same effect as glucose.

4. Galactose in single doses has no effect on the inorganic phosphate content of the blood.

5. After ingestion of glucose or of lactose there is a decrease in the amount of phosphate excreted in the urine. This does not occur after the administration of galactose.

6. Three cases of chronic parathyroid tetany are reported in which symptoms were present in spite of the oral administration of large doses of calcium lactate. The addition of lactose resulted in complete relief, associated with a lowering of the phosphate content of the blood.

7. One case of chronic parathyroid tetany is reported in which large doses of calcium lactate alone failed to give complete relief and very large doses of parathyroid extract (Collip) alone failed to give relief. The symptoms could be controlled by the oral administration of large doses of calcium lactate, together with the subcutaneous injection of parathyroid extract. Calcium lactate in large doses in combination with lactose gave relief without the addition of parathyroid extract.

8. The mechanism of the action of carbohydrates in lowering the amount of phosphates in the blood is discussed.

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