THE FUNCTIONAL PATHOLOGY OF HYPER-PARATHYROIDISM

By HAROLD A. BULGER, HENRY H. DIXON, AND DAVID P. BARR, WITH THE TECHNICAL ASSISTANCE OF OLIVE SCHREGARDUS

(From the Department of Medicine, Washington University and the Barnes Hospital, St. Louis)

(Received for publication March 3, 1930)

For many years a few physicians have conceived of a condition the direct opposite of parathyroid tetany. Lundborg (53) and later Chvostek (21) believed this was manifest in myasthenia gravis but clinical observations did not confirm their belief. It was not until the use of Collip's (23) active parathyroid extract in animals had indicated the symptoms of such a state that hyperparathyroidism was recognizable as a clinical syndrome. It is now known that it constitutes a picture of disease as clearly defined as hyperthyroidism and follows closely the abnormalities which may be produced by parathyroid extract in animals. The literature and clinical features have been discussed in another paper (2).

Many facts concerning functional abnormalities in hyperparathyroidism have already been determined.

Collip (23) has shown that the various well-known manifestations following removal of the parathyroid gland are reversed after the parenteral administration of parathyroid extract. No longer is the theory tenable that the fall in serum calcium after parathyroidectomy is but a secondary phenomenon. Active extracts will prevent it and by raising the serum calcium entirely relieve the symptoms. Extracts readily cause an increase in the serum calcium in normal animals. It seems obvious now that the parathyroid glands are concerned with the regulation of the calcium concentration in the blood. They appear as an essential component in one of those remarkable regulatory mechanisms characteristic of the higher animals. The constancy of the serum calcium even under many of the most abnormal conditions is worthy of special emphasis. Although an increase in serum phosphate is typical of parathyroid tetany a reduction has not commonly been found in experiments in which parathyroid intoxication was rapidly produced. Robinson, Huffman and Burt (62), however, report a reduction in the serum phosphate of calves receiving parathyroid extract. Greenwald and Gross

(39) and later other investigators have definitely shown that effective parenteral administration of parathyroid extract causes an increased excretion and especially an increased urinary excretion of both calcium and phosphorus, phenomena quite the reverse of those following parathyroidectomy.

A change in the tone and irritability of muscles which might be considered the opposite of tetany is suggested in the hypotonia often noted in animals with hypercalcemia. Berman (9) using galvanic currents has demonstrated a definite decrease in the electrical response in the peroneal nerve of normal dogs after a moderate increase of serum calcium produced by parathormone. These results were emphasized by the contrast with his parathyroidectomized dogs.

Another noteworthy result of administering excessive amounts of parathyroid extracts, is the deposition of calcium in various tissues. This has been described by Hueper (48) and occurs characteristically in the lungs, gastric mucosa and kidneys. As one might predict from the negative calcium balance, long continued administration of parathyroid extract results in decalcification of the bones, a phenomenon which has been studied from the histological point of view by Bauer, Aub and Albright (3).

In the clinical literature one finds many cases of extensive bone diseases complicated by parathyroid tumors or hyperplasia. These cases are now recognizable as probable examples of hyperparathyroidism. The predominating type of bone disease was that characterized by multiple cyst and giant cell tumor formation and usually classified as ostitis fibrosa cystica. Less frequently other types of bone diseases, such as osteomalacia, metastatic carcinoma or multiple myeloma, revealed this association. Many of these cases with enlarged parathyroids displayed certain interesting features probably attributable to excessive parathyroid activity. General decalcification, fragility and bowing of the bones were usually evident. A prominent symptom in some cases was extreme muscle weakness. Many had kidney stones with pyelonephritis and cystitis. In some instances there was calcium deposition in various tissues, characteristically in the lungs, gastric mucosa and kidneys. The cases presented a variety of other symptoms possibly related to hypercalcemia, such as marked constipation, attacks of severe abdominal pain and vomiting as well as symptoms suggesting cardiac insufficiency.

Studies of calcium and phosphate metabolism in the cases of the older literature were infrequent and the doubt which often surrounds the diagnosis makes them generally inapplicable to the study of functional pathology in hyperparathyroidism. Since 1926, however, considerable data has accumulated. Mandl (56) who was the first clinician to search for abnormal parathyroid tissue with therapeutic possibilities in mind studied the urinary excretion of calcium before and after removal of a parathyroid tumor. Before the operation excessive amounts of calcium appeared in the urine and the excretion fell below normal after the operation. Gold (37) has reported a case with ostitis fibrosa, a parathyroid tumor and moderate hypercalcemia. Extirpation of the parathyroid tumor was attended with marked improvement and resulted in a definite fall of the serum calcium and of the calcium excreted in the urine. Hannon, Shorr, McClellan and DuBois (44) and later

Bauer, Albright and Aub (44) have studied a patient with a generalized bone disease characterized by decalcification and tumor formation. This patient showed a hypercalcemia, hypophosphatemia, a negative calcium balance and excessive excretion of calcium in the urine. After removing two apparently normal parathyroids the patient improved, although there was little change in the calcium and phosphorus metabolism. Belden (5) has described a case of a woman with a mottled decalcification of the bones without tumor formation and presenting other symptoms characteristic of this group. The serum calcium was 15.2 to 18.8 mgm. per 100 cc., the serum phosphate normal. Operation was attempted but no parathyroid tissue obtained. Duken (30) has described two cases of generalized bone disease with high serum calcium and in one a tumor in the region of one parathyroid gland.

While the studies reported here were in progress, Wilder (79) reported detailed observation of a patient with marked muscle weakness, rarefaction and giant cell tumors of bones and a palpable parathyroid tumor. There was a moderate increase in serum calcium, a definite decrease in serum phosphate and excessive excretion of calcium in the urine. Following the resection of the parathyroid tumor, the serum calcium fell almost to the tetany level and calcium all but disappeared from the urine. The patient improved markedly. Beck (4) removed two parathyroid tumors from a patient with ostitis fibrosa. The patient developed extreme tetany and died on the twentieth day after operation. Recently a case was reported by Boyd, Milgram and Stearns (13) as hyperparathyroidism whose symptoms and associations may be considered classical. The serum calcium was high, the phosphate within normal limits. After removing the parathyroid tumor there was a marked fall in the serum and urinary calcium and the calcium balance became strongly positive. Snapper (73) records a case showing similar changes in the serum and urinary calcium after operation. Hunter (49) has described another typical case which had an excessive excretion of calcium both in the urine and the stools.

The following study of the functional pathology of the disease was started in April 1928, and has been continued to the present time. It will indicate the abnormalities encountered and will emphasize factors to be considered in diagnosis and treatment.

METHODS OF STUDY

The patients with hyperparathyroidism were studied in the Metabolism Division of Barnes Hospital. Their diets were prepared in the special kitchen of the division. The food and fluid intake was under the supervision of a trained dietitian, assisted by nurses especially assigned to the individual cases. At least two persons checked the foods as well as the dietary calculations. Refused food was weighed

and the proper adjustment made at once. Calcium and phosphorus intake was calculated, with few exceptions, from the analysis of foods collected from the literature by Sherman (69). It was obviously necessary to make analysis of some foods. The same type of bread was always used and analysed repeatedly. Water from the city supply was given and the calcium from this source calculated from the analyses furnished by the St. Louis Water Works. This amounted to only a few milligrams a day and could have been neglected without serious error.

The stool and urine collections were under the supervision of the head nurse of the division, who is well trained in the management of metabolic studies. The stools were collected in four-day periods, being marked off by carmine taken with the breakfast with the beginning of each period. Because of the possible difficulties from constipation, all patients received liquid petrolatum and granulated agar-agar with each meal. The urine was collected in 12 hour periods and combined into the four-day periods.

The calcium in the urine was determined by the method of Shohl and Pedley (70), that of the feces by the method of Corley and Dennis (24). The total phosphorus of the urine was determined by the method of Fiske and Subbarow (33) after complete oxidation with sulphuric and nitric acids. Care was taken to expel finally all the nitric acid and at the same time not to continue the heating to dryness. This same method was employed for the total phosphorus of feces by using an aliquot from the filtered digested stool mixture of the Corley and Dennis fecal calcium method. Serum calcium was determined by the Clark and Collip (22) modification of the Kramer-Tisdall method; serum phosphorus by the method of Benedict and Theis (6). The serum was always separated from the cells within two hours after the blood was obtained.

CASES STUDIED

Three patients with hyperparathyroidism were studied. Their histories are only briefly summarized as they have been reported in considerable detail in another paper (2).

Case 1 was a farmer's wife, 58 years old, with generalized ostitis fibrosa cystica. Her past history was noteworthy in that early in life she developed a striking

dislike for certain foods, especially milk, and it is reasonable to believe her calcium intake was deficient throughout life. For about 20 years she had had urinary symptoms attributed to "inflammation of the bladder." For nearly ten years she had been slowly developing difficulty in walking until finally she was quite unable to support herself. About two years before this study was started, she developed, following trauma, a fusiform swelling of the first phalanx of the right index finger This proved to be a bone tumor containing many giant cells. Rather slight trauma caused a fracture of a clavicle and later a humerus. Following the extraction of a tooth a tumor developed in one maxilla. A tumor also appeared on the shaft of the left ulna which showed on biopsy many giant cells similar to the tumor of her finger. Physical examination revealed a remarkable degree of muscle hypotonia. Electrical tests showed no response of the muscles to faradic stimulation. There was a marked kyphosis and moderate bowing of the thighs. The tumor of the left maxilla caused marked asymmetry of the face. The teeth were quite loose. Urine examination showed evidence of inflammation of the urinary tract. X-ray revealed marked decalcification of all the bones and irregular areas of rarefaction suggesting tumor formation. Flat plates of the kidneys showed a large collection of stones in both pelves. Examination of the blood showed a slight anemia, negative Wassermann reaction, normal nonprotein nitrogen, calcium 16 mgm., and phosphorus 1.4 mgm. per 100 cc. Later a tumor the size of a small walnut was discovered rising from behind the inner end of the left clavicle as the patient swallowed. Histological examination after removal showed this to be parathyroid tissue. The course following operation is described in detail in a later section.

Case 2 was a farmer, 38 years old, with multiple epulis. Several years before admission he had had, because of gastric ulcer, two operations, the second of which was followed by complete relief. There was no history of any dietary abnormality, he had always liked milk and frequently drank as many as five glasses at a meal. There was no evidences of muscle hypotonia and there had been no urinary disturbances. About 8 months before admission to the hospital he noticed what he called a "gumboil" of the upper jaw. It was at no time painful, but gradually became larger. Three teeth at the site of the lesion became loose and were extracted by the patient. On examination he was well nourished. The muscles were well developed and of good tone. In place of the left upper canine and the first and second bicuspid teeth a tumor was present which extended into the hard palate posteriorly and beyond the alveolar margin anteriorly. X-ray disclosed a smaller tumor of the opposite maxilla and three separate and distinct tumors of the lower jaw. The urine was normal. There was no anemia. The blood Wassermann was negative and the blood nonprotein nitrogen was normal. The phenolsulphonephthalein excretion was 55 per cent in two hours.

At two operations all of the tumors were removed by curette and cautery and treated with radium and deep x-ray therapy. Microscopic examination of the

tissue showed characteristic giant cell tumors. About six weeks after the operation on the jaw, the serum calcium and phosphorus were studied for the first time. Calcium values ranged from 13.3 to 16.7 mgm. and phosphorus from 1.6 to 2.9 mgm. per 100 cc. A more careful examination of the neck now revealed a small mass just above the inner end of the left clavicle. This was elevated and more easily felt when the patient swallowed. There was still no evidence of hypotonicity of the muscles. X-ray of the skull and long bones showed no other bone tumors and no decalcification. X-ray of the urinary tract revealed no stones. The course following the removal of the parathyroid tumor is described in a later section.

Case 3, was a housewife, 46 years old, with multiple myeloma, who had been ill for two and a half years with pain, weakness fever and night sweats Clinically there was found to be a destructive involvement of vertebrae and ribs, enlarged and tender liver and kidney insufficiency. Values for nonprotein nitrogen ranged from 65 to 75 mgm. per 100 cc. and the phenolsulphonephthalein excretion was very low. No Bence-Jones protein was found in the urine, although albumin and casts were abundant. Serum calcium was found to be high and a study of phosphorus and calcium metabolism was started. A few days after the last studies reported in the text she developed broncho-pneumonia and died. The post-mortem examination demonstrated typical plasma cell multiple myeloma involving chiefly the vertebrae, pelvis and ribs. Three parathyroid glands were moderately enlarged. There was a remarkable degree of metastatic calcification of the lungs, gastric mucosa and kidneys.

TOTAL CALCIUM BALANCE

Sherman (68) after reviewing the literature offered what he considered to be a satisfactory estimate of the average amount of calcium required for maintenance of equilibrium. It appears that this should be, in normal adults, approximately 0.45 gram per 70 kilograms of body weight. All of our patients were studied for a considerable period, first while on a low calcium intake but on an intake well above the amount estimated by Sherman for equilibrium under normal conditions. In summary form, a part of the extensive data recorded at the end of the paper has been placed in table 2 to illustrate the type of calcium metabolism presented by these patients. There can be no doubt of the abnormality. Although their intake was theoretically adequate, they excreted excessive amounts. In each case, over one-half gram per day failed to keep them in balance. Even on a high intake, the first patient excreted more calcium then ingested; in Period 7 while taking 2.2 grams of calcium daily, the average output was 3.9

grams. The second patient barely maintained equilibrium on a very high intake and it seems probable that a negative balance might finally have ensued if the studies had been followed longer. The third patient who had generalized hyperplasia of the parathyroids and evident kidney insufficiency retained calcium for a long time when the intake was raised to about 1.3 gram daily, but here some unrecognized factors probably complicated the results because during these periods the calcium output was even less than in the former periods of low intake. The kidney insufficiency with its associated phosphate retention may have been of great importance. The probable significance of this factor will be discussed later. The clinical consequence of the failure to retain calcium is evident. Bone changes would be expected. Cases 1 and 3 showed marked generalized decalcification, a finding not infrequently associated with specific diseases of the skeleton.

URINARY CALCIUM EXCRETION

In 1884 Davies-Colley (27) described to the Pathological Society of London a case which was remarkably similar to Case 1 in this report. This was a girl 13 years old with generalized bone disease including a tumor of the jaw, nephrolithiasis and paraplegia. He stated that the urine "showed about one-third the amount of phosphate of normal, but the calcium in excess." Since then studies of the metabolism in bone disease have occasionally shown cases with an increased urinary output of calcium. The possible significance of the distribution of calcium excretion between the feces and urine has not been sufficiently emphasized in its relation to specific types of bone disease.

The most striking and noteworthy feature of the metabolism of the patients with hyperparathyroidism was the excessive excretion of calcium in the urine, corroborating exactly the experiments on animals with parathyroid extract. Normally the urinary excretion of calcium is relatively small and is not materially increased by high calcium intake. Even intravenous calcium administration may have little influence on urinary excretion (65). The great differences in output resulting from variations in calcium intake occur chiefly in the stools. It hardly seems necessary to review the literature concerning the excretion of calcium in the urine; one may refer to Givens' article (36) for a discussion of the older literature. The average quantity

excreted in twenty-four hours is usually 100 to 200 mgm. Frequently much less, and occasionally two or three times this amount has been recorded. One gets the impression that studies on active adults show a greater urinary calcium excretion than studies on inactive subjects with various diseases. This is also indicated by the data presented in

TABLE 1

Calcium excreted in the urine in 24 hours by hospital patients and normal individuals

Case number	Diagnosis	Urine calcium	Case number	Diagnosis	Urine calcium
		grams			*grams*
2	Arteriosclerotic heart disease	0.012	6	Diabetes insipidus	0.038
2	Arteriosclerotic heart disease	0.064	16	Diabetes insipidus	0.202
2	Arteriosclerotic heart disease	0.013	22	Diabetes mellitus	0.011
3	Arteriosclerotic heart disease	0.004	11	Diabetes mellitus	0.007
3	Arteriosclerotic heart disease	0.061	10	Diabetes mellitus	0.008
4	Arteriosclerotic heart disease	0.018	8	Diabetes mellitus	0.093
5	Arteriosclerotic heart disease	0.011	7	Diabetes mellitus	0.057
5	Arteriosclerotic heart disease	0.024	7	Diabetes mellitus	0.107
14	Arteriosclerotic heart disease	0.065	9	Diabetes mellitus	0.197
20	Arteriosclerotic heart disease	0.015	21	Streptothricosis of bone	0.012
27	Arteriosclerotic heart disease	0.005	30	Scleroderma	0.048
12	Arteriosclerotic heart disease	0.007	30	Scleroderma	0.080
23	Rheumatic heart disease	0.043	29	Spondylitis deformans	0.243
28	Rheumatic heart disease	0.013	29	Spondylitis deformans	0.329
28	Rheumatic heart disease	0.136	17	Mild acute nephritis	0.082
18	Pulmonary emphysema	0.049	31	Nephritis with edema	0.003
18	Pulmonary emphysema	0.081	31	Nephritis with edema	0.020
19	Lobar pneumonia	0.011	31	Aneurysm, bronchopneumonia	0.018
26	Hypernephroma	0.063	25	Normal	0.042
15	Carcinoma of stomach	0.054		Normal	0.045
24	Carcinoma of stomach	0.202		Normal	0.124
1	Carcinoma of liver; jaundice	0.018		Normal, high calcium intake	0.288
13	Diaphragmatic hernia	0.075		Normal, high calcium intake	0.312

table 1 showing the 24-hour urinary calcium excretion of hospital patients with various conditions and of a few normal individuals. The patients were taking regular ward diets and were allowed milk as desired. The data are also presented for comparison with the subjects having hyperparathyroidism. Acidosis especially when caused by mineral acids is associated with an increase in urinary calcium output.

Acid and basic diets produce similar changes. These facts are often cited but the studies of Zucker (83), Bogert and Kirkpatrick (11), and others indicate that the variations are not extreme. As the four adult subjects of Bogert and Kirkpatrick shifted from control diets to base forming diets the average urinary calcium excretion decreased from 99 to 66 mgm. in 24 hours, while 144 mgm. was excreted with

TABLE 2

Summary of calcium metabolism in hyperparathyroidism. The data are selected from tables 9, 10, and 11 and are expressed in daily averages in grams

Period number	Days	Calcium. Daily averages				Serum	
		Intake	Output	Urine	Stools	Calcium	Phosphorus
		Case 1					
		grams	*grams*	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
1–5	20	0.56	1.36	0.319	1.04	16.4	1.5
6	4	0.91	0.72	0.780	1.94	16.5	
7	4	2.21	3.90	2.32	1.58	16.4	1.3
8	4	0.98	1.76	1.08	0.68	16.4	
		Case 2					
1–4	16	0.89	1.08	0.432	0.65	16.8	1.6
5	4	3.69	3.40	0.587	2.81	14.9	1.9
6–7	8	2.33	2.46	0.532	1.93	14.0	2.1
9–10	12	0.99	1.22	0.451	0.77	14.1	2.4
		Case 3					
1–4	16	0.56	1.15	0.246	0.90	15.4	2.6
5–8	16	1.37	0.91	0.144	0.77	15.7	5.3
9–10	8	3.58	2.15	0.226	1.92	17.8	4.8

acid-producing diets. Zucker found changes of a similar magnitude in men after hydrochloric acid and sodium bicarbonate. The various anions of physiological importance also appear to produce small but demonstrable alterations in urinary calcium excretion.

The data recorded in table 2 leave no doubt of the abnormal excretion of calcium in the urine of these patients with hyperparathyroidism. Even on a low calcium intake it is excessive. Especially impressive is

the output which ensued in Case 1 when the calcium intake was increased. In Period 7, the excretion amounted to 1.3 gram per day. The urinary output of Case 3 was less impressive but was greater than that of the patients included in table 1 who were studied under somewhat similar hospital regime. Here the evidence of kidney insufficiency complicated the picture and it seems reasonable to conclude that the abnormality was markedly limiting the capacity to excrete calcium by this route. Evidence is available indicating this effect. Halverson, Mohler and Bergeim (42) found a very low calcium excretion in a number of cases of nephritis. Administration of calcium causes only a slight increase. The same phenomena were also noted by Boyd, Courtney and MacLachlan (12) in children with nephritis and by Schriver (66) in two cases which were studied in great detail. In extensive observations of a case in this clinic the urinary calcium was found to be almost negligible. Hetenyi and Nogradi (45) showed that nephritics excreted less than normal subjects after intravenous injections of calcium salts.

Certain conclusions may be drawn from these studies regarding the relation of the urine reaction to this abnormal calcium excretion. The astonishing urinary calcium excretion of Case 1 was associated with a very acid urine. Under certain conditions to be discussed later, however, the urine calcium was subsequently reduced to normal (Period 16 to 19, table 9) at times when the urine was even more acid. The other patients produced urine which was nearly neutral or at times slightly alkaline. It seems obvious that the reaction of urine cannot be a factor of primary importance although an increase in acidity may exaggerate the tendency to abnormal excretion of calcium.

Hypercalcemia was found in all three cases and it is natural to assume a relationship between this and the excessive urinary calcium. Certain circumstances, however, indicated that the connection is more complicated than might at first appear. When excessive amounts of calcium were given the increase in urinary excretion was not necessarily attended by any further rise in the serum calcium. The most striking example of this was presented by Case 1 in Periods 7 and 8 (table 2). Very significant appears the fact that in Period 8 the great increase in urinary calcium excretion was association with no further increase in hypercalcemia but with the lowest phosphate concentration which was

encountered in our studies. Calcium and phosphorus are so intimately related in body processes through their conspicuous compound, calcium phosphate, that it seems we are seldom justified in considering their functions and abnormalities separately.

FECAL CALCIUM EXCRETION

Bearing in mind that the rate of excretion of urinary constituents depends so largely on their concentration in the blood the excessive urinary calcium excretion of these patients might logically have been inferred. The influence of hypercalcemia on intestinal excretion would depend more on factors inherent in the functional activity of the intestinal epithelium and chemical reactions in the intestinal content. Greenwald and Gross (40) found an unmistakable increase in the fecal calcium excretion of dogs who were receiving parathyroid extract for several days. In other experiments (41) of about two months' duration the increase in fecal calcium was less marked. Hoag et al. (46) studied the influence of parathyroid extract on the calcium metabolism of seven infants, one normal, four rachitic and two with infantile tetany. Two rachitic infants showed a fairly definite increase in fecal calcium while receiving the extract; one with tetany, a definite decrease; while the others showed little or no variation from normal. Brehme and György (14) determined the effect of parathyroid extract on two infants. While the urinary excretion of calcium was markedly increased there was no change in the stool excretion. Stewart and Percival (75) during periods of a few hours found no increase in the rate of calcium excretion into the intestines of cats which had been given parathyroid extract. In calves receiving parathyroid extract, Robinson, Huffman and Burt (62) demonstrated a considerable increase in serum calcium but only a slight increase in urinary excretion and no decided change in fecal excretion. Shohl, Wakeman and Shorr (71) studied the calcium metabolism of two infants with tetany. Parathyroid extract did not alter the calcium excretion in the stools. After a very extensive investigation of the effect of parathyroid extract, on eight individuals, Albright, Bauer, Ropes and Aub (1) concluded that it had no influence on the fecal excretion of calcium. Hunter's case (49) of hyperparathyroidism had excessive amounts of calcium in the stools in addition to the increase in the urine.

The data showing the relative amounts of calcium excreted in the stools of three patients with hyperparathyroidism are summarized in table 2 together with the corresponding calcium intake and urinary output.

The fecal excretion in Cases 1 and 3 is quite impressive. Both patients on an intake which should have been adequate, excreted more calcium in the stools alone than they ingested. Case 1 for the first twenty days received in her diet an average of 0.56 gram of calcium daily. During this period she excreted by way of the intestinal tract an average of 1.04 gram daily. In the following period a daily oral intake of 0.91 gram of calcium resulted in the excretion of 1.94 gram in the stools. Thereafter on an excessive calcium intake the stool output did not exceed the intake. Case 3 gave a similar figure: for 16 days an average intake of 0.56 gram was accompanied by a stool output of 0.90 gram daily. The data are thus definite and leave no doubt that these two patients tended to have an excessive fecal calcium excretion. Case 2, however, presented quite a different picture. Clinically the case was typical of hyperparathyroidism with giant cell bone tumors, hypercalcemia, increased urinary calcium excretion and a tumor proved microscopically to be composed of parathyroid tissue. In no period of study was there any indication that the fecal excretion of calcium was excessive.

The possibility arises that some factor or factors other than hyperparathyroidism were operative in Cases 1 and 3 to produce increased excretion in the stools. One striking contrast existed between these patients and Case 2. They were bedridden and had been for months while Case 2 was up and about, moderately active and allowed to take daily walks in the vicinity of the hospital. It is not unlikely that the striking difference in activity of these patients may have had a most significant influence on their calcium metabolism. Bone must be looked upon as living tissue with an inherent capacity for adjustment to functional demands. We have no knowledge of the effects of inactivity on calcium and phosphorus metabolism but are well aware of the bone atrophy which may develop with disuse. Since it appears that most studies of calcium metabolism in disease have been made upon subjects who are quite inactive, this factor may have influenced the results. Further insight into the problem may suggest more ade-

quate means of preventing ununited fracture in old age. Maxwell and Miles (58), and Vaughan (77), and especially Hutchison and Stapleton (50) have presented clinical evidence from which we may conclude that diminished muscular activity must be looked upon as of considerable importance as a causative factor in the development of osteomalacia. It is also interesting to note that Degkwitz (29) appears to have been able to prevent rickets in young dogs grown in the dark by giving them vigorous daily exercise.

The reaction of stools of Cases 1 and 3 was determined by the method of Tisdall and Brown (76). The pH ranged from 5.8 to 7.1, corresponding to that of patients with other conditions.

PHOSPHORUS METABOLISM IN HYPERPARATHYROIDISM

While in the literature on bone diseases much prominence has been given to changes in calcium metabolism, we must bear in mind the fact that one could as consistently put the same emphasis on the behavior of phosphorus for these two elements are inseparably involved in bone structure. A rôle of considerable importance has been assigned to phosphorus in the extensive investigation of rickets where defects in phosphorus metabolism have even been thought to be primary. There seems to be no good reason for denying that many of our apparent abnormalities of calcium utilization may be primarily disturbances of phosphorus metabolism. We have at present no certain knowledge whether the parathyroid glands or vitamin "D" or ultra violet radiation are concerned primarily with the physical chemical reactions of calcium or of phosphorus. From their experiences with human subjects, Albright, Bauer, Ropes and Aub (1) felt that the primary effects of parathormone was on phosphorus rather than on calcium. Greenwald and Gross (39) have stressed the marked change in phosphorous excretion following parathyroidectomy and parathormone injections.

A study of our three patients, however, has not presented us with any typical abnormality of phosphorus metabolism in hyperparathyroidism. It so happened that three cases presented distinct differences. Case 1 for 24 days (Periods 1 to 6, table 9) on a low and average calcium intake showed a definitely negative phosphorus balance excreting each day 300 to 400 mgm. more than she ingested.

Following this on a high calcium intake, a slight amount of phosphorus was stored. Case 3 (table 11) with evident kidney insufficiency stored phosphorus while on a negative calcium balance. Case 2 (table 10) continually retained a slight amount of phosphorus; otherwise there was no evident abnormality of phosphorus metabolism. It seems almost paradoxical that he should, for such a long time, have retained phosphorus while continually losing calcium. McCrudden (54), and Miles and Feng (59) and others have noted a retention of phosphorus in

TABLE 3

Summary of the phosphorus metabolism of three patients with hyperparathyroidism. The data are selected from tables 9, 10, and 11 and are expressed in the daily averages in grams

	Period number	Serum		Phosphorus				Urine phosphorus / Stool phosphorus	Comment
		Calcium	Phosphorus	Intake	Output	Urine	Stool		
		mgm. per 100 cc.	*mgm. per 100 cc.*	*grams*	*grams*	*grams*	*grams*		
Low calcium intake:									
Case 1.....	1–5	16.4	1.5	0.90	1.39	1.311	0.076	17.1	Bed-ridden
Case 2.....	1–4	16.8	1.6	1.42	1.24	0.976	0.269	3.6	Moderate activity
Case 3.....	1–4	15.4	2.6	0.81	0.71	0.380	0.330	1.2	Bed-ridden. Kidney insufficiency
High calcium intake:									
Case 1.....	7	16.4	1.3	0.90	0.80	0.785	0.020	39.2	Bed-ridden
Case 2.....	5	14.9	1.9	1.46	1.08	0.826	0.260	3.2	Moderate activity
Case 3.....	9, 10	17.8	4.8	0.99	0.68	0.200	0.480	0.4	Bed-ridden. Kidney insufficiency

the presence of a negative calcium balance. In this connection it is interesting to note that McCrudden found little variation from normal in phosphorus in the ash of bones of osteomalacia although the calcium was definitely reduced.

When the metabolism of phosphorus in these patients is examined in greater detail and the distribution of the excretion of phosphorus between the stool and urine is noted, interesting contrasts are manifest. The characteristic differences are illustrated by the data selected in table 3. Here are recorded the daily average phosphorus balances of

the three patients together with the phosphorus excreted in the stool and in the urine on a low and on a high calcium intake. The phosphorus metabolism of Case 1 is notable for the minute amount in the stool and the great quantity in the urine. Even when the calcium ingested was excessively high there was no increase in phosphorus in the stool. In fact, these periods exhibited the lowest stool excretion we have encountered. The great urinary excretion was no doubt related to some extent to the acidity of the urine, but it is questionable whether this was the sole basis for the unusual distribution of phosphorus between stool and urine. Evidence against this as an adequate explanation is the fact that in later periods (Periods 15 to 19) under different circumstances the urinary excretion was less when the urine was even more acid. A phenomenon worthy of special emphasis was the association of only minute quantities of phosphorus with the excessive fecal calcium. It is commonly assumed that calcium phosphate is precipitated in the gastrointestinal tract and that an excess of one element will increase the elimination of the other. This reaction may at times be very important. Briggs (15) has recently demonstrated to what extent calcium may increase fecal phosphorus excretion and has suggested the application of this action to the treatment of nephritis with phosphorus retention. However, the very significant studies of Bergeim (7) showed a surprising independence between these two elements in their absorption from the intestines. The findings just noted in Case 1, serve to emphasize the importance of Bergeim's work. It seems of interest to refer here to a case of true osteomalacia which we have recently studied. The phosphorus metabolism stood in marked contrast to that of Case 1. A large fecal calcium excretion was associated with an increased amount of phosphorus in the stools and a remarkably small quantity of phosphorus in the urine.

The distribution of the phosphorus excretion in Case 2 may be considered normal. The deviation from the normal in Case 3 was the reverse of the first case. Presumably because of the kidney insufficiency the urinary excretion of phosphorus was diminished. A more detailed study of the urinary excretion in table 11 indicates a progressive lowering of the ability of the kidney to excrete phosphorus. The stools show a moderate increase in phosphorus associated with excessive calcium output. The increase of both calcium and phosphorus

in the stools presents a picture simulating osteomalacia. This, together with the fact that the patient lacked exercise and vitamin "D," barely suggests we were dealing with such a complication. It might be noted that in the literature where phosphorus metabolism has been determined in that heterogenous group of cases termed "*osteomalacia*" no constant changes were recorded; the calcium and phosphorus metabolism did not run parallel and in the majority of cases the phosphorus balance was positive.

In table 9 are recorded both the total and the inorganic phosphorus in the urine of Case 1. The discrepancy between the figures point to a large amount of organic phosphorus up to a time when orthophosphate was administered. Since this discrepancy was not observed in the other patients the inorganic phosphorus determinations were omitted from the tables. More recently determinations of organic phosphorus have been made by more accurate methods on a large number of patients with various diseases, including a fourth case of hyperparathyroidism (74). The amount of organic phosphorus in the urine was constantly quite small.

Experience in administering orthophosphate to patients with hyperparathyroidism was very instructive from a theoretical point of view and suggested important therapeutic possibilities. It seemed probable that if sufficient phosphate could be absorbed serum phosphate might be increased and serum calcium lowered. If this alteration could be accomplished it was predicted that the calcium metabolism might be restored to normal. In order to obtain maximal absorption of both elements, it seemed advisable to administer one at as remote a time as possible from the administration of the other and thus reduce to a minimum the precipitation of insoluble calcium orthophosphate. Therefore, 1 gram of sodium acid phosphate together with 3 grams sodium bicarbonate was given at 6:00 A.M., 10:30 A.M., 3:00 P.M., and double this amount at 10:00 P.M. while the calcium lactate was given three times each day with meals at 7:30 A.M., 11:30 A.M., and 5:00 P.M. The result of the procedure was quite striking. The data obtained from Case 1 is taken from table 9 and summarized in table 4. Period 8, preceding the first administration of phosphate, is recorded in the top row of figures for comparison. The results of this period were similar to the preceding periods but were complicated

by the fact that it followed a period of high calcium and during the period the patient received 8 grams of sodium bicarbonate daily. During Period 9, the patient received sodium acid phosphate four times each day in the manner described above. The following significant observations were made: (1) Almost all of the phosphate was absorbed for only a minute quantity appeared in the feces; (2) 70 per cent of the phosphorus ingested was excreted in the urine, and 27 per cent was retained in the body; (3) the serum phosphate rose to

TABLE 4

Data illustrating the influence of sodium orthophosphate per os on the abnormal calcium metabolism of hyperparathyroidism. The data are collected from table 9 and are expressed in daily averages in grams

Period number	Calcium				Phosphorus				Serum		Comment
	Intake	Output	Urine	Stool	Intake	Output	Urine	Stool	Calcium	Phosphorus	
	grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	
8	0.98	1.77	1.085	0.68	0.90	0.85	0.84	0.01	16.7	1.3	$NaHCO_3$, 8 grams daily
9	0.97	1.34	0.195	1.15	2.07	1.52	1.49	0.03	12.5	3.8	Phosphate as described in text
10	0.98	1.96	1.625	0.33	0.86	1.02	0.60	0.42	12.4	1.4	$NaHCO_3$, 8 grams daily
11	1.19	0.48	0.112	0.37	2.05	1.09	0.87	0.23	12.8	5.9	Phosphate as described in text
12	1.21	0.97	0.142	0.83	2.08	1.48	1.14	0.34			Phosphate as described in text
13	1.18	1.47	0.107	1.36	2.10	1.86	1.18	0.68	12.9	3.0	Phosphate as described in text

normal; (4) the serum calcium fell to a level within the range of normal variations; (5) the urinary calcium excretion for the first time fell to normal; (6) a large amount of calcium appeared in the stools associated with almost no phosphorus. Period 10 intervening before further administration of phosphate served to emphasize the marked alterations which were produced. Here, the patient received sodium bicarbonate as in Period 8 but no phosphate. Conditions tended to revert to their former state. The following facts were evident: (1) There

was a negative phosphorus balance; (2) the serum phosphate fell again to an exceedingly low level; (3) the calcium balance was markedly negative; (4) there was a remarkable increase in the urinary calcium excretion; (5) this amazing output of calcium in the urine was associated with no increase in serum calcium. Attention was called above to the fact that the level of the serum phosphate may have an important influence on the excretion of calcium by the kidneys. The associations here attest the fact. Without any alterations in the serum calcium and while practically normal, the calcium excretion increased remarkably as the serum phosphate fell from normal to a very low level. In the next periods, 11, 12, and 13, phosphate was resumed. Again the serum phosphate rose and the urinary calcium excretion was controlled. This was not attended by excessive calcium in the stools until Period 3. So for the first time it was possible not only to maintain the patient on calcium equilibrium but to see her store appreciable amounts.

These results should be emphasized because of their possible therapeutic application. There is a rather extensive early literature on the effects of phosphorus in bone disease, and in a number of instances records of metabolic studies (47). But these seem in no way comparable to the results recorded here for they involve the administration of small doses, such as one or two milligrams of yellow phosphorus. There appeared to be no definite influence on calcium metabolism.

An apparently significant fact should be noted here. For one month (Periods 14 to 20, table 9) while other studies were in progress, there was no further administration of phosphate. Periods 14, 15, and 16 were used as controls and conditions were similar to the early periods of study. It would appear that the former phosphate administration produced a lasting change for the urinary calcium excretion remained low. This was associated with a continually negative phosphorus balance from excessive phosphorus in the stool. During these seven periods more phosphorus was excreted than had been stored during phosphate administration. In four periods the patient had stored 9.42 grams of phosphorus while in these seven periods she lost 18.49 grams. The serum phosphate remained normal. These periods again suggested the possibility that the level of the serum phosphate might be an important factor influencing urinary calcium excretion.

Urinary calcium remained low even though the serum calcium gradually rose to its former high level. There was a continually negative calcium balance due to the excess of calcium in the stool.

Periods 21, 22, 23, and 24 are recorded in table 9 for the sake of completeness. Sodium phosphate was administered as before. But unfortunately through a misunderstanding and in the absence of the authors the type of sodium orthophosphate given was not recorded. It is certain that during part of the time, perhaps throughout these periods, she received disodium orthophosphate. The outstanding feature of this series is the extremely large amount of calcium excreted in the stools. This may have been related to excessive ingestion of alkali. In Period 25 where the phosphate had been stopped and sodium bicarbonate given, the fecal calcium excretion was amazing. However, one might refer back to Periods 8 and 10 where alkali seemed to have the opposite effect, or Periods 19 and 20, where no influence on fecal excretion was evident.

Other instructive data showing possible effects of orthophosphate were presented during the study of Case 3. For eight days (Periods 9 and 10, table 11) on an exceedingly high calcium intake she stored considerable calcium. During this time the serum calcium rose to 17.8 mgm. per 100 cc. and with this there was a striking change in her general condition. She became stuporous and irrational. She developed râles at her lung bases, distended cervical veins and dependent edema, signs which were interpreted as circulatory failure. These prominent changes were thought to be directly related to the high serum calcium. Prompt reduction seemed imperative. This was accomplished by neutral sodium orthophosphate by mouth and attended by marked improvement. A solution of monosodium and disodium phosphate was prepared, the two proportioned to give a pH 7.2.[1] It was administered as in Case 1. The transition to her former state was most impressive. Within 24 hours she was alert again, quite rational and appeared stronger. In 48 hours the serum calcium had fallen to 11.7 and the serum phosphate risen to 8.6 mgm.

[1] NaH_2PO_4 (Merck C. P.) 12.8 grams and $Na_2HPO_4 \cdot 12H_2O$ (Baker) 138.7 grams dissolved in 500 cc. of distilled water gives a solution with a pH 7.2 and containing 0.3 gram of phosphorus in each 10 cc.

per 100 cc. The condition presented by this patient appears to be the same as that frequently seen with animals when the serum calcium has risen to a high level after parathyroid extract administration. Edwards and Page (32) particularly noted the depression of shock-like character with dulling of sensory reactions which occurred in some of their dogs.

THE EFFECT OF IRRADIATED ERGOSTEROL

Numerous investigators have shown that antirachitic vitamin promptly increases the intestinal absorption of both calcium and

TABLE 5

Data showing the results obtained when irradiated ergosterol was administered in hyperparathyroidism. The data are selected from table 11 and are expressed in the daily averages in grams

Period number	Calcium				Phosphorus				Comment
	Intake	Output	Urine	Stool	Intake	Output	Urine	Stool	
	grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	
14	0.67	0.67	0.187	0.48	0.95	1.96	0.66	1.30	Control
15	0.67	1.16	0.250	0.91	0.97	2.48	0.64	1.84	Control
16	0.67	1.11	0.185	0.93	1.05	1.84	0.67	1.17	Control
17	0.67	0.73	0.082	0.65	0.87	1.31	0.71	0.60	Irradiated ergosterol
18	0.70	1.32	0.222	1.10	0.96	1.16	0.73	0.43	Irradiated ergosterol
19	0.69	0.97	0.142	0.83	0.88	1.00	0.66	0.34	$NaHCO_3$, 8 grams daily
20	0.69	0.99	0.140	0.85	0.89	1.54	0.59	0.95	$NaHCO_3$, 16 grams daily

phosphorus in experimental rickets and in infants with rickets. No such effect has been found in normal human adults. Wilder (79) reports improvement of his patient with hyperparathyroidism on a regimé which included a high vitamin "D" intake. Metabolic studies of his patient during this period showed a slight retention of calcium and a more marked retention of phosphorus. An attempt was made in these studies to determine the effect of irradiated ergosterol on the calcium and phosphorus metabolism of hyperparathyroidism. The results were rather indefinite but seem worthy of presentation. Relevant data obtained from Case 1 are summarized in table 5. The three 4-day control periods followed directly after periods of high phosphorus administration, otherwise they were similar to the first periods of the

series. Irradiated ergosterol was given for only eight days. During periods 17 and 18 she received 18 drops of Acterol (Mead-Johnson and Company), each day. In Period 17, there was a slight drop in the calcium excretion which may have been unrelated to the irradiated ergosterol. The decrease in the total phosphorus in the stools appears more significant. This was associated with a moderate increase in urinary phosphorus excretion. The sodium bicarbonate in the two following periods seemed to have little influence on the calcium and phosphorus excreted. The experiment indicated a definite increase in the absorption of phosphorus by the gastrointestinal tract which appeared to be related to the irradiated ergosterol. The experiments of Warkany (78) are noteworthy in considering this point. After administering irradiated ergosterol to rachitic infants disodium-phosphate by mouth caused a great increase in serum phosphorus within two hours whereas previously it had had practically no effect.

THE EFFECT OF REMOVING PARATHYROID TUMORS

The most impressive experiences encountered in these studies were the amazing events after the first patient reverted from hyperparathyroidism to extreme tetany following the removal of a parathyroid tumor. They emphasize the relationship of the phenomena to parathyroid activities. On August 2, 1929, (the third day of Period 26) a tumor about 2.5 cm. in diameter was excised from the region of the lower pole of the left thyroid. Microscopically this proved to be parathyroid tissue. The chemical changes which followed are summarized in table 6. On the third day after operation the patient noted a change in her general condition, although the complaints were rather indefinite. There was a feeling of weakness and a sensation of tingling about the face and in the hands. There were obscure cramp-like pains in the extremities. Chvostek's sign could be demonstrated repeatedly. By the fourth day the serum phosphate was 2.2 mgm. and the serum calcium had fallen to 11.3 mgm. per 100 cc. By the seventh day the above symptoms had become exaggerated and she had become very much distressed and apprehensive. She had been nauseated and this day vomited. There was at times definite hyperventilation causing slight dyspnea. The numbness and tingling of the face and hands was marked. Twitching about the face was evident. The pain in her

TABLE 6

Summarizing the changes in the blood and in the calcium and phosphorus metabolism of case 1 following the extirpation of a parathyroid tumor

Period number	Day	Parathormone*	Calcium lactate	Intravenous calcium chloride	Serum		Calcium, daily average				Phosphorus, daily average			
					Calcium	Phosphate	Intake	Output	Urine	Stool	Intake	Output	Urine	Stool
		units	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
1–5	Pre-operative				16.4	1.3	0.60	1.36	0.319	1.04	0.90	1.28	1.19	0.09
27	2nd post-operative				12.9	3.0								
	3rd post-operative													
	4th post-operative				11.3	2.2	0.35	0.56	0.182	0.38	0.50	0.33	0.03	0.29
	5th post-operative													
28	6th post-operative													
	7th post-operative				10.8	5.2	0.39	0.42	0.180	0.24	0.55	0.28	0.14	0.14
	8th post-operative													
	9th post-operative				7.4	11.3								
29	10th post-operative		6		7.5	10.2								
	11th post-operative		12											
	12th post-operative		10		7.5	3.0	1.26	1.26	0.005	1.26	0.18	0.42	0.18	0.24
	13th post-operative													
30	14th post-operative	25	6											
	15th post-operative	35	18		6.5	3.4	1.67	0.28	0.004	0.28	0.48	0.28	0.15	0.13
	16th post-operative	75	12		4.1	3.2								
	17th post-operative	50	18											

31	18th post-operative	200	18		5.0	3.0								
	19th post-operative	125	18		5.1	3.2	3.02	1.15	0.006	1.14	0.50	0.24	0.10	0.14
	20th post-operative	250	40		5.4									
	21st post-operative	100	22	1.7	5.5	3.7								
32	22nd post-operative	50	0	1.0										
	23rd post-operative	25	12	2.0	6.6	3.1	2.24	1.95	0.026	1.92	0.57	0.20	0.05	0.15
	24th post-operative	50	24	2.0	6.0	2.4								
	25th post-operative	50	24	2.0	6.8	2.3								
33	26th post-operative	50	25	2.0	7.8									
	27th post-operative	50	25	2.0	7.4	2.3	3.39	0.64	0.015	0.63	0.88	0.37	0.03	0.34
	28th post-operative	50	25	2.0										
	29th post-operative	50	25	2.0	7.4	1.7								
34	30th post-operative	50	41	2.0										
	31st post-operative	50	25	2.0	8.5		3.88	1.05	0.035	1.02	0.88	0.15	0.02	0.13
	32nd post-operative	50	25	2.0										
	33rd post-operative	50	25	2.0	8.7	2.5								
35	34th post-operative	50	25											
	35th post-operative	50	25	2.0	9.1	2.5	3.45	0.63	0.008	0.62	0.87	0.27	0.03	0.24
	36th post-operative	50	25											
	37th post-operative	50	25		9.7	2.3								

* Parathormone kindly furnished by Eli-Lilly and Company.

extremities continued. Chvostek's sign was present. Attempts to demonstrate Trousseau's sign caused marked tingling in the arms and forearms, but no definite contracture. The serum phosphate was 5.2 and calcium 10.8 mgm. per 100 cc. The patient had obvious tetany with normal serum calcium. The urine contained large quantities of ketone bodies and the serum CO_2 was 37 volumes per cent. This marked ketosis was unexpected. Although the food intake had been limited because of nausea, the ingested carbohydrate was quite enough to have prevented ketosis under ordinary conditions. Blood sugar determinations were normal.

On the ninth day the patient's distress appeared almost unbearable. The occasional attacks of vomiting continued. Trousseau's sign was no more definite than before. The patient described momentary attacks which indicated spasm of the larynx. She complained at times of inability to see. The eyelids drooped suggesting a paresis although they could be raised with voluntary effort. The serum phosphorus had risen to 11.3 and the calcium fallen to 7.4 mgm. The blood nonprotein nitrogen was 42 mgm. indicating the absence of any marked kidney insufficiency. The blood pressure was 132/80.

On the tenth day, at the beginning of Period 29 the patient started to receive calcium lactate by mouth in the amounts indicated in the table. After two days the only effect of calcium administration was a remarkable fall of serum phosphate to normal. This extreme alteration in serum phosphate had no influence whatever on the tetany which was becoming alarming. There was great pain in the muscles, which were not especially tense. The patient stated that the muscles had a sensation of worms crawling through them. No fibrillary twitchings could be seen. She now had a definite Trousseau's sign and occasional spontaneous contractures of muscles of the forearm were observed. There were also spasms of the extraocular muscles and short but definite attacks of laryngismus stridulus.

During the next four-day period (No. 30) the calcium lactate was increased and parathormone was given without any influence on the patient's condition. The serum calcium fell to 4.1. Vigorous forcing of the carbohydrate had cleared the ketosis. The following period was characterized by the fact that large amounts of calcium by mouth and parathormone administered subcutaneously and intravenously

did not alter the serum calcium. On the 18th day she received 40 grams of calcium lactate and 250 units of parathormone yet the next morning serum calcium was only 5.4 mgm. Tetany was not influenced until the 21st day when intravenous calcium chloride in relatively small doses was started. This caused prompt and dramatic alleviation of symptoms. On the morning of the 21st day after operation she was given 0.7 gram of calcium chloride intravenously and that evening 1.0 gram. The improvement was not noted immediately following the injections but occurred more gradually during the day. Twenty-four hours after the first injection she had received only 1.7 gram but was stronger, quite rational, and able to sit up in bed and eat breakfast without assistance. It is strange that with the marked improvement there was only a very slight increase in the serum calcium. For the next two weeks calcium chloride, two grams daily intravenously, was continued in addition to calcium lactate and parathormone. The serum calcium rose gradually to normal.

From this experience it was natural to conclude that the excessive quantity of calcium given by mouth was not absorbed, but examination of the data in table 6 shows that after parathormone was started large amounts of calcium were retained without its having any influence on the level of the serum calcium. During the eight days included in Periods 30 and 31, 13 grams of calcium were retained, while the tetany advanced in severity and a low serum calcium persisted. The regulation of serum calcium appears to be almost entirely independent of calcium absorption and to depend chiefly upon internal factors existing in the blood and other body fluids. The striking contrast between the effects of a little calcium chloride intravenously and a large quantity of calcium absorbed from the gastrointestinal tract is impressive but the reasons for this are quite obscure.

With the transformation which followed the resection of a parathyroid tumor there was a change in the urinary calcium excretion. For over a week it remained normal and then almost ceased. The change was so sudden as to suggest a kidney-threshold phenomenon. The calcium disappeared from the urine when the serum calcium had fallen to 7.5 mgm. per cent. Further studies, however, did not establish an absolute threshold, for later appreciable amounts of calcium were excreted by the kidneys in periods during which the serum cal-

cium was quite low. The remarkable fall in urinary calcium after operation was also observed by Mandl (56), Gold (37), Wilder (79), Hannon et al. (44), Boyd et al. (13), and Snapper (73).

Greenwald and Gross (39) noted in their experiments with dogs that the most striking change in metabolism after parathyroidectomy was a marked retention of phosphorus. This was not necessarily accompanied by any increase in serum phosphorus. They also found a decrease in the urinary phosphorus excretion. Changes in the phosphorus metabolism similar to Greenwald's were noted in Case 1 as she reverted to hypoparathyroidism following the removal of the parathyroid tumor. There was an immediate drop in the phosphorus excretion with the production of a positive balance. In comparison with the early periods of study (1 to 5) there was a slight increase in fecal excretion. The change to a positive balance was due to a decrease of phosphorus in the urine. This was at first associated with a remarkable increase in the serum phosphorus which reached the surprising figure of 11.3 mgm. per 100 cc. on the 9th day. It is noteworthy that there was an immediate fall in the serum phosphorus without modification of the urinary phosphorus when calcium was administered. The administration of parathormone at this time was not attended by any alteration in the phosphorus metabolism.

The study of the phosphorus and calcium metabolism of Case 1 was continued for over ten months following her operation. The interval was characterized by marked retention of both calcium and phosphorus. From the data we can summarize the calcium and phosphorus balance of the entire period as follows:

Total calcium intake	927.27
" " output	577.19
Calcium retained	350.08
Total phosphorus intake	311.67
" " output	131.76
Phosphorus retained	179.91

Calcium exists in bone chiefly as $Ca_3(PO_4)_2$ together with a small quantity as carbonate. If we calculate the amount of calcium which would combine with the 179 grams of phosphorus to form $Ca_3(PO_4)_2$ a

value of 348 grams is obtained to compare with the 350 grams of calcium actually stored.

For a year and a half following operation, Case 1 required an excessive calcium intake and parathormone to prevent tetany. The bones became rigid. The tumor of the maxilla receded. The teeth became tight. She gained considerable strength but the chronic urinary tract infection associated with bilateral nephrolithiasis continued in spite of treatment. A moderate retention of nitrogen gradually developed. Removal of the kidney stones seemed unjustifiable because of her poor general condition. She finally died fourteen months after the parathyroid tumor was removed, from uremia and the progressing urinary tract infection.

On June 18, 1929, at the beginning of Period 12 parathyroidectomy was performed on Case 2. A tumor about 3 cm. in diameter was removed under local anesthesia from the region of the left lower pole of the thyroid and behind the inner end of the clavicle. Microscopic examination proved this to be parathyroid though the section showed very little normal parathyroid tissue. The bulk of the tissue was made up of deeply stained cells with large nuclei with apparent attempts to form acinar arrangement. The day following operation the patient was able to be up and resume his usual activities. Twenty-four hours after operation the serum calcium had fallen to 10.6 mgm. per 100 cc. In 48 hours it had fallen to 9.7 mgm. with no change in the serum phosphorus. At this time, in response to questioning, he stated he had a little tingling about his face and fingers. Trousseau's or Chvostek's signs were not present. On the fifth day at a time when the serum calcium was 8.6 mgm. and phosphorus 3.7 the patient developed a slight diarrhea having four watery bowel movements during the morning accompanied by some adbominal cramps. There was nothing unusual in the diet that might account for this. The lowest serum calcium, 8.3 mgm. per 100 cc. was encountered on the 7th day; the serum phosphorus had increased to normal. There was no change whatever in his general body sensation. There was no evidence of any definite change in muscle tone. Chvostek's and Trousseau's signs had never been elicited. He had had some slight cramps in the calves of his legs at night but insisted this had been a common experience for years.

TABLE 7

Summary of the changes in the blood and in the calcium and phosphorus metabolism of Case 2 following extirpation of a parathyroid tumor

Period number	Day	Serum		Calcium. Daily average				Phosphorus. Daily average			
		Calcium	Phosphorus	Intake	Output	Urine	Stool	Intake	Output	Urine	Stool
		mgm. per 100 cc.	*mgm. per 100 cc.*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
5	Pre-operative	14.9	1.9	3.69	3.41	0.587	2.82	1.46	1.08	0.82	0.26
11	Pre-operative	14.0	2.4	0.99	1.17	0.501	0.67	1.51	1.46	1.18	0.28
12	1st post-operative										
	2nd post-operative	10.6	2.1								
	3rd post-operative	9.7	2.2	0.74	0.59	0.080	0.51	0.67	0.45	0.23	0.22
	4th post-operative	9.1	2.4								
13	5th post-operative										
	6th post-operative	8.6	3.7	0.87	0.79	0.044	0.75	1.36	0.93	0.55	0.38
	7th post-operative										
	8th post-operative	8.3	3.1								
14	9th post-operative										
	10th post-operative	8.8	3.1	0.97	0.73	0.019	0.71	1.59	0.97	0.60	0.37
	11th post-operative										
	12th post-operative										
15	13th post-operative										
	14th post-operative	9.2	2.1	0.64	0.60	0.019	0.58	1.53	1.18	0.83	0.35
	15th post-operative										
	16th post-operative										
16	17th post-operative										
	18th post-operative			3.61	2.85	0.010	2.84	1.51	0.91	0.39	0.52
	19th post-operative										
	20th post-operative										
	58th post-operative	10.5	2.9								
	172nd post-operative	10.9	4.5								

The changes in the phosphorus and calcium metabolism which were encountered in Case 2, after removing the parathyroid tumor are summarized in table 7. The most striking change was the marked drop in the urinary calcium excretion. There was an immediate decrease in the calcium output due entirely to a fall in the urinary excretion. There was no evidence of any decided alteration in the calcium excretion in the stools. In 7 periods of low calcium intake before operation the average fecal excretion was 0.70 gram daily, while in four similar periods after operation the fecal excretion averaged 0.64 gram daily. In the preoperative period, 5, and the postoperative period 16, the high calcium intake was similar. In the first instance the average fecal excretion was 2.82 grams; in the second 2.84 grams daily. After operation there was a slight decrease in phosphorus output due to a slight decline in the urinary excretion.

NITROGEN, CREATINE AND CREATININE METABOLISM

A great part of the earlier literature on the function of the parathyroid glands concerns their relation to various aspects of nitrogen metabolism. Investigators have reported, in parathyroid tetany, an increased excretion of total nitrogen, ammonia, purine bodies, creatine, creatinine and guanidine bases. There seems to be no doubt of the increased nitrogen excretion in parathyroid tetany but Greenwald (38) showed this did not appear until after convulsions had started. Salvesen (64) found normal nitrogen excretion in latent tetany. After parathyoid extract in dogs, Greenwald and Gross (40) discovered an increased nitrogen excretion. Wilder's patient with hyperparathyroidism (79) stored considerable nitrogen during a ten-day period while on a high vitamin diet. The total nitrogen of Case 1 was studied before and after extirpation of a parathyroid tumor. For one hundred days before operation, while in the hyperparathyroid state, she appeared to be on nitrogen equilibrium. During this period the total nitrogen intake was 722 grams, the output 668 grams. For 100 days following the operation the nitrogen intake was 675 grams, the output 411 grams. At the end of this period, however, she was approximately in equilibrium again. These studies, therefore, do not indicate that there is any marked abnormality of nitrogen metabolism in hyperparathyroidism.

The relation of the guanidine bases to the parathyroid glands has aroused considerable interest, which has been stimulated by the fact that guanidine esters may produce a condition simulating parathyroid tetany. The large amount of creatine in muscle, the muscle phenomena associated with tetany and the chemical similarity of creatinine and the guanidine esters naturally suggests a possible relation between creatine metabolism and the parathyroids or calcium. Greenwald (38) and Burns (18) found a decrease in creatinine excretion after parathyroidectomy and Greenwald (38) an increase in creatine excretion. Hammett (43) reports that addition of parathyroid tissue to muscle extract retards the formation of creatinine which normally occurs. Woodman (82) found that feeding parathyroid to rats caused an alteration in the ratio of creatine and creatinine excretion resulting in the elimination of more creatine and less creatinine. Berglund, Medes and Lohmann (8) found no change in the creatinine in myasthenia gravis after increasing the serum calcium by parathormone.

Case 2 with typical hyperparathyroidism, yet free from complications and in good physical conditions except for a moderate anemia, offered ideal conditions for the study of creatine metabolism in this disease. The urinary excretion of creatine and creatinine nitrogen was determined during the eight days preceding and the eight days following operation. In the hyperparathyroid state an average of 25 mgm. of creatine nitrogen and 410 mgm. of creatinine nitrogen was excreted daily. Following the extirpation of a parathyroid tumor there was an immediate slight increase in creatine and a definite decrease in creatinine elimination. For the first four days a daily average of 81 mgm. of creatine nitrogen and 83 mgm. of creatinine nitrogen were excreted. Thereafter the excretion was similar to the preoperative days; creatine nitrogen 29 mgm. and creatinine nitrogen 406 mgm. daily. Except for the few days after operation the creatinine excretion was quite normal, corresponding to Shaffer's normal creatine coefficient.

SERUM ELECTROLYTES IN HYPERPARATHYROIDISM

That the activity of the parathyroid glands regulate the level of two inorganic constituents of the plasma and may cause profound alteration in their concentration appears of considerable physiological

interest. As far as we are aware no phenomenon in animal economy is entirely comparable to this unless we consider the remote similarity to the hormone influence on acid and alkali secretion of the stomach, pancreas and intestines. We have, at present, no knowledge as to the mechanism of this action. The characteristic alteration consists of a reciprocal rise and fall of the phosphorus and calcium; with a high calcium, a low phosphorus is usually encountered, and vice-versa, with high phosphorus as in tetany, low calcium is found. This behavior is typical of the effect of the solubility product of electrolytes in saturated inorganic solution and appears especially significant since the body fluids are in contact with an extensive surface of the undissolved phase, calcium phosphate in bone. But one mysterious feature appears. The quantity of calcium and phosphates in blood serum is far greater than can exist in simple aqueous solution of their salts. The parathyroids appear to increase the amount of calcium which may exist in serum yet in such a manner that it still maintains its reciprocal relationship to phosphorus as though following the laws of simple inorganic solutions. The marked physiological effects, which result from changes in serum calcium hint that the hormone may actually influence the ionic concentration instead of undissociated compounds as suggested by Greenwald and Gross (40).

The fact that the parathyroid glands may cause such marked changes in the calcium and phosphorus of the blood serum urged a careful investigation of the state of the other inorganic constituents in patients with hyperparathyroidism.

Collip (23) found that in dogs which had received parathyroid extract, carbon dioxide of serum gradually increased with a consistent slight increase in pH. The whole blood chloride was diminished but as the erythrocytes contain considerably less chloride than plasma this may have been due to the great concentration of blood. In a parathyroidectomized dog there was no change in the chloride of the blood after parathormone. Cantarow (19) et al. studied the effect on the blood of patients with pulmonary tuberculosis after relatively small doses of parathyroid extract. They found no constant change in plasma CO_2 or chloride. Brehme and György (14) found no change in the CO_2 in normal or tetanic children after parathormone although the alteration of phosphorus and calcium was quite typical. In 23

TABLE 8

Serum electrolytes of cases with hyperparathyroidism

Date	Calcium	Phosphorus	Carbon dioxide	Chloride	Protein	Total determined acids	Total base	Undetermined acids	pH	Remarks
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	
Case 1										
	mgm. per 100 cc.	*mgm. per 100 cc.*	*volumes per cent*	*mgm. per 100 cc.*	*per cent*	*mM*	*mM*	*mM*		
May 24, 1928	16.4	1.3	50.4	402	8.09	150.7	164.8	14.1		$NaHCO_3$, 8 grams daily for the previous 4 days
May 28, 1928	12.5	3.8	48.2		7.67					$NaHCO_3$, 8 grams and NaH_2PO_4, 5 grams daily for previous 4 days
June 1, 1928	12.8	5.8	46.0	399	6.85	147.0	161.4	14.4		$NaHCO_3$, 8 grams daily for previous four days
June 13, 1928	13.8	3.1	36.9		7.17					
June 23, 1928*	14.6	3.0	37.3	380	7.42	137.5	158.0	20.5	7.35	Blood lactic acid 18.9 mgm. per cent
July 3, 1928*	16.6	3.6	44.2	380	6.55				7.41	Irradiated ergosterol for the previous 8 days
August 4, 1928*	12.9	3.0	41.3	358	6.34				7.37	2 days after extirpation of parathyroid tumor
August 11, 1928	7.4	11.3	35.3	382	6.67	140.9	160.3	19.4		9 days after extirpation of parathyroid tumor. Marked ketosis
September 6, 1928	9.1	2.5	51.3	413	4.91	142.7	158.3	15.5		35 days after extirpation of parathyroid tumor. No ketosis
November 5, 1928	8.2	2.6		413						
December 2, 1928	6.8		28.3	452						NH_4Cl 4.5 grams daily for 16 days
December 25, 1928	6.1	4.2		408						No NH_4Cl for 10 days

Case 2										
June 18, 1929.....	14.0	2.4	56.4	410	6.04	150.2	161.0	10.8		The day preceding operation
July 1, 1929.....	9.2	3.1	48.5	420	5.98	151.2	160.6	9.4		13 days after extirpation of parathyroid tumor
Case 3										
November 17, 1928.....	14.6	5.6	45.1	337	4.46	125.5	162.5	37.0		After low calcium diet
December 18, 1928.....	17.0	4.8	52.8	324	4.05	123.5	162.0	39.1		After high calcium intake for 8 days

* During the absence of the authors, Dr. Alexis F. Hartmann of the Department of Pediatrics kindly made the determinations on June 23, July 3 and August 4, 1929.

patients with various diseases Csepai and St. Weiss (25) found no constant change in serum pH as the result of parathormone. Wilson and Riegel (81) studied the effect of parathormone on certain blood electrolytes in dogs. In the serum they observed a fall in the chloride and sodium and a delayed rise in potassium, while in the corpuscles, a decrease in the sodium and an increase in the potassium. There was little change in the water of the corpuscles or serum.

The total electrolyte equilibrium of the serum of three patients with hyperparathyroidism was studied in detail. The methods were exactly the same as those described in a previous publication (17). The results are recorded in table 8. The total determined acids in Column 6 show the sum of the bicarbonate, chloride, phosphate and protein, expressed in millimols of base combining capacity. The difference between the determined acids and the total base has been placed in Column 8, as undetermined acids, and includes the organic acid fraction and the normally small amount of sulfate.

As serum is practically neutral the total acids equal the total base and since there are no significant organic bases total base determinations may be used as a measure of that part of the total osmotic pressure which is due to the electrolytes. Gamble, Ross and Tisdall (35) and Peters, Bulger, Eisenman, and Lee (61) have emphasized the fact that the total base of serum is maintained at a remarkably constant level. They demonstrated how bicarbonate, chloride and protein may fluctuate to a greater extent yet reciprocate in their changes in such a manner as to keep the total acid relatively constant. The determinations of the total base on these patients will serve to emphasize further its remarkable stationary value. In the three patients it was continually quite normal and hardly varied outside the limits of experimental error even after considerable base had been administered in Case 1 and under conditions which had altered the serum anions. Case 1 reverted to severe tetany after removal of a parathyroid tumor and developed a ketosis without any change in the total base. Following extirpation of the parathyroid tumor in Case 2 there was no change in the total base concomitant with the striking decrease in serum calcium. There was no indication in the examinations of the other serum electrolytes of any abnormality characteristic of hyperparathyroidism except the shift in phosphate and calcium. It is

curious, however, that in both Case 1 and Case 2 the chloride concentration was definitely higher than that generally encountered in normal individuals. This was associated with relatively low bicarbonate in both patients; especially low in Case 1. In other words these patients had a mild chloride acidosis. But in neither case was this state altered by removing the hyperparathyroid condition.

The undetermined acid fraction in Case 2 was normal. The slight elevation of this fraction in Case 1 on August 11th, nine days after operation, was probably due to the organic acids resulting from the ketosis which developed on a low carbohydrate intake. No explanation can be offered for the slight increase on June 23rd. The two determinations of the serum electrolytes of Case 3 after a low calcium intake and after a high calcium intake both presented the same definite abnormality. The total electrolyte level as indicated by the total base was the same in both instances and normal. The undetermined acids were markedly increased while the other anions were low. This increase in undetermined acids was undoubtedly related to the associated kidney insufficiency and most likely represents a considerable retention of sulphate.

There appears to be no characteristic change in serum protein concentration associated with hyperparathyroidism. The first estimation of protein in Case 1 was definitely elevated. Thereafter the concentration tended to fall until the last determination almost four months later when it was quite low. The serum protein of the second case was moderately reduced. These downward deviations were possibly a result of chronic malnutrition. In neither case was the transition from hyperparathyroidism to hypoparathyroidism accompanied by any evident change in the concentration of serum protein. The very low protein of Case 3 was associated with extreme undernutrition.

In these studies we find, therefore, no evidence of any definite change in serum electrolytes which can be related to the increased activity of the parathyroid gland, except the alteration in phosphorus and calcium.

DISCUSSION

In 1923 Morton (60) suggested that in generalized osteitis fibrosa there might be an abnormality of calcium metabolism comparable to the abnormal carbohydrate metabolism of diabetes mellitus. He sug-

TABLE 9

*Calcium and phosphorus metabolism of Case 1. Four-day periods**

4-day periods	Period	Calcium				Phosphorus				Urine inorganic phosphorus	Urine titratable acidity	Serum	
		Intake	Output	Urine	Stool	Intake	Output	Urine	Stool			Phosphate	Calcium
		grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*cc. N acid per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
April 19 to 22	1	2.12	3.57	1.15	2.42	3.60	5.19	4.72	0.47	1.24			
April 23 to 26	2	2.13	4.01	1.21	2.80	3.60	4.38	4.04	0.34	1.27			
April 27 to 30	3	2.13	5.52	1.27	4.25	3.60	4.94	4.58	0.36	1.87			
May 4 to 7	4	2.35	5.47	0.97	4.50	3.60	6.03	5.79	0.24	2.53	4.32		
May 8 to 11	5	2.44	8.60	1.79	6.81	3.60	5.07	4.70	0.37	1.75	5.12		16.4
May 12 to 15	6	3.65	10.88	3.12	7.76	3.60	4.81	4.70	0.115	1.66	1.60		16.5
May 16 to 19	7	8.85	15.63	9.29	6.34	3.60	3.22	3.14	0.081	1.35	14.09	1.31	16.4
May 20 to 23	8	3.92	7.08	4.34	2.74	3.60	3.39	3.38	0.013	1.66	13.80		16.4
May 24 to 27	9	3.87	5.38	0.78	4.60	8.28	6.08	5.96	0.124	2.97	7.45	3.82	12.5
May 28 to 31	10	3.94	7.84	6.50	1.34	3.46	4.07	2.41	1.66	2.41	10.09	1.45	12.4
June 1 to 4	11	4.77	1.94	0.45	1.49	8.23	4.35	3.48	0.87	3.49	5.90	5.95	12.8
June 5 to 8	12	4.84	3.899	0.57	3.33	8.34	5.94	4.57	1.37	3.62	5.91		
June 9 to 12	13	4.74	5.89	0.43	5.46	8.39	7.45	4.71	2.74	4.18	8.18	3.0	13.8
June 13 to 16	14	2.69	2.69	0.75	1.94	3.82	7.84	2.64	5.20	2.15	4.77		
June 17 to 20	15	2.71	4.66	1.00	3.66	3.89	9.51	2.55	6.96	2.34	13.59	2.78	15.0
June 21 to 24	16	2.71	4.45	0.74	3.71	4.21	7.34	2.67	4.67	2.38	16.82	3.0	14.6
June 25 to 28	17	2.71	2.94	0.33	2.61	3.47	5.27	2.85	2.42	2.14	21.59		
June 29 to July 2	18	2.81	5.28	0.89	4.39	3.83	4.64	2.91	1.73	2.13	25.22	2.50	13.6
July 3 to 6	19	2.77	3.89	0.57	3.32	3.52	4.01	2.65	1.36	2.01	17.73	3.6	16.6
July 7 to 10	20	2.77	3.97	0.56	3.41	3.55	6.17	2.36	3.81	1.89	8.05	1.75	16.6
July 11 to 14	21	4.76	6.20	0.14	6.06	8.54	7.43	3.95	3.48	3.04	2.31		
July 15 to 18	22	4.82	10.40	0.16	10.24	8.40	7.38	4.08	3.30	3.89	5.38		

July 19 to 22	23	4.83	7.18	0.48	6.70	9.59	9.64	4.24	5.40	3.85	4.30		
July 23 to 26	24	4.83	11.50	1.00	10.50	9.57	10.90	4.37	6.53	4.17	9.68		
July 27 to 30	25	4.78	17.79	0.41	17.56	4.89	6.82	3.61	3.21	2.41	7.79		
July 31 to August 3	26	1.54	2.99	0.85	2.14	1.99	1.94	1.19	0.75	1.09	Alkaline	3.0	12.9
August 4 to 7	27	1.41	2.25	0.73	1.52	2.07	1.30	0.13	1.17	0.09	Alkaline	2.2	11.3
August 8 to 11	28	1.58	1.67	0.72	0.95	2.20	1.02	0.55	0.57	0.42	Alkaline	11.3	7.5
August 12 to 15	29	5.04	5.05	0.021	5.03	0.72	1.69	0.71	0.98	0.65	Neutral	3.0	7.5
August 16 to 19	30	6.70	1.13	0.018	1.11	1.93	1.11	0.59	0.52	0.52	Neutral	3.2	4.1
August 20 to 23	31	12.10	4.59	0.025	4.57	2.02	0.97	0.39	0.58	0.30	Neutral	3.0	5.0
August 24 to 27	32	8.95	7.78	0.105	7.67	2.27	1.78	0.190	0.59	0.105	Neutral	3.1	6.6
August 28 to 31	33	13.55	2.58	0.062	2.52	3.52	1.50	0.120	1.37	0.095	Neutral	2.3	7.8
September 1 to 4	34	15.52	4.23	0.139	4.09	3.51	0.61	0.090	0.52	0.082	Neutral	2.5	8.7
September 5 to 8	35	13.82	2.52	0.033	2.49	3.48	1.06	0.109	0.95	0.109	Alkaline	2.3	9.7
September 9 to 12	36	13.45	3.38	0.095	3.28	3.09	0.87	0.084	0.78	0.076	Alkaline	3.0	9.0
September 13 to 16	37	13.69	3.36	0.058	3.30	3.27	0.21	0.090	0.12	0.069	Alkaline	3.3	9.9

* The studies were continued during the following nine months and will be reported in detail in a paper on *hypo*parathyroidism

TABLE 10

Calcium and phosphorus metabolism of Case 2. Four-day periods

4-day periods (1929)	Period	Calcium				Phosphorus				Serum phosphate	Serum calcium
		Intake	Output	Urine	Stool	Intake	Output	Urine	Stool		
		grams	grams	grams	grams	grams	grams	grams	grams	mgm. per 100 cc.	mgm. per 100 cc.
May 5 to 8.....	1	3.04	4.25	1.474	2.78	6.00	4.47	3.22	1.25	1.6	16.8
May 9 to 12.....	2	3.25	2.75	1.063	1.69	5.02	4.19	3.28	0.91		
May 13 to 16.....	3	4.18	5.19	2.220	2.97	6.23	5.85	4.78	1.07	1.8	15.2
May 17 to 20.....	4	3.79	5.13	2.162	2.97	5.52	5.39	4.32	1.07		
May 21 to 24.....	5	14.77	13.61	2.348	11.26	5.85	4.34	3.30	1.04		
May 25 to 28.....	6	15.34	19.69*	2.421	15.43*	5.84	10.45*	3.86	2.396*	1.9	14.9
May 29 to June 1..	7	3.30		1.835		4.83		4.19		2.1	14.0
June 2 to 5.....	8	3.68		1.978	Lost	5.36		4.69	Lost		
June 6 to 9.....	9	3.92	5.01	1.509	3.51	5.81	5.62	4.14	1.48		
June 10 to 13.....	10	4.00	4.97	1.900	3.07	6.11	5.35	3.71	1.64	2.6	14.1
June 14 to 17.....	11	3.96	4.69	2.004	2.69	6.04	5.84	4.71	1.13	2.4	14.0
June 18 to 21.....	12	2.98	2.39	0.320	2.07	2.69	1.82	0.92	0.90	2.1	9.7
June 22 to 25.....	13	3.58	3.19	0.176	3.02	5.44	3.75	2.21	1.54	2.4	9.1
June 26 to 29.....	14	3.89	2.91	0.075	2.84	6.36	3.92	2.42	1.50	3.1	8.3
June 30 to July 3..	15	2.58	2.41	0.078	2.33	6.13	4.70	3.31	1.39	2.1	9.2
July 4 to 7.....	16	14.46	11.40	0.041	11.36	6.06	3.67	1.59	2.08		

* The stool specimen in this instance was collected during two periods: 6 and 7, from May 25th to June 1st.

TABLE 11

Calcium and phosphorus metabolism of Case 3. Four-day periods

4-day periods	Period	Calcium				Phosphorus				Serum phosphate	Serum calcium
		Intake	Output	Urine	Stool	Intake	Output	Urine	Stool		
		grams	grams	grams	grams	grams	grams	grams	grams	mgm. per 100 cc.	mgm. per 100 cc.
November 9 to 12.....	1	2.17	4.34	1.107	3.23	3.82	2.76	1.63	1.13	2.6	15.4
November 13 to 16.....	2	2.57	7.00	1.101	5.90	3.57	3.36	1.68	1.68	3.57	14.6
November 17 to 20.....	3	1.72	4.35	1.011	3.34	2.62	2.82	1.35	1.47	5.6	14.6
November 21 to 24.....	4	2.53	2.71	0.724	1.98	2.94	2.44	1.47	0.97		
November 25 to 28.....	5	5.25	4.13	0.753	3.38	3.51	2.84	1.56	1.28		
November 29 to December 2.....	6	5.14	3.42	0.561	2.85	2.95	2.28	1.27	1.01		
December 3 to 6.....	7	5.19	1.55	0.183	1.37	3.44	1.83	0.93	0.90	5.26	15.7
December 7 to 10.....	8	5.40	5.45	0.808	4.65	3.68	3.02	1.05	1.97		
December 11 to 14.....	9	14.26	10.83	0.760	10.07	3.84	3.05	0.68	2.37		
December 15 to 18.....	10	14.38	6.35	1.051	5.30	4.10	2.33	0.89	1.44	5.3	17.8
December 19 to 22.....	11	4.10	2.57	1.598	0.98	7.48	5.41	1.07	4.34	8.6	11.7

gested that the calcium in the blood might be higher than normal and might occasion a loss of calcium through the kidneys. The accuracy of his analogy is well borne out by the studies of hyperparathyroidism. The general character of the abnormal metabolism of both diseases is similar. In diabetes a *deficient* production of an internal secretion results in an elevation of the blood sugar. In hyperparathyroidism an *increased* production of an internal secretion causes a rise of the serum calcium. In both conditions the alteration gives rise to certain general disturbances in the body and effects a loss of the involved substance through the kidneys.

Many of the clinical manifestations of hyperparathyroidism appear to be directly or indirectly related to hypercalcemia. From our knowledge of the influence of calcium on muscle physiology, symptoms referable to the muscular system could have been predicted. Muscle weakness, sometimes extreme, appears as a prominent feature. A decrease in muscle irritability was evidenced by three patients presented here who had absent or diminished response to faradic stimulation. It appears from numerous studies in the literature that an *increase* in the calcium concentration causes an *increase* in the tone of smooth muscle and of the heart (63) (16). The hypercalcemia of parathyroid extract appears to cause similar changes (32) (48). The cases of hyperparathyroidism reported by Gold (37) and by Boyd, Milgram and Stearns (13) had definite gastrointestinal symptoms which conceivably were due to the influence of high calcium on smooth muscle. Apparent circulatory failure developed in Case 3 as the serum calcium became very high after excessive calcium administration. It would seem that sudden cardiac episodes might be expected in hyperparathyroidism. Such an occurrence is suggested in the case of osteitis fibrosa reported by Dawson and Struthers (28) who succumbed four hours after unexpected and mysterious collapse. Two cases observed here became stuporous and irrational with exceedingly high serum calcium. The metastatic calcification is probably related to the hypercalcemia but we have as yet little knowledge concerning the mechanism of its production and its relationship to clinical features of the disease. As noted above it is most often found in the lungs, gastric mucosa and the kidneys, in tissues where acid is excreted. Cases in the literature with evidence of hyperparathyroidism have

shown a high incidence of urinary tract disease. Nephrolithiasis with secondary pyelitis and cystitis has been common. The possible relationship of this phenomenon to the excessive urinary calcium excretion is obvious.

These studies have indicated that the metabolism of calcium and phosphorus in bone disease should be examined more critically. So often only the total calcium and phosphorus balance has been emphasized. Such factors as distribution of calcium and phosphorus between the urine and the feces appear to show at times certain characteristics, an emphasis of which may present important differential diagnostic features and therapeutic indications. In the literature there is great confusion even as to the terminology of bone diseases. One notes the tendency to use the term osteomalacia in connection with almost any generalized disease of the skeleton occurring in adult life. Even though etymologically the term could be used in a general sense, it seems desirable to limit it quite strictly. There seems to be ample evidence that there is a specific type of disease with a distinct pathological physiology for which this name should be reserved. Maxwell (57) points out that it must be differentiated from hyperparathyroidism. The calcium and phosphorus metabolism in the two diseases present striking contrasts. The study of Miles and Feng (59) has shown most completely the abnormalities encountered in osteomalacia. It demonstrates the low serum calcium, the diminished calcium output in the urine and the excessive excretion of both calcium and phosphorus in the stools. Earlier but less complete studies have shown similar changes. A case of non-puerperal osteomalacia investigated in this clinic has shown abnormalities identical with those presented by Miles and Feng.

It is apparent that the metabolic changes in hyperparathyroidism are quite unlike those of osteomalacia. Early in this report the chemical studies of Mandl (56), Gold (37), Hannon et al (44), Wilder (79), Boyd et al. (13) and Hunter (49) were briefly reviewed. They showed abnormalities which paralleled the changes recorded here, the most characteristic features being the hypercalcemia and hypercalcinuria. Similar changes were found by certain earlier investigators who, however, did not determine serum calcium or examine the parathyroids. Again there is difficulty in the confused nomenclature of

these conditions to decide which of their cases should be included as hyperparathyroidism. The clinical features of some were so similar that there seems little doubt that they should be included in the group under discussion. One notes especially the case reported by McCrudden and Fales (55) as non-puerperal osteomalacia. This patient had multiple bone tumors, decalcification of the bones, difficulty in walking, gastrointestinal symptoms and kidney stones; a picture similar to Case 1 in this present report. Jacoby and Schrott (51) studied a typical case of osteitis fibrosa with the same characteristic changes in calcium metabolism. The case reported by Freund and Lockwood (34) as osteomalacia had less marked clinical characteristics but excessive urinary calcium excretion.

There are other studies showing alterations of the same character in multiple myeloma. Hypercalcemia in multiple myeloma has been reported by Charlton (20), Durman (31), Smith (72) and Soper and Stroud (74). Seegelken's (67) investigation of a case of multiple myeloma showed values for the calcium metabolism which were normal. Blatherwick (10) reports a case with a negative calcium balance and an increased output of calcium in the urine. Williams (80) and Currie (26) both record cases showing excessive urinary calcium excretion. The question arises whether these manifestations are the result of hyperparathyroidism or simply an incident to a disease causing in itself a rapid destruction of bone. From our knowledge of serum calcium regulation it seems unlikely that anything can cause such a constant high level of serum calcium except an increased activity of the parathyroid gland. It is difficult to cause more than slight changes in the serum calcium by giving large quantities of calcium by mouth. After intravenous administration the serum calcium promptly returns to normal. With the evidence at hand, it seems more logical to assume that hypercalcemia and hypercalcinuria arising in multiple myeloma indicates that hyperparathyroidism has developed as a complication.

Suggesting this possibility that hyperparathyroidism may arise in generalized bone disease, it is well to point out that a diversity of experiments have shown the parathyroid to possess a remarkable power to develop hyperplasia. Significant appears the case reported by Klemperer (52) with metastatic bone carcinoma and a parathyroid

tumor, as well as the numerous cases of chronic nephritis with hyperplasia or tumor of the parathyroid gland.

While obvious treatment of hyperparathyroidism is the surgical removal of excessive parathyroid tissue, the therapeutic application of orthophosphate administration was suggested in a former section of this report. Caution should be employed in applying this procedure. One must be aware of the fact that phosphate may increase the intestinal excretion of calcium and thus exaggerate the negative calcium balance. There also appears the theoretical possibility of increasing the metastatic calcification. Orthophosphate administration may at least be reserved for treating alarming conditions which may arise with extreme hypercalcemia.

SUMMARY

A study of three cases of hyperparathyroidism, two with osteitis fibrosa cystica and the other with multiple myeloma, has presented certain abnormalities of calcium and phosphorus metabolism. Most characteristic of these were a high serum calcium, possibly accounting for many of the clinical features, and an excessive excretion of calcium by the kidneys, apparently explaining the urinary tract complications. The increase of calcium in the urine was sufficient to cause a negative calcium balance, although two patients showed, in addition, an excessive output in the stools. Low serum phosphorus was repeatedly found except in one patient with marked kidney insufficiency. Altered phosphorus metabolism was encountered but no specific abnormality presented. There was no indication that the total nitrogen metabolism or creatinine metabolism is abnormal in hyperparathyroidism. Although there were marked changes in calcium and phosphorus other serum electrolytes were normal.

By the administration of orthophosphate it was possible to cause an increase in the serum phosphate, a decrease in serum calcium, a reduction of the calcium in the urine to normal and establish a positive calcium balance. It appears, however, that a continuation of this procedure resulted in an excessive output of calcium in the stools.

Following parathyroidectomy in two patients the disturbances of calcium and phosphorus metabolism were reversed. The calcium almost disappeared from the urine and large amounts of calcium and

phosphorus were retained in the proportion in which they occur in the bone. One patient reverted to tetany which was almost fatal. It was controlled with difficulty by the administration of large amounts of parathormone and calcium.

The metabolism of hyperparathyroidism differs almost completely from that of osteomalacia. In the literature, however, great confusion exists in nomenclature. Cases have been called osteomalacia which probably were examples of hyperparathyroidism. This state is perhaps most often seen with von Recklinghausen's disease of bones, but accompanies hyperplasia of the parathyroid from a variety of causes which include multiple myeloma, extensive carcinoma of bone and possibly other destructive bone processes.

These studies indicate that improvement in the clinical state of hyperparathyroidism may be accomplished by the administration of orthophosphate. The possible dangers of such a procedure have been made evident. It would appear that the only effective method of treatment is the removal of parathyroid tissue.

BIBLIOGRAPHY

1. Albright, F., Bauer, W., Ropes, Marion, and Aub, J. S., J. Clin Invest., 1929, vii, 139. Studies of Calcium and Phosphorus Metabolism. IV. The Effects of the Parathyroid Hormone.
2. Barr, D. P., and Bulger, H. A., Am. J. Med. Sci., 1930, clxxix, 449. The Clinical Syndrome of Hyperparathyroidism.
3. Bauer, W., Aub., J. C., and Albright, F., J. Exp. Med., 1929, xlix, 145. Studies of Calcium and Phosphorus Metabolism. V. A Study of the Bone Trabeculae as a Readily Available Reserve Supply of Calcium.
4. Beck, Alfred, Arch. f. klin. Chir., 1928, clii, 123. Discussion before the Deutsch. Gesellsch. f. Chirurgie.
5. Belden, W. W., Radiology, 1928, xi, 281. Bone Diseases.
6. Benedict, S. R., and Theis, R. C., J. Biol. Chem., 1924, lxi, 63. A Modification of the Molybdic Method for the Determination of Inorganic Phosphorus in Serum.
7. Bergeim. Olaf, J. Biol. Chem., 1926, lxx, 47. Intestinal Chemistry. VII. The Absorption of Calcium and Phosphorus in the Small and Large Intestines.
8. Berglund, Hilding, Medes, Grace, and Lohmann, Anne., Proc. Soc. Exp. Biol. and Med., 1927, xxv, 204. The Effect of Hypercalcemia on the Creatin Output in Myasthenia Gravis.
9. Berman, Louis, Am. J. Physiol., 1926, lxxv, 358. The Effect of a Protein-free Acid-alcohol Extract of the Parathyroid Glands upon the Calcium Content

of the Blood and the Electrical Irritability of the Nerves of Parathyroidectomized and Normal Animals.

10. Blatherwick, N. R., Am. J. Med. Sci., 1916, cli, 432. Calcium and Bence-Jones Protein Excretion in Multiple Myeloma.
11. Bogert, L. J., and Kirkpatrick, E. E., J. Biol. Chem., 1922, liv, 375. Studies in Inorganic Metabolism. The Effects of Acid-forming and Base-forming Diets upon Calcium Metabolism.
12. Boyd, Gladys L., Courtney, Angelia M. and MacLachlan, Ida F., Am. J. Dis. Child., 1926, xxxii, 29. The Metabolism of Salts in Nephritis. I. Calcium and Phosphorus.
13. Boyd, J. D., Milgram, J. E., and Stearns, Genevieve, J. Am. Med. Assoc., 1929, xciii, 684. Clinical Hyperparathyroidism.
14. Brehme, Th. and György, P., Jahrbuck f. Kinderheilkunde, 1927, cxviii, 143. Stoffwechselwirkung und Klinische Verwendbarkeit des Epithelkörperchenhormons (Collip).
15. Briggs, A. P., Arch. Int. Med. 1926, xxxvii, 440. Some Metabolic Aspects of Calcium Therapy.
16. Brull, Lucien, Arch. Intern. de Med. Exp., 1924, i, 613. Recherches Expérimentales sur les Action Cardiovasculaire et Diurétique des Sels Calciques.
17. Bulger, H. A., Allen Duff, and Harrison, Lee B., J. Clin. Invest., 1928, v, 561. Studies of the Chemical Mechanism of Hydrochloric Acid Secretion. II. Observations on the Blood Passing through the Stomach of Dogs.
18. Burns, D., Quart. J. Exp. Physiol., 1916, x, 361. A Comparison of the Influence on the Protein Metabolism of Parathyroidectomy and of the Administration of Guanidin.
19. Cantarow, A., Caven, W. R., and Gordon, B., Arch. Int. Med., 1926, xxxviii, 502. Changes in the Chemical and Physical Characteristics of the Blood Following the Administration of Parathyroid Hormone.
20. Charlton, Thomas J., Arch. Int. Med., 1927, xl, 98. Multiple Myeloma with Report of a Case.
21. Chvostek. F., Wien. klin. Wchnschr., 1908, xxi, 37. Myasthenia Gravis und Epithelkörper.
22. Clark, E. P. and Collip, J. B., J. Biol. Chem., 1925, lxiii, 461. A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification.
23. Collip, J. B., Medicine, 1926, v, 1. The Parathyroid Glands.
24. Corley, R. C. and Denis, W. J. Biol. Chem., 1925, lxvi, 601. The Determination of Calcium in Tissues, Feces, and Milk.
25. Csepai, K. and St. Weiss, Ztschr. f. d. ges. exp. Med., 1928, lx, 133. Über die Wirkung des Parathormones auf die Aktuelle Reaktion des Blutes.
26. Currie, R. A., Glasgow Med. J., 1927, cvii, 31. Case of Bence-Jones Proteinuria, with a Note on the Urinary Excretion of the Mineral Elements.

27. Davies-Colley, Brit. Med. J., 1884, i, 667. Juvenile Osteomalacia.
28. Dawson, J. W. and Struthers, J. W., Edinburgh Med. J., 1923, xxx, 421. Generalized Osteitis Fibrosa.
29. Degkwitz, R., Ztschr. f. Kinderheilk, 1924, xxxvii, 27. Über Einflüsse der Ernährung und der Umwelt auf Wachsende Tiere.
30. Duken, J., Ztschr. f. Kinderh., 1928, xlvi, 114. Beitrag zur Kenntnis der Malacischen Erkrankungen des Kindlichen Skelettsystems. Spätrachitis und Osteodystrophia Fibrosa.
31. Durman, D. C., Ann. Surg., 1928, lxxxviii, 975. Myeloma of the Spine.
32. Edwards, D. F. and Page, I. H., Am. J. Physiol., 1926, lxxviii, 235. The Effects of Parathyroid Extract on the Heart and Circulation.
33. Fiske, C. and Subbarow, Y., J. Biol. Chem., 1925, lxvi, 375. The Colorimetric Determination of Phosphorus.
34. Freund, H. A. and Lockwood, B. C., Ann. Med., 1920, i, 67. Osteomalacia. A Study of the Effects of Certain Organ Extracts and Oophorectomy on the Metabolism of Calcium and Magnesium.
35. Gamble, J. L., Ross, G. S. and Tisdall, F. F., J. Biol. Chem., 1923, lvii, 633. The Metabolism of Fixed Base during Fasting.
36. Givens, M. H., J. Biol. Chem., 1918, xxxiv, 119. Studies in Calcium and Magnesium Metabolism. IV. Experiments on Man.
37. Gold, Ernst, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1928, xli, 63. Ueber die Bedeutung der Epithelkörpervergrösserung der Ostitis Fibrosa Generalisata Recklinghausen.
38. Greenwald, I., Am. J. Physiol., 1911, xxviii, 103. The Effect of Parathyroidectomy upon Metabolism.
39. Greenwald, I. and Gross, J., J. Biol. Chem., 1925, lxvi, 185. The Effect of Thyroparathyroidectomy in Dogs upon the Excretion of Calcium, Phosphorus, and Magnesium.
40. Greenwald, I. and Gross, J., J. Biol. Chem., 1925, lxvi, 217. The Effect of the Administration of a Potent Parathyroid Extract upon the Excretion of Nitrogen, Phosphorus, Calcium, and Magnesium, with Some Remarks on the Solubility of Calcium Phosphate in Serum and on the Pathogenesis of Tetany.
41. Greenwald, I. and Gross, J., J. Biol. Chem., 1926, lxviii, 325. The Effect of Long Continued Administration of Parathyroid Extract upon the Excretion of Phosphorus and Calcium.
42. Halverson, J. O., Mohler, H. K. and Bergeim, Olaf, J. Biol. Chem., 1927, xxxii, 171. The Calcium Content of the Blood Serum in Certain Pathological Conditions.
43. Hammett, F. S., J. Biol. Chem., 1921, xlviii, 143. Studies of the Thyroid Apparatus. IV. The Influence of Parathyroid and Thyroid Tissue on the Creatinine-creatine Balance in Incubated Extracts of Muscle Tissue of the Albino Rat.

44. Hannon, R. R., Shorr, E., McClellan, W. S. and DuBois, E. F., J. Clin. Invest., 1930, viii, 215. A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies. Metabolic Study I. Bauer, W. Albright, F. and Aub, J. C., Ibid., 229. Metabolic Study II. McClellan, W. S. and Hannon, R. R., Ibid. 249. Metabolic Study III.
45. Hetényi, G. and Nógrádi, St. V., Klin. Wchnschr., 1925, iv, 1308. Über die Kalkausscheidung der Gesunden und Kranken Niere.
46. Hoag, L. A., Rivkin, H., Weigele, C. E. and Berliner, F., Am. J. Dis. Child., 1927, xxxiii, 910. Effect of Potent Parathyroid Extract on Calcium Balance in Infants.
47. Hotz, C., Ztschr. f. exp. Path. u. Therap., 1906, iii, 605. Phosphorsäure-und Kalkstoffwechsel bei Osteomalacie unter dem Einfluss der Phosphortherapie.
48. Hueper, Wilhelm, Arch. Path. and Lab. Med., 1927, iii, 14. Metastatic Calcifications in the Organs of the Dog after Injections of Parathyroid Extract.
49. Hunter, Donald, Proc. Roy. Soc. Med., 1929, xxiii, 227. Hyperparathyroidism (Hyperfunction of a Parathyroid Tumor in a Case of Generalized Osteitis Fibrosa).
50. Hutchison, H. S. and Stapleton, G., Brit. J. Child Dis. 1924, xxi, 96. On Late Rickets and Osteomalacia.
51. Jacoby, Martin and Schrott, Mitt. a. d. Grenzgeb. d., Med. u. Chir., 1913, xxv, 383. Ueber die Einwirkung von Calcium Lactate auf Einen Fall von Ostitis Fibrosa mit Escperimentell-therapeutischen. Stoffevechseluntersuchungen.
52. Klemperer, Paul, Surg. Gyn. and Obst., 1923, xxxvi, 11. Parathyroid Hyperplasia and Bone Destruction in Generalized Carcinomatosis.
53. Lundborg, H., Deutsch. Ztschr. f. Nervenh. 1904, xxvii, 217. Spielen die Glandulae Parathyreoideae in der Menschlichen Pathologie eine Rolle?
54. McCrudden, F. H., Arch. Int. Med., 1910, v, 596. Studies of Bone Metabolism, Especially the Pathological Process, Etiology and Treatment of Osteomalacia.
55. McCrudden, F. H. and Fales, H., Arch. Int. Med., 1912, ix, 273. Studies in Bone Metabolism: The Etiology of Non-puerperal Osteomalacia.
56. Mandl, F., Arch. f. klin. Chir., 1926, cxliii, 245. Klinisches und Experimentelles zur Frage der Lokalisierten und Generalisierten Ostitis Fibrosa.
57. Maxwell, J. Preston, Proc. Staff Meetings of the Mayo Clinic, 1929, iv, 319. Osteomalacia.
58. Maxwell, J. P. and Miles, L. M., J. Obst. and Gyn. of Brit. Empire, 1925, xxxii, 433. Osteomalacia in China.
59. Miles, L. M. and Feng, C., J. Exp. Med., 1925, xli, 137. Calcium and Phosphorus Metabolism in Osteomalacia.
60. Morton, J. J., Arch. Surgery, 1922, iv, 534. The Generalized Type of Osteitis Fibrosa Cystica.

61. Peters, J. P., Bulger, H. A., Eisenman, A. J. and Lee, Carter, J. Biol. Chem., 1926, lxvii, 141. Total Acid-base Equilibrium of Plasma in Health and Disease. I. The Concentration of Acids and Bases in Normal Plasma.
62. Robinson, C. S., Huffman, C. F. and Burt, K. L., J. Biol. Chem., 1927, lxxiii, 477. The Effect of the Administration of Parathyroid Extract on Normal Calves.
63. Rosenmann, Max, Ztschr. f. d. ges. Exp. Med., 1922, xxix, 334. Zur Pharmakologie der K- und Ca-Ionen.
64. Salvesen, H. K., Acta. Med. Scand., 1923, Supp. 6; 94. Studies on the Physiology of the Parathyroids.
65. Salvesen, H. A., Hastings, A. B. and McIntosh, J. F., J. Biol. Chem., 1924, lx, 327. The Effect of the Administration of Calcium Salts on the Inorganic Composition of the Blood.
66. Scriver, W. de M., J. Clin. Invest., 1928, vi, 115. Observations on the Excretion of Calcium in Two Cases of Nephrosis Treated with Parathyroid Extract.
67. Seegelken, Deutsch. Arch. f. klin. Med., 1897, lviii, 276. Ueber Multiples Myelom und Stoffwechseluntersuchungen bei Demselben.
68. Sherman, H. C., J. Biol. Chem., 1920, xliv, 21. Calcium Requirement of Maintenance in Man.
69. Sherman, H. C., Chemistry of Food and Nutrition, 1924, MacMillan Co., New York.
70. Shohl, A. T. and Pedley, F. G. J. Biol. Chem., 1922, l, 537. A Rapid and Accurate Method for Calcium in Urine.
71. Shohl, A. T., Wakeman, A. M. and Shorr, E. Y., Am. J. Dis. Child., 1928, xxxv, 392. The Effect of Parathyroid Extract on Mineral Metabolism in Infantile Tetany
72. Smith, F. M., La Jolla, Cal., Personal Communication.
73. Snapper, I., Nederlandsch Tijdschrift voor geneeskunde, 1929, lxxiii, 4758. Gezwel van een Bijschildklier en Skeletafijkingen.
74. Soper, H. W., and Stroud, C. M., To be published.
75. Stewart, C. P. and Percival, G. H., Biochem. J., 1927, xxi, 301. Studies on Calcium Metabolism. I. The Action of the Parathyroid Hormone on the Calcium Content of the Serum and on the Absorption and Excretion of Calcium
76. Tisdall, F. F. and Brown, Alan, Am. J. Child. Dis., 1924, xxvii, 312. Studies on the Acidity (Hydrogen Ion Concentration) of Infants' Stools.
77. Vaughan, Kathleen, Brit. Med. J., 1926, i, 413. Osteomalacia in Kashmir.
78. Warkany, J., Ztschr. f. Kinderh, 1928, xlvi, 1. Die Phosphatämische Kurve des normalen und Rachitischen Organismus.
79. Wilder, Russell M., Endocrinology, 1929, xiii, 231. Hyperparathyroidism: Tumor of the Parathyroid Glands Associated with Osteitis Fibrosa.
80. Williams, O. T., Biochem. J., 1911, v, 225. Some Observations on the Nature of the Bence-Jones' Protein.

81. Wilson, D. W. and Riegel, C., Am. J. Med. Sci., 1927, clxxiii, 154. The Inorganic Constitutents of the Blood after the Injection of Parathyroid Extract.
82. Woodman, Dorothy, Biochem. J. 1925, xix, 595. The Effects of Parathyroid Feeding on Calcium and Creatine Metabolism.
83. Zucker, T. F., Proc. Soc. Exp. Biol. and Med., 1921, xviii, 272. The Relation of Acid Base Equilibrium in the Body to Excretion of Phosphorus and Calcium.