A COMPARISON OF THE EFFECTS OF VITAMIN D, DIHYDRO-TACHYSTEROL (A.T. 10), AND PARATHYROID EXTRACT ON THE DISORDERED METABOLISM OF RICKETS

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In a previous paper (1) it was concluded that vitamin D has two fundamental and separate actions: (*a*) to increase the absorption of calcium from the gastro-intestinal tract, and (*b*) to increase the phosphate excretion in the urine. In a later paper (2) evidence was brought forth which suggested that A.T. 10 (dihydrotachysterol) has both these properties but that the ratio of the calcium absorption factor to the phosphate excretion factor is less with A.T. 10 than with vitamin D. It was pointed out (2), furthermore, that the effect of either A.T. 10 or vitamin D on phosphate excretion may be masked in patients with their parathyroids intact by a tendency in the opposite direction resulting from decreased parathyroid activity occasioned by the increased calcium absorption. It was thought that the reason A.T. 10 was not antirachitic was because of this increased effect on phosphate excretion, a property obviously not antirachitic. Finally, it was pointed out (2) that the parathyroid hormone differed in action from both vitamin D and A.T. 10 in having only the effect on phosphate excretion in the urine without any effect on calcium absorption.

It was decided to test the above conclusions by studies on a patient with chronic infantile rickets. The subject of the investigation was a boy of 17 with vitamin D resistant rickets. He was the same boy who was previously reported (3) on whom it was shown that the disordered metabolism was essentially the same as in the usual form of rickets but to whom it was necessary to give massive doses of vitamin D before therapeutic results were obtained. In the present investigation the metabolic effects of A.T. 10 and parathyroid extract were studied. These data can be compared with those from similar studies already reported with vitamin D on the same patients (3). Whereas these latter studies were conducted approximately 5 years before, the underlying metabolic disorder was essentially the same during both studies. To be sure, the bones were much less rachitic during the present investigation. On the other hand the blood values—serum calcium, phosphorus, and phosphatase—were almost identical at the beginning of both investigations.

METHODS

Vitamin D therapy was discontinued 78 days before the present investigation was commenced. The patient received a weighed low calcium, moderately high phosphorus diet of similar composition throughout the 16 3-day metabolic periods. Five grams of calcium lactate were added to the diet daily. The patient was on this régime for 4 days before collections were started. It should be noted that it is much better when one wants a constant high calcium diet to give a low calcium diet and add a pure calcium salt. The inevitable slight fluctuation in the composition of the food thus becomes negligible.

DISCUSSION OF RESULTS

The data are shown in Table I and Figure 1. During the three control periods (I, II, III), the serum calcium was almost normal (9.9 and 9.3 mgm. per 100 cc.), the serum phosphorus was very low (1.7 and 1.9 mgm. per 100 cc.), there was a large amount of calcium and phosphorus in the feces, the calcium metabolism was practically in balance, and there was a negative phosphorus balance partly attributable to a loss in weight.

During Periods IV, V, VI, and VII the patient received 25 mgm. of A.T. 10 twice daily. The fecal calcium excretion was markedly decreased going from 1.60 grams in Period III to 0.20 gram in Period VIII, the first period after cessation of therapy. The blood serum calcium rose to a high level of 13.3 mgm. per 100 cc. on

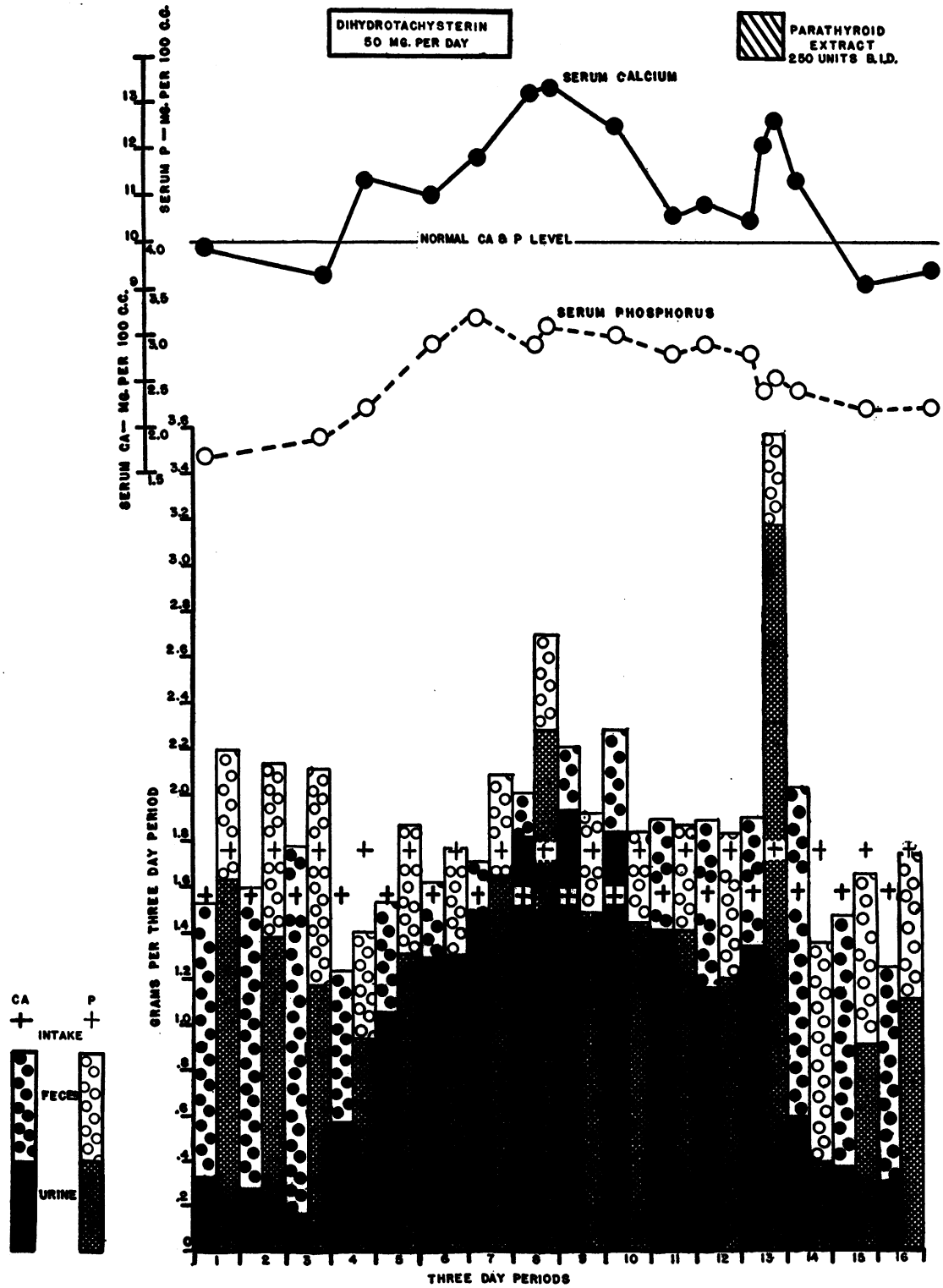

FIG. 1. A GRAPHIC PRESENTATION OF DATA IN TABLE I SHOWING EFFECTS OF A.T. 10 AND OF PARATHYROID EXTRACT ON DISORDERED CALCIUM AND PHOSPHORUS METABOLISM OF INFANTILE RICKETS

Division marks in columns representing urinary excretions for Period 13 are to indicate amount of excretion on each of the three days.

TABLE I

Metabolic data showing effect of A.T. 10 and of parathyroid extract

Period	Date	Weight of patient	Calcium				Phosphorus				Serum			Treatment
			Urine	Feces	Intake	Balance	Urine	Feces	Intake	Balance	Calcium	Phosphorus	Phosphatase	
	Dec. 1937	*kgm.*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*Bodansky units*	
I....	12-13-14	46.5	0.33	1.19	1.56	+0.04	1.63	0.57	1.76	−0.44	9.9 I*	1.7	10	
II...	15-16-17	46.2	0.28	1.32	1.56	−0.04	1.38	0.75	1.76	−0.37				
III..	18-19-20	45.9	0.16	1.60	1.56	−0.20	1.17	0.93	1.76	−0.34	9.3 III	1.9	7	
IV...	21-22-23	45.8	0.57†	0.65	1.56	+0.34	0.94†	0.46	1.76	+0.36	11.3 III	2.2	10	A.T.10–5 cc. b.i.d.
V....	24-25-26	46.0	1.06	0.47	1.56	+0.03	1.31	0.56	1.76	−0.11				A.T.10–5 cc. b.i.d.
VI...	27-28-29	45.8	1.29	0.34	1.56	−0.07	1.30	0.47	1.76	−0.01	11.0 I	2.9	9	A.T.10–5 cc. b.i.d.
VII..	30-31-Jan. 1	45.9	1.46	0.25	1.56	−0.15	1.64	0.44	1.76	−0.32	11.8 I	3.2	8	A.T.10–5 cc. b.i.d.
VIII.	2-3-4	45.8	1.81	0.20	1.56	−0.45	2.28	0.42	1.76	−0.94	13.2 II	2.9	6	
											13.3 III	3.1	7	
IX ..	5-6-7	45.3	1.93	0.28	1.56	−0.65	1.48	0.44	1.76	−0.16				
X....	8-9-10	45.2	1.84	0.45	1.56	−0.73	1.44	0.39	1.76	−0.07	12.5 I	3.0	9	
XI..	11-12-13	45.2	1.40	0.49	1.56	−0.33	1.41	0.45	1.76	−0.10	10.6 II	2.8	8	
XII.	14-15-16	45.3	1.16	0.73	1.56	−0.33	1.20	0.62	1.76	−0.06	10.8 I	2.9	11	
	17	*45.2*	*0.46*				*1.15*				*10.5*	*2.8*	*11*	*Parathyroid extract 500 U.*
XIII	*18*	*44.8*	*0.46*				*1.16*				*12.1*	*2.4*	*12*	*Parathyroid extract, 500 U.*
	19	*44.7*	*0.42*				*0.87*				*12.8*	*2.5*	*11*	*Parathyroid extract, 500 U.*
	17-18-19		1.34	0.56	1.56	−0.34	3.18	0.38	1.76	−1.80				Parathyroid extract 1,500 U.
XIV.	20-21-22	44.7	0.59	1.44	1.56	−0.47	0.38	0.96	1.76	+0.42	11.3 I	2.4	10	
XV..	23-24-25	45.3	0.37	1.10	1.56	+0.09	0.91	0.74	1.76	+0.11	9.1 III	2.2	13	
XVI.	26-27-28	45.1	0.30	0.95	1.56	+0.31	1.10	0.64	1.76	+0.02	9.4 III	2.2	10	

* Roman numerals indicate to which day of period data pertain.

† One of three urine specimens lost during this period. Figures obtained by multiplying values for other two days by 3/2. This probably not justified as values were undoubtedly changing rapidly from day to day.

the third day of Period VIII. The urinary calcium excretion rose as much as and finally more than the fecal calcium excretion decreased so that the calcium balances instead of becoming positive eventually became negative.

The urinary phosphorus excretions are most instructive. Period IV had best be disregarded as the urine for one day was lost by accident and the values recorded were obtained by multiplying the excretions during the remaining two days by 3/2. It is quite clear that A.T. 10 (see Periods V to VIII) caused a definite increase in the urinary phosphorus excretion. The increase was not tremendous as occurs when A.T. 10 is given to an individual without parathyroid tissue (2). This may be explained by the hypothesis that the phosphorus-excretion-property of A.T. 10 was masked by the decreased activity of the parathyroid glands secondary to the elevated serum calcium (*v. supra*). On the other hand, phosphorus excretion in the urine was increased whereas with vitamin D it had been decreased (Table II). This is in accordance with the hypothesis that A.T. 10 has a relatively greater effect on phosphorus excretion than vitamin D.

The fecal phosphorus excretion with A.T. 10 was decreased but not to the same extent as the fecal calcium excretion. The serum phosphorus values rose (1.9 mgm. to 3.1 mgm. per 100 cc.) presumably because of decreased parathyroid activity resulting from increased calcium absorption. This rise of the serum phosphorus does not occur, of course, when A.T. 10 is given to parathyroidless individuals (2). The phosphorus balances on the whole tended to become more negative. This fact becomes more definite if one compares the balances with the two control periods at the end of the experiment (Periods XV and XVI) as well as with Periods I, II, and III when there was a negative phosphorus balance probably attributable to a negative nitrogen balance (*cf.* weights in Table I).

During the remainder of the experiment, except for Periods XIII and XIV when there was a temporary disturbance resulting from the administration of parathyroid extract in Period XIII, one can note the gradual return of the values to the pre-A.T. 10 levels.

On each day of Period XIII the patient received 250 units of parathyroid extract twice daily. This resulted immediately in an almost threefold increase in the urinary phosphorus excretion and a large negative phosphorus balance. The moderate decreases in the fecal calcium and phos-

TABLE II †

Metabolic data showing the effect of vitamin D.

Three-day period	Calcium				Phosphorus				Serum		Vitamin D
	Urine	Feces	Intake	Balance	Urine	Feces	Intake	Balance	Calcium	Phosphorus	
	grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*U. S. P. units*
I.....	0.03	1.95	2.28	+0.30	1.59	1.62	3.21	0.00			
II.....	0.03	1.83	2.01	+0.15	1.53	1.26	2.85	+0.06			
III.....	0.03	2.22	2.28	+0.03	1.32	1.47	3.21	+0.42	9.9 I*	2.7	
IV.....	0.03	1.80	2.28	+0.45	1.65	1.11	3.21	+0.45			
V.....	0.03	2.34	2.28	−0.09	1.59	1.59	3.21	+0.03			150,000 daily
VI.....	0.06	1.77	2.28	+0.45	1.68	1.17	3.15	+0.30	8.8 II	3.1	150,000 daily
VII.....	0.03	1.68	2.28	+0.57	1.68	0.93	3.21	+0.60			150,000 daily
VIII.....	0.03	1.68	2.28	+0.57	1.47	0.81	3.21	+0.93	9.8 III	2.7	300,000 daily
IX.....	0.03	1.14	2.28	+1.11	1.29	0.78	3.21	+1.14	9.2 II	2.7	1,100,000 daily
X.....	0.12	0.51	2.28	+1.65	1.29	0.48	3.21	+1.44			1,500,000 daily
XI.....	0.12	0.63	2.28	+1.53	1.68	0.60	3.21	+0.93	9.6 I	2.9	
XII.....	0.09	0.84	2.28	+1.35	1.71	0.60	3.21	+0.90	11.0 III	2.5	

* Roman numerals indicate on which day of period determination was made.
† Table is constructed from Table III of previous publication (3).

phorus excretion in Period XIII can probably be accounted for by constipation as these values markedly increased in Period XIV and as it is clear from many other experiments (4) that the parathyroid hormone does not effect absorption of calcium and phosphorus. The serum calcium rose during Period XIII from 10.5 to 12.6 mgm. per 100 cc. and the urinary calcium excretion became slightly elevated. As often stressed in papers from this Clinic, it will be noted that the effect of the parathyroid hormone was predominantly on urinary phosphorus excretion. Furthermore, this effect was not masked by a decreased activity of the patient's own parathyroids as occurred when A.T. 10 was administered because the parathyroid hormone does not have an effect on calcium absorption.

During Period XIV there was the expected marked compensatory retention of phosphorus (4). By Period XV, all after-effects of the parathyroid hormone treatment had entirely disappeared.

Comparison of effect of A.T. 10 with that of vitamin D

In Table II are published again the 1933 metabolic data showing the effect of vitamin D. The table will not be discussed in detail but it should be noted that the urinary phosphorus excretion was slightly decreased with vitamin D and the phosphorus balance was markedly increased.

It will thus be noted that the hypotheses suggested from previous experiments and set forth in the opening paragraph have all received support from the present studies.

SUMMARY AND CONCLUSIONS

1. The metabolic effects of A.T. 10 and of the parathyroid hormone have been studied on a patient with vitamin D-resistant rickets (not vitamin D-refractory rickets) on whom previous studies had been made with vitamin D.

2. A.T. 10 did not cause the marked rise in urinary phosphorus excretion which it causes in patients with deficient parathyroid glands. This difference is explained by the hypothesis that the other action of A.T. 10—to increase calcium absorption—leads to a decreased activity of the patient's own parathyroid glands which in turn leads to a decreased urinary phosphorus excretion.

3. A.T. 10, however, did cause an increase in the urinary phosphorus excretion and did lead to an increased negative phosphorus balance. In these respects its action was different from that of vitamin D. These observations support hypotheses of previous publications which held that both A.T. 10 and vitamin D have two actions —to increase calcium absorption and to increase phosphorus excretion in the urine—but which also stated that the ratio of the second of these actions to that of the first was greater with A.T.

10 than with vitamin D. The data support the hypothesis, furthermore, that it is because of this difference alone that A.T. 10 is not antirachitic.

4. The most striking effect of the parathyroid hormone was in increasing the urinary phosphorus excretion.

5. The data support the contention that the actions of vitamin D, A.T. 10, and the parathyroid hormone on calcium and phosphorus metabolism can be depicted as follows:

	Calcium absorption	Phosphorus excretion in urine
Vitamin D	+++	+
A.T. 10	+	+++
Parathyroid extract	0	++++

6. As one proceeds down the series—vitamin D, A.T. 10, parathyroid hormone—the action on calcium and phosphorus metabolism asserts itself more rapidly and lasts a shorter time.

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