URINARY CALCIUM AND PHOSPHORUS HOMEOSTASIS IN HYPERCORTISOLISM

I. EVALUATION BY MEANS OF CALCIUM INFUSION TEST

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ABSTRACT

Calcium infusion tests were carried out on 8 normal controls, 4 patients with Cushing's syndrome and 4 normal subjects receiving dexamethasone. Patients with excess glucocorticoids either retained significantly more calcium or had a smaller urinary output of calcium than did normal controls on the infusion day due to increased renal tubular reabsorption. A normal decrease of phosphorus excretion after induction of hypercalcemia indicates persistence of parathyroid suppressibility and/or thyrocalcitonin release.

Normal subjects respond to calcium infusion with hypercalcemia, hyperphosphatemia, hypercalciuria and reduction of phosphorus excretion rate. This last response, already extensively studied, reflects a reduced parathyroid hormone secretion, as recently shown by radioimmunoassay[1] and the production of thyrocalcitonin[2], which may also contribute to the phosphaturic response[3]. On the other hand, much less is known about factors influencing the development of hypercalcemia and hypercalciuria.

The results published on calcium infusion in hypercortisolism have been contradictory, particularly when urinary responses were correlated with the state of bone metabolism. Thus, Finlay et al.[4] and Molinatti and co-workers[5] reported a greater than normal calcium excretion rate in Cushing's syndrome after calcium infusion. These findings were attributed to the characteristics low retention of osteoporosis[6]. However, an increased calcium retention was observed in three of the patients studied by Molinatti

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et al.[5] as well as in eight out of the ten patients with Cushing's syndrome and in a longterm study of corticoid hyperfunction by Haas et al.[7]. Since over half of Haas's patients, as well as the three of Molinatti, showed a slight or distinct elevation of serum alkaline phosphatase, coupled, in all cases, with radiologically unequivocal osteoporosis, these authors suggested that osteoporosis and osteomalacia were both present.

There are no data in the literature about the effect of calcium infusion on urinary phosphorus excretion in hypercortisolism.

Since observations concerning the effects of calcium infusion on urinary calcium and phosphorus in patients with hypercortisolism are as yet very few and contradictory, we shall report our studies on normal controls, before and after dexamethasone administration, as well as on patients with spontaneous chronic hypercortisolism, Cushing's syndrome.

MATERIALS AND METHODS

Subjects: The normal group comprised 3 men and 5 women, ages 22-45 yr. There were 3 women and 1 man with Cushing's syndrome, ages 23-30 yr: each had radiologically demonstrable osteoporosis.

Protocols: All subjects received a low calcium, low phosphorus diet (200-270 mg calcium and 400-570 mg phosphorus daily) beginning one week before the test. The sodium and potassium intakes were 145 and 100 mEq daily, respectively. Urine was collected in 12-hr aliquots the day prior to and the day of the calcium infusion. The infusion consisted of 15 mg of calcium/kg body weight as calcium gluconate given in 1000 ml of a 5% glucose solution between 8:00 AM and noon.

Two of the normal subjects were studied after treatment

with dexamethasone (9α-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione), 9 mg daily in 4 divided doses for 14 days. Two of the subjects received 12 mg daily in divided doses for 16 days. The calcium infusion was then repeated.

Two of the normal controls (MBA and WAM) received an intravenous infusion of 1 g of calcium gluconate in 1000 ml of a 5% glucose solution over 4 hr (from 8 AM till noon) before and after induction of a hyperglucocorticoid state with dexamethasone, the latter 10 days after the last calcium infusion (15 mg/kg), that is, 27 days after dexamethasone treatment, 12 mg/day.

The infusions were performed on these patients in a state of water diuresis induced by administration of 20 ml of water/kg of body weight, over 1 hr, and subsequent maintenance for the duration of the experiment, by replacement of urinary losses plus 1 ml/min (insensible losses). Urine was collected every hour, without indwelling catheters, and all samples analyzed for creatinine and calcium. Venous blood samples for ultrafiltrable calcium and creatinine determinations were obtained through an indwelling needle in the middle of each urine collecting period.

Two patients, one normal control (WAM) and AJO with Cushing's syndrome, had calcium kinetic studies as described previously[9]. WAM was studied before and after dexamethasone treatment (9 mg daily for 27 days); AJO was studied during and after remission of Cushing's syndrome.

Methods: The following methods were used: serum alkaline phosphatase[10], urine and plasma ultrafiltrable calcium[11], as modified for spectrophotometry[12], urine and serum phosphorus[13], urine and plasma creatinine[14]. Endogenous creatinine clearance was used to estimate glomerular filtration rate. Plasma ultrafiltration was carried out at 10 C for 12 hr by Toribara, Terepka and Dewey's method[15] and the results correct-

ed to 36 C, according to the same authors. In all the experiments ultrafiltrable calcium clearance was calculated as the ratio of the observed ultrafiltrable calcium clearance to that of the simultaneously measured cretinine clearance (C_{Ca}/C_{Cr} x 100), which represents the percentage of the filtered load excreted or the calcium cleared per 100 ml of glomerular filtrate in ml/min.

Statistical studies utilized tests of differences between means and of sample homogeneity[16].

RESULTS

1. Urinary calcium. Results were expressed in two ways:

a. Through Nordin and Fraser's method[8]: calcium net output on test day, from 8 AM to 8 PM, given as percentage of administered dose after deduction of basal excretion (calcium excretion on control day, calculated from 8 AM to 8 PM).

b. Through Haas and co-workers' method[7]: calcium retention, calculated by subtracting 24-hour urinary calcium on control day from urinary calcium on infusion day, which leaves the net amount of calcium excreted from the infused load (Δ Ca-mg/24 hr) and, once subtracted from the amount infused, will indicate the amount of calcium retained, as percentage of the infused load.

The results of the eight normal controls, of the patients with Cushing's syndrome, as well as of those after dexamethasone treatment, are presented on Table 1.

The results of the patients with Cushing's syndrome and with induced hyperglucocorticoid state were pooled since their mean values did nor show significant difference, at a 5% level, either as net output of calcium ($t_{observed} = 0.346$; $t_{0.05} = 2.447$), or as retained calcium ($t_{observed} = 0.117$; $t_{0.05} = 2.447$), both being percentages of the load infused. Common means were therefore used

TABLE 1. Effect of calcium infusion* on urinary calcium

Patient	Age (yr) Sex	Infused Ca (mg)	Calcium excretion (mg/period)						Increase Ca excretion (infusion day)	Net Ca excretion (8 AM–8 PM) (% infused Ca)	Δ Ca (mg/24 hr)	Ca retention	
			Basal day			Infusion day						Δ Ca (mg/24 hr)	% infused Ca
			8 AM–8 PM	8 PM–8 AM	Total	8 AM–8 PM	8 PM–8 AM	Total	8 AM–8 PM (mg)				
Normal controls													
MTC	29 F	682.5	28	24	52	261	17	278	233	34	226	456	67
ML	25 F	826.5	32	40	72	323	71	394	291	35	322	504	61
RPR	44 F	805.5	36	36	72	310	73	383	274	34	311	493	61
MBA	22 M	770.0	114	68	182	432	30	462	318	41	280	490	63
WAM	24 F	844.5	73	119	192	596	162	758	523	62	566	278	35
NB	30 F	750.0	76	41	117	483	39	522	407	54	405	344	46
TMC	32 F	697.5	73	44	117	551	45	596	478	68	479	219	31
IJS	45 M	1026.0	34	32	66	595	189	784	561	55	718	308	30
Cushing's syndrome													
AC	29 F	906.0	101	132	233	183	60	243	82	9	10	897	99
AJO	30 M	1070.0	146	133	279	162	123	285	16	1.5	6	1064	99
EL	28 F	856.5	151	134	285	320	121	441	169	20	156	701	82
WMS	23 F	859.5	83	151	234	318	203	521	235	27	287	572	67
Dexamethasone treatment													
MBA†	22 M	735.0	129	151	280	219	145	364	90	12	84	651	89
WAM†	24 M	846.0	153	157	310	297	197	494	144	17	184	662	78
NB‡	30 F	750.0	52	67	119	170	56	226	118	16	107	643	86
TMC‡	32 F	691.5	56	161	217	175	221	396	119	17	179	512	74

* 15 mg Ca/kg body wt.
† 17th day of dexamethasone (12 mg/day).
‡ 20th day of dexamethasone (9 mg/day).

for the pool of the patients with glucocorticoid excess.

On comparing the results of calcium infusion tests of normal controls and the pool of patients with Cushing's syndrome and after dexamethasone treatment, one sees that the mean of the percentage of the infused load excreted (from 8 AM to 8 PM) by normal controls was significantly greater than that of patients with glucocorticoid excess ($t_{observed} = 5.890$) at a 5% level ($t_{0.05} = 2.145$). Inversely, the mean of the percentage of administered calcium retained (in 24 hr) was significantly greater in cases of glucocorticoid excess ($t_{observed} = 4.169$; $t_{0.05} = 2.145$).

2. Urinary phosphorus. Excretion of phosphorus was expressed as the ratio of phosphorus on infusion day/phosphorus on basal

day (mg/volume), in the periods from 8 AM to 8 PM, from 8 PM to 8 AM, and total (24 hr).

The results of normal controls and of patients with glucocorticoid excess are shown on Table 2.

TABLE 2. Effect of calcium infusion* on urinary phosphorus

Patient	Age (yr) Sex	Infused Ca (mg)	Phosphorus excretion (mg/period)						P 8 AM–8 PM infusion day / P 8 AM–8 PM basal day	P 8 PM–8 AM infusion day / P 8 PM–8 AM basal day	Total P infusion day / Total P basal day
			Basal day			Infusion day					
			8 AM–8 PM	8 PM–8 AM	Total	8 AM–8 PM	8 PM–8 AM	Total			
Normal controls											
MTC	29 F	709.5	212	297	509	412	127	539	1.9	0.4	1.1
ML	25 F	826.5	54	198	252	76	27	103	1.4	0.1	0.4
RPR	44 F	805.5	183	163	346	164	55	219	0.9	0.3	0.6
MBA	22 M	770.0	264	260	524	196	69	265	0.7	0.3	0.5
WAM	24 M	844.5	147	147	294	267	65	332	1.8	0.4	0.1
NB	30 F	750.0	149	281	430	119	130	249	0.8	0.5	0.6
TMC	32 F	697.5	251	221	472	283	84	367	1.1	0.4	0.8
IJS	45 M	1026.0	78	214	292	149	42	191	1.9	0.2	0.7
Cushing's syndrome											
AC	29 F	906.0	245	101	346	263	18	281	1.1	0.2	0.8
AJO	30 M	1070.0	250	202	452	302	73	375	1.2	0.4	0.8
EL	28 F	856.5	248	219	467	121	70	191	0.5	0.3	0.4
WMS	23 F	859.5	211	209	420	223	7	230	1.1	0.04	0.6
Dexamethasone treatment											
MBA†	22 M	735.0	384	518	902	464	206	670	1.2	0.4	0.7
WAM†	24 M	846.0	599	513	1112	430	208	683	0.7	0.4	0.6
NB‡	30 F	750.0	369	309	678	270	155	425	0.7	0.5	0.6
TMC‡	32 F	691.5	174	290	464	232	72	304	1.3	0.2	0.7

*,†,‡ See Table 1.

The results on patients with Cushing's syndrome and after dexamethasone treatment were pooled, because the mean of the ratios for urinary phosphorus from 8 AM to 8 PM ($t_{observed}$ = 0.202), from 8 PM to 8 AM ($t_{observed}$ = 1.707) and 24 hours ($t_{observed}$ = = 0.154) did not differ significantly at a 5% level ($t_{0.05}$=2.447) between the two groups.

Comparison of the phosphaturia of normal controls and patients with glucocorticoid excess (Cushing's syndrome and dexame-

thasone therapy) indicated that the means of the ratios during all urine collecting periods, of urinary P infusion day/basal day, did not differ significantly between groups at a 5% level ($t_{8\ AM-\ 8\ PM} = 1.643$; $t_{8\ PM-\ 8\ AM} = 0.373$; $t_{24\ hr} = 0.527$; $t_{0.05} = 2.145$).

Comparison of phosphate excretion from 8 AM to 8 PM wich that from 8 AM to 8 PM showed, in each group, the mean urinary P infusion day/basal day ratio from 8 PM to 8 AM to be significantly lower, at a 5% level, than that from 8 AM to 8 PM .... ($t_{normal\ controls} = 6.180$; $t_{hypercort} = 5.375$; $t_{0.05} = 2.145$).

3. Serum alkaline phosphatase. Values of serum alkaline phosphatase are indicated in Table 3. In normal controls treated with dexamethasone, serum alkaline phosphatase fell below the normal range {3-5 Bodansky units[17]}. Two of the patients with Cushing's syndrome had enzyme levels below normal limits.

TABLE 3: Effect of Cushing's syndrome and induced glucocorticoid excess on serum alkaline phosphatase levels.

Cushing's syndrome				
Patient	Age (yr)	Sex	Alkaline phosphatase (Bodansky U)	
AC	29	F	2.6	
AJO	30	M	3.1	
EL	28	F	2.5	
WMS	23	F	3.5	
Dexamethasone treatment				
			Alkaline phosphatase (Bodansky U)	
			Control	After dexamethasone
MBA†	22	M	5.0	2.7
WAM†	24	M	4.7	2.5
NB‡	30	F	3.4	1.7
TMC‡	32	F	3.8	1.9

† ‡ See TABLE 1.

4. ^{47}Ca kinetic studies. Radioactivity data were fitted satisfactorily by a model with two exchanging compartments[9]. The parametes of the model, that is, compartmental sizes and flow rates - constants of compartmental analysis - for both periods of the study in the normal subjects and in the patient with Cushing's syndrome, as well as the mean values in normal subjects[9], are presented in Table 4.

TABLE 4: Constants of compartmental analysis

Patient	Period	Ro_{1F} (g/day)	Ro_{14} (g/day)	Ro_{15} (g/day)	Ro_{13} (g/day)	$Ro_{12,21}$ (g/day)	Compartment 1(S_1) (g)	Compartment 2(S_2) (g)	Total exchangeable Ca (1+2) (g)	R (g/day)
WAM	Control	1.269	0.216	0.143	0.940	3.901	1.371	2.497	3.868	0.790
	Dexamethasone	1.342	0.359	0.011	0.972	4.031	1.057	2.789	3.846	1.163
AJO	Remission	1.379	0.018	0.172	1.189	4.914	1.385	2.674	4.059	0.556
	Cushing's syndrome	0.961	0.041	0.225	0.715	5.272	2.347	1.529	3.876	0.668
	Control§	1.299	0.244	0.291	0.764	4.282	1.211	2.734	3.945	0.652
	Dexamethasone§	1.314	0.400*	0.149°	0.765	4.856	1.147	2.538	3.684	0.839*

§ Mean values in normal subjects (ref. 9).
* Statistically significant change ($p<0.05$).
Ro_{1F}= Ro_{14}+ Ro_{15}+ Ro_{13}(Ca loss rate from compartment 1).
Ro_{14}= urinary Ca excretion rate.
Ro_{15}= endogenous fecal Ca (Ca_{Fe}) excretion rate.
Ro_{13}= Ca transfer rate to bone.
Ro_{12}= Ca flow rate from compartment 1 to 2.
Ro_{21}= Ca flow rate from compartment 2 to 1.
R = Ca transfer rate from bone to exchangeable pool.

Dexamethasone induced in normal subjects, as the sole statistically significant change, an increase in urinary calcium levels (Ro_{14}) ($t = 3.120$), a fall in endogenous fecal calcium (Ro_{15}) ($t = 4.314$) and an increase in bone reabsorption rate (R) ($t = 2.930$). No significant changes were demonstrated in the remaining parameters for $t_{0.05} = 2.353$[9].

In patient AJO, during remission of Cushing's syndrome, all constants of compartmental analysis were within normal limits. During the active phase there was, when compared with dexamethasone treatment, a significant fall in Ro_{1F}, Ro_{13} and S_2 and an increase

in Ro_{14}.

5. Ultrafiltrable calcium clearances. Results of creatinine clearance, plasma ultrafiltrable calcium and the ratio $C_{Ca}/C_{Cr} \times 100$, during calcium infusion in patients NBA and WAM, are given in Table 5.

TABLE 5: Effect of dexamethasone on the endogenous creatinine clearance, plasma ultrafiltrable calcium and clearance of diffusible calcium, during calcium infusion (4 hr).

		MBA Periods*				WAM Periods*			
		1	2	3	4	1	2	3	4
Creatinine clearance (ml/min)	Pre †	101	108	101	101	90	97	92	118
	Post‡	117	125	112	113	137	123	135	120
Plasma Ultrafiltrable calcium (mg/100ml)	Pre †	6.4	8.2	9.2	9.9	6.5	8.0	9.3	10.8
	Post‡	6.4	8.2	9.7	10.2	6.3	7.8	9.3	9.9
$C_{Ca}/C_{Cr} \times 100$	Pre †	3.76	3.82	4.00	5.18	2.50	3.66	6.64	8.36
	Post‡	2.11	2.60	2.87	3.34	2.00	2.69	4.18	5.41

* Periods (1 hr) of urine collection.
† Prior to the administration of dexamethasone.
‡ 28th day of dexamethasone (14 mg/day).

In comparison to the control study, dexamethasone increased creatinine clearance during calcium infusion. On the other hand, there was no consistent alteration in ultrafiltrable plasma calcium when calcium infusion during the hyperglucocorticoid state was compared to that of the control study.

There was, therefore, an increase in the filtered load of calcium (creatinine clearance x plasma ultrafiltrable calcium) in all periods after dexamethasone treatment.

Finally, the $C_{Ca}/C_{Cr} \times 100$ ratio decreased in all periods after dexamethasone.

DISCUSSION

The net calcium output from 8:00 AM to 8:00 PM during the calcium infusion tests in our normal subjects was comparable to the normal range established by Nordin and Fraser[8]: 33 to 53% of the infused load. Similarly, the normal range of calcium retention as 40 to 60% of the infused load[7] is in agreement with ours: 30 to 67% (Table 1).

In glucocorticoid excess there was a significantly greater calcium retention or a lower urinary calcium output on the day of infusion than in normal controls[5,7], generally coupled with elevation of the serum alkaline phosphatase levels, "reflecting increased bone matrix formation, in the absence of liver disease"[18].

However, none of our patients with Cushing's syndrome and induced hyperglucocorticoid state had increased levels of alkaline phosphatase in serum (Table 3) but, on the contrary, lower than normal values were seen in all except two of the patients with Cushing's syndrome.

On the other hand, histological[19], quantitative microradiographic[20] and tetracycline bone labeling[21] show glucocorticoids to decrease the rate of bone formation with absence of uncalcified bone matrix. From our studies of the effects of dexamethasone on ^{47}Ca kinetics in normal subjects (Table 4), we have shown that bone deposition rate was increased in some subjects and decreased in others[9]. Patient AJO, with Cushing's syndrome and the greatest calcium retention (99% of the infused load - Table 1) of our series, presented a striking reduction in the bone deposition rate when in active phase, as compared to the stage of remission (Table 4). The longer presistence of high steroid levels in cases of Cushing's syndrome in relation to the acute administration of pharmacological doses of dexamethasone could explain the discrepancies observed in both situations. The only constant and significant change in induced and spontaneous Cushing's syndro

me was an increase in the rate of bone reabsorption (Table 4), a combination of a slow bone deposition rate with an accelerated bone reabsorption, explaining osteoporosis in Cushing's syndrome[9].

Among factors that may contribute to reduction of urinary calcium on the day of infusion, increases of the available calcium pool, of bone deposition rate or of the ratio of bone deposition/bone reabsorption can be discarded from our studies of calcium kinetics (Table 4).

A possibility to be considered would be to postulate that glucocorticoids increase the extrarenal (fecal) route of calcium loss, giving a falsely high calcium retention on infusion day. Our dynamic studies[9], however, showed a decreased rate of calcium transfer across the intestinal wall, in both directions (from lumen to plasma and vice versa).

Thus, deviations from normal behavior, in Cushing's syndrome as well as during dexamethasone treatment, must be due, on final analysis, to one of two factors:

1. A less than normal increase in the filtered load of calcium, following calcium infusion.

This may be due to different responses in glomerular filtration rate, the degree and duration of hypercalcemia or the binding of calcium (as measured by calcium levels in plasma ultrafiltrate).

Many references in the literature indicate an increase in glomerular filtration rate after administration of glucocorticoids, and we ourselves proved in two of our normal subjects that dexamethasone produced a slight, but nonetheless significant, increase in creatinine clearance during calcium infusion. On the other hand, no significant change in ultrafiltrable calcium occurred during the calcium infusion after dexamethasone treatment compared with

that of the control study. There was, then, an increase in the filtered load of calcium via GFR (Table 5).

2. Increased tubular reabsorption of filtered calcium in hyperglucocorticoid state.

In the two patients mentioned, when ultrafiltrable calcium clearance was corrected for changes in the filtered load ($C_{Ca}/C_{creatinine} \times 100$), its value decreased significantly in the hyperglucocorticoid state, indicating an increase in tubular reabsorption of filtered calcium (Table 5).

Unfortunately, we lack data to analyse factors influencing tubular reabsorption of calcium, such as concentration of citrate, sodium and magnesium in tubular fluid, as well as the degree of parathyroid hormone secretion.

As far as parathyroid hormone secretion is concerned, the absence of a significant difference between normal subjects and patients with glucocorticoid excess, covering total 24 hour phosphate excretion and that from 8 AM to 8 PM and from 8 PM to 8 AM (as ratios to corresponding values on basal day), is and indication of persisting parathyroid suppressibility and/or thyrocalcitonin release in patients under glucocorticoid action.

Therefore, after calcium infusion, the significantly greater reduction in phosphate excretion from 8 PM to 8 AM, both in normal controls and patients with glucocorticoid excess, is what should have been expected in the presence of functioning parathyroid glands, since it indicates the effect of hypercalcemia on parathyroid function (as judged by the effect on urine phosphorus) at a time when response would by maximal - eight to ten hours following induction of hypercalcemia[22,25]. However, direct blood hormone measurements by radioimmunoassay show infusions of calcium causing a rapid fall in parathyroid hormone concentration[1].

However, in the hyperglucocorticoid state, slight changes in the degree of parathyroid hormone control probably cannot be evaluated through urinary phosphorus changes.

RESUMO

Testes de infusão de cálcio foram realizados em 8 indivíduos normais, 4 pacientes com a síndrome de Cushing e 4 indivíduos normais recebendo dexametasona. Os pacientes sob a ação de um excesso de glicocorticóide retém significativamente mais cálcio ou tem menor excreção dêste elemento do que os contrôles normais, no dia da infusão, por aumento da reabsorção tubular renal do catíon. A queda normal na excreção de fósforo após a indução da hipercalcemia indica a persistência da ação supressora da paratireóide ou também de liberação de tireocalcitonina.

RÉSUMÉ

L'auter a realizé des épreuves d'infusion de calcium chez 8 subjets normaux, 4 malades atteints de sindrome de Cushing et 4 sujets normaux, pendant l'administration de dexamethasone.

Chez les sujets avec un excès de glucocorticoides, on a observé une retention ou une diminuition de l'excrétion urinaire du calcium, par rapport aux sujets normaux il y a d'une réabsorption tubulaire augmentée.

Une baisse normale des chiffres de la phosphaturie, après l'induction de la hypercalcémie, est indicative de la manutention du mécanisme de suppression de la parathyroide ou de la libération de thyrocalcitonine.

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REFERENCES

1. Aurbach, G.D., and J.T. Potts, Jr., Amer J. Med. 42: 1, 1967.

2. Copp, D.H., Amer. J. Med. 43: 648, 1967.

3. Robinson, C.J., T.J. Martin, and I. Mac-Intyre, Lancet 2: 83, 1966.

4. Finlay, J.M., B.E.C. Nordin, and R. Fraser, Lancet 1: 826, 1956.

5. Molinatti, G.M., F. Camanni, and M. Olivetti, Acta Endocr.

(Kobenhavn) 34: 323, 1960.

6. Sprague, R.G., R.V. Randall, R.M. Salassa, D.A. Scholz, J.T. Priestley, W. Walters, and A.H. Bulbulian, Arch Intern. Med. (Chicago) 98: 388, 1956.

7. Haas, H.G., J.J. Canary, L.H. Kyle, R.J. Meyer, and M. Schaaf, J. Clin. Endocr. 23: 605, 1963.

8. Nordin, B.E.C., and R. Fraser, Lancet 1: 823, 1956.

9. Wajchenberg, B.L., V.G. Pereira, J. Kieffer, and S. Ursic, Acta Endocr. (Kobenhavn) 61: 173, 1969.

10. Bodansky, A.J., J. Biol. Chem. 101: 93, 1933.

11. Clark, E.P., and J.B. Collip, J. Biol. Chem. 63: 461, 1923.

12. Loureiro, J.A., and C.J. Janz, Biochem. J. 38: 16, 1944.

13. Fiske, C.H., and Y. Subbarow, J. Biol. Chem. 66: 375, 1925.

14. Owen, J.A., B. Iggo, F.J. Scandrett, and C.P. Stewart, Biochem. J. 58: 426, 1954.

15. Toribara, T.Y., A.R. Terepka, and P.A. Dewey, J. Clim. Invest. 36: 738, 1957.

16. Snedecor, G.W., Statistical Methods Applied to Experiments in Agriculture and Biology, ed. 5, Iowa State College Press,Ames, 1956.

17. Cintra, A.B.U., Doenças Ósseas Metabólicas (Thesis), 1949.

18. Irving, J.T., Calcium Metabolism, Methuen & Co. Ltd., London, 1957.

19. Sissons, H.A., In Rodahl, K., J.T. Nicholson, Jr., and E.M.

Brown (eds.), Bone as a Tissue, McGraw-Hill Book Company. Inc, New York, 1960, p.3.

20. Riggs, B.L., J. Jowsey, and P.J. Kelly, Metabolism 15: 773, 1966.

21. Frost, H.M., Henry Ford Hosp. Med. Bull 10: 119, 1962.

22. Hiatt, H.H., and D.D. Thompson, J. Clin. Invest. 36: 573, 1957.

23. Hastings, A.B., and C.B. Huggins, Proc. Soc. Exp. Biol. Med. 30: 458, 1933.

24. Nordin, B.E.C., and R. Fraser, Clin. Sci. 13: 477, 1954.

25. Kyle, L.H., J.J. Canary, D.H. Mintz, and A. Leon, J. Clin. Endocr. 22: 52, 1962.