A New Clinical Presentation of Primary Hyperparathyroidism

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7-10 novembre 2013

Normocalcemic Primary Hyperparathyroidism ("Form Fruste" of an old disease)

Silverberg & Bilezikian et al. J Clin Endocrinol Metab 2003

"Normocalcemic PHPT"

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- First coined by Wills et al. (1969)

Wills MR, Pak CY, Hammond WG, Bartter FC.
Normocalcemic primary hyperparathyroidism.
Am J Med. 1969 ;47(3):384-91

- Cited mutiple series from 1950's
- Mainly in patients with severe & recurrent renal stones disease
- Series obtained from "stone" clinics
- Patients were often intermittently hypercalcemic (which is typical of modern PHPT)

Normocalcemic PHPT
Definition

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- The **total serum calcium** is normal, virtually "all the time"
- The **ionized serum calcium** is also normal

Silverberg & Bilezikian et al. J Clin Endocrinol Metab 2003

Normocalcemic PHPT
Monchik & Gorgun, Surgery, 2004

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Patients with osteoporosis who had PTx

15/64 had "normocalcemic hyperparathyroidism"

- Only six had persistent normal serum calcium

- Ionized calcium elevated in 95% of values in these patients

Normocalcemic PHPT
Koumakis et al, J Clin Endocr Metab, 2013

Patients who had PTx

39/60 had “normocalcemic hyperparathyroidism”

- Only 16 had normal ionized serum calcium

- Ionized calcium elevated in 41% of values in these patients

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Normocalcemic PHPT
sharpening the definition further
exclude the following:

Any secondary causes for elevated PTH

- ✓ Vitamin D insufficiency (25-hydroxyvitamin D < 30 ng/ml)
- ✓ Renal insufficiency (GFR <60 ml/min)
- ✓ Medications that could alter calcium homeostasis
- ✓ Hypercalciuria
- ✓ Any other known metabolic bone disease

Prevalence of Vitamin D Insufficiency in an Adult Normal Population

M.-C. Chapuy[1], P. Preziosi[2], M. Maamer[3], S. Arnaud[1], P. Galan[2], S. Hercberg[2] and P. J. Meunier[1]

[1]INSERM U. 403, Hôpital Edouard Herriot, Lyon; [2]ISTNA/CNAM, Paris; and [3]Laboratoire Innothéra, Arcueil, France

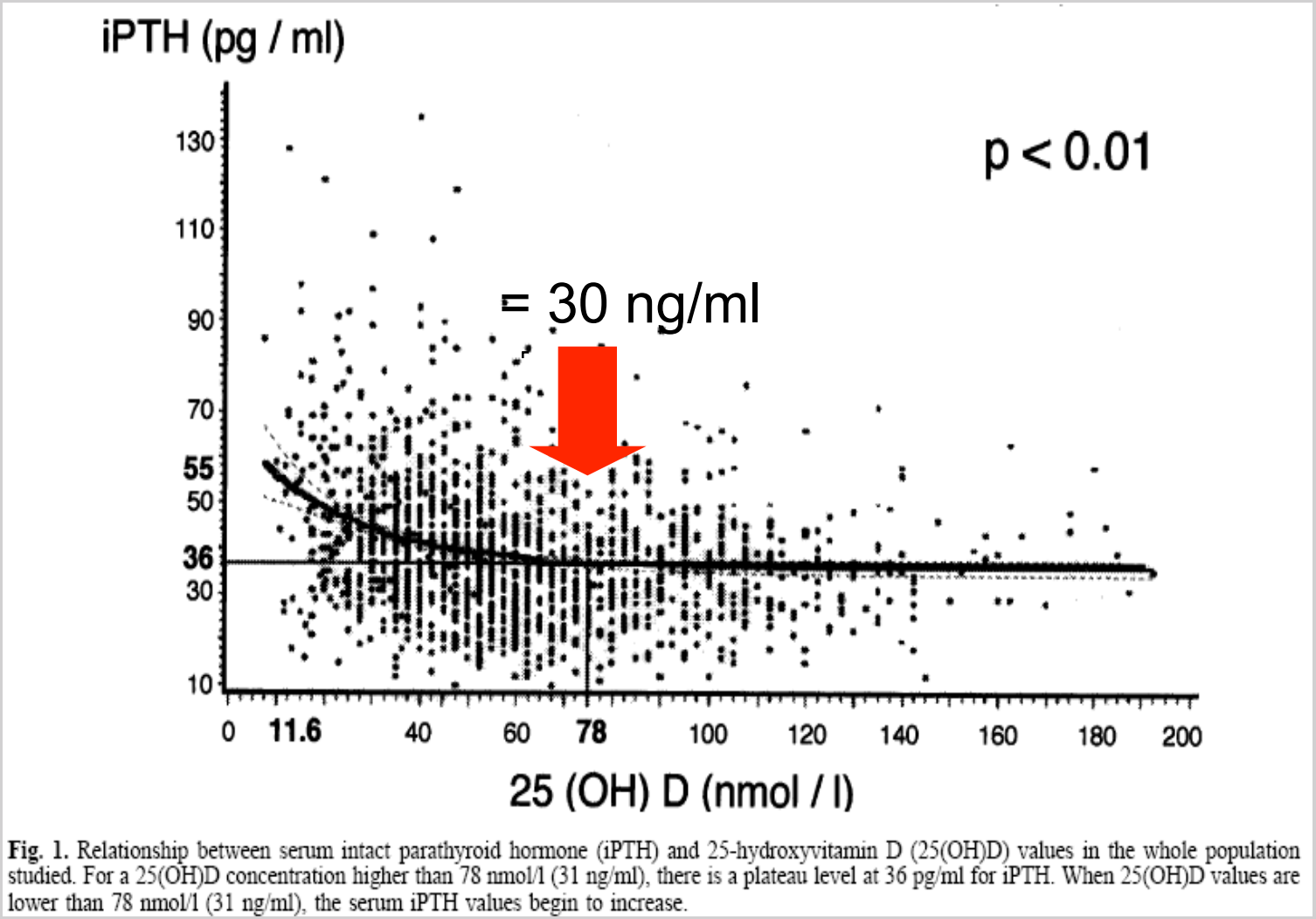

Fig. 1. Relationship between serum intact parathyroid hormone (iPTH) and 25-hydroxyvitamin D (25(OH)D) values in the whole population studied. For a 25(OH)D concentration higher than 78 nmol/l (31 ng/ml), there is a plateau level at 36 pg/ml for iPTH. When 25(OH)D values are lower than 78 nmol/l (31 ng/ml), the serum iPTH values begin to increase.

Osteoporos Int 1997

These studies are confounded by the lack of any prospective data that would track an individual's PTH level as the 25-hydroxyvitamin D levels is increased from 20 to 30 ng/mL.

Example:
Individual with a "normal" PTH level of 40 pg/mL when the 25-hydoxyvitamin D level is 20 ng/mL might show reduction to a PTH level 25 pg/mL when the 25- hydroxyvitamin D level is raised to 30 ng/mL.

[a] UL indicates level above which there is risk of adverse events. The UL is not intended as a target intake (no consistent evidence of greater benefit at intake levels above the RDA).

[b] Measures of serum 25OHD levels corresponding to the RDA and covering the requirements of at least 97.5% of the population.

[c] Reflects AI reference value rather than RDA. RDAs have not been established for infants.

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Normocalcemic Primary Hyperparathyroidism

*Natalie E. Cusano, Shonni J. Silverberg, and John P. Bilezikian**

Division of Endocrinology, Department of Medicine, College of Physicians & Surgeons, Columbia University, New York, NY, USA

Journal of Clinical Densitometry: Assessment of Skeletal Health, vol. 16, no. 1, 33–39, 2013

To be confident in the diagnosis of normocalcemic primary hyperparathyroidism, it would seem advisable to:

Ensure that the 25-hydroxyvitamin D level is greater than 30 ng/ml

Normocalcemic pts with high PTH levels will become hypercalcemic when 25- hydroxyvitamin D levels are raised to higher than 30 ng/ml

The correct diagnosis is **traditional hypercalcemic primary hyperparathyroidism** that is masked by the vitamin D deficiency

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Relationship between PTH and creatinine clearance

PTH rises out of the normal range until the creatinine clearance fell to less than 60 ml/min

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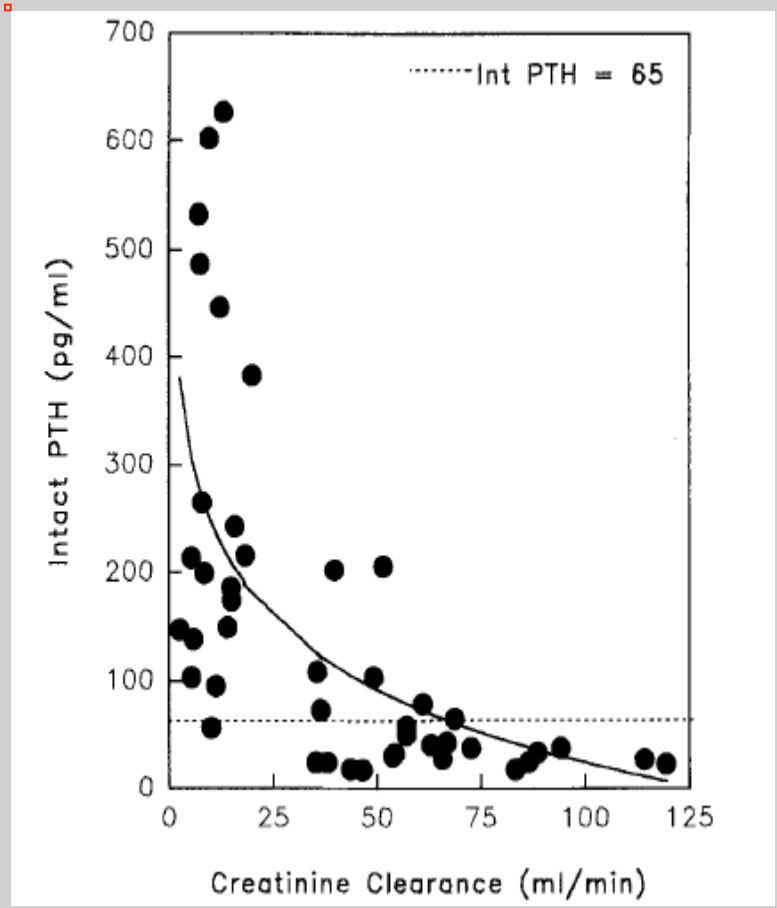

Fajtova et al. Calcif Tissue Int 1995

GFR <60 ml is associated with increased parameters of bone resorption

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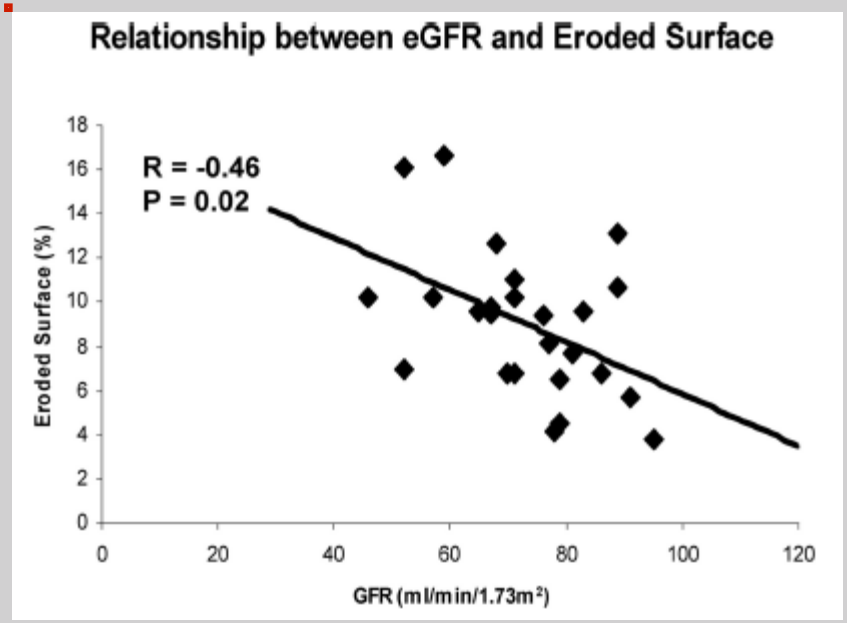
TABLE 4. Histomorphometry by renal function

	GFR <60 (n = 5)	GFR ≥60 (n = 25)	*P* value
Structural indices			
Cortical width (μm)	695 ± 184	626 ± 209	0.51
Cancellous bone volume (%; BV/TV)	22.1 ± 6.2	23.2 ± 7.0	0.75
Trabecular number (1/mm)	1.82 ± 0.23	1.93 ± 0.42	0.61
Trabecular separation (μm)	435 ± 92	424 ± 134	0.88
Trabecular width (μm)	121 ± 35	119 ± 25	0.89
Remodeling indices			
Osteoid surface (%)	25.2 ± 12.7	29.3 ± 12.6	0.52
Osteoid width (no. lamellae)	13.3 ± 1.3	13.5 ± 3.1	0.88
Mineralization lag time (d)	34 ± 14	50 ± 34	0.59
Mineralizing surface (%)	19.0 ± 11.3	19.3 ± 10.3	0.95
Mineral apposition rate (μm/d)	0.65 ± 0.09	0.63 ± 0.12	0.69
Bone formation rate ($\mu m^3/\mu m^2 \cdot d$)	0.13 ± 0.09	0.11 ± 0.06	0.63
Eroded surface (%)	12.0 ± 4.2	8.3 ± 2.7	0.02[a]
Activation frequency (cycles/yr)	0.62 ± 0.15	1.07 ± 0.62	0.25

Values represent mean ± SD. BV/TV, Bone volume/tissue volume.

[a] Statistically significant when controlling for multiple comparisons.



Walker et al. J Clin Endocrinol Metab, 2012

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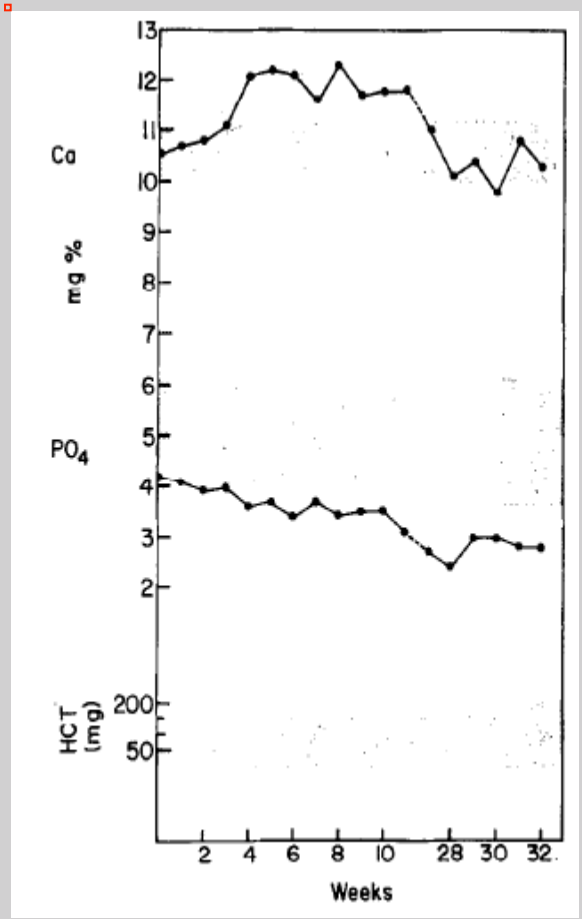
Thiazide-induced Parathyroid Stimulation

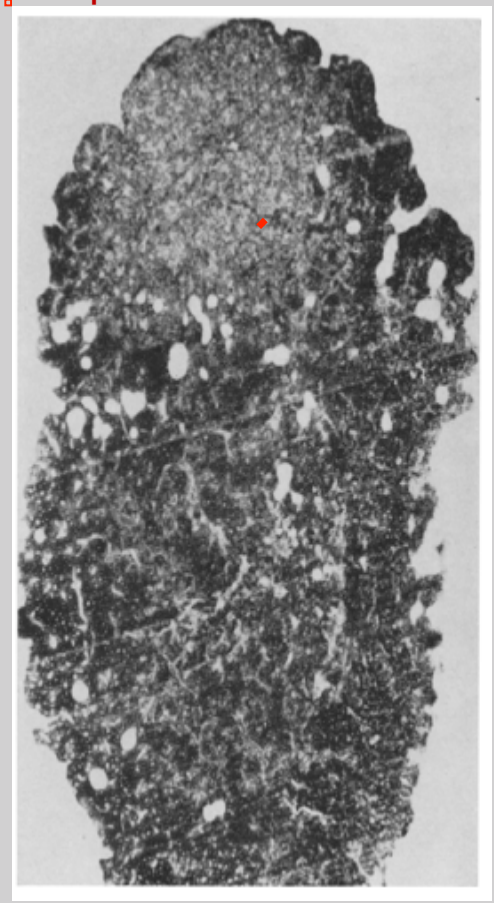
By Jack R. Pickleman, Francis H. Straus II, Marvin Forland and Edward Paloyan

Metabolism, Vol. 18, No. 10 (October) 1969

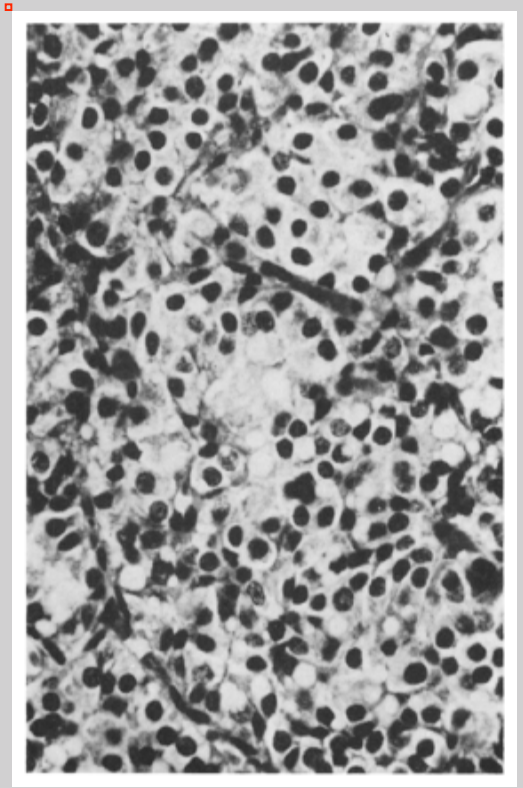
Serum Ca and P in dogs on increasing doses of HCT



Parathyroid from thiazide-fed dog
Note area of less dense cells at the top



Bulging, granular cytoplasm and vacuolar change



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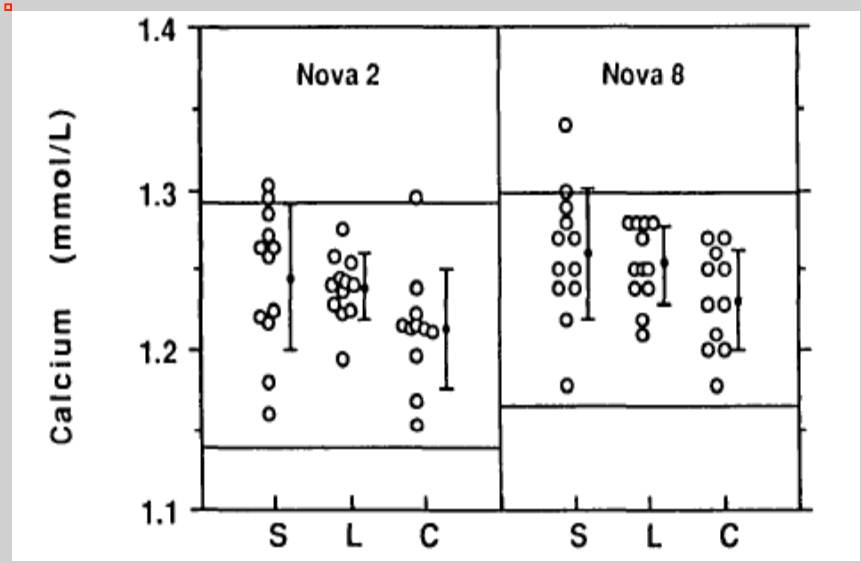
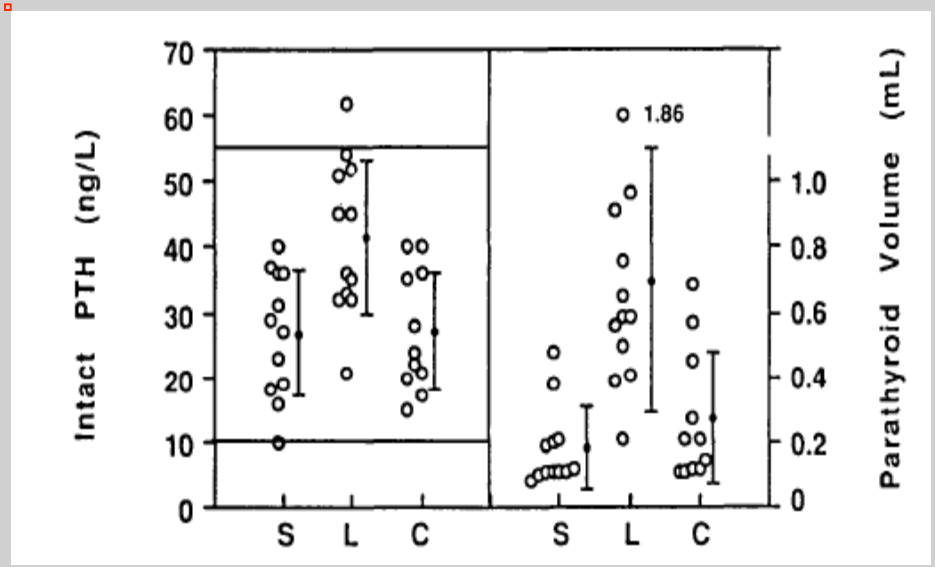
Lithium Treatment Increases Intact and Midregion Parathyroid Hormone and Parathyroid Volume*

LAWRENCE E. MALLETTE, KHALIL KHOURI, HIRAM ZENGOTITA,
BRUCE W. HOLLIS, AND SRINI MALINI

J Clin Endocrinol Metab 68: 654, 1989

Long term lithium treatment increases circulating PTH and causes parathyroid enlargement





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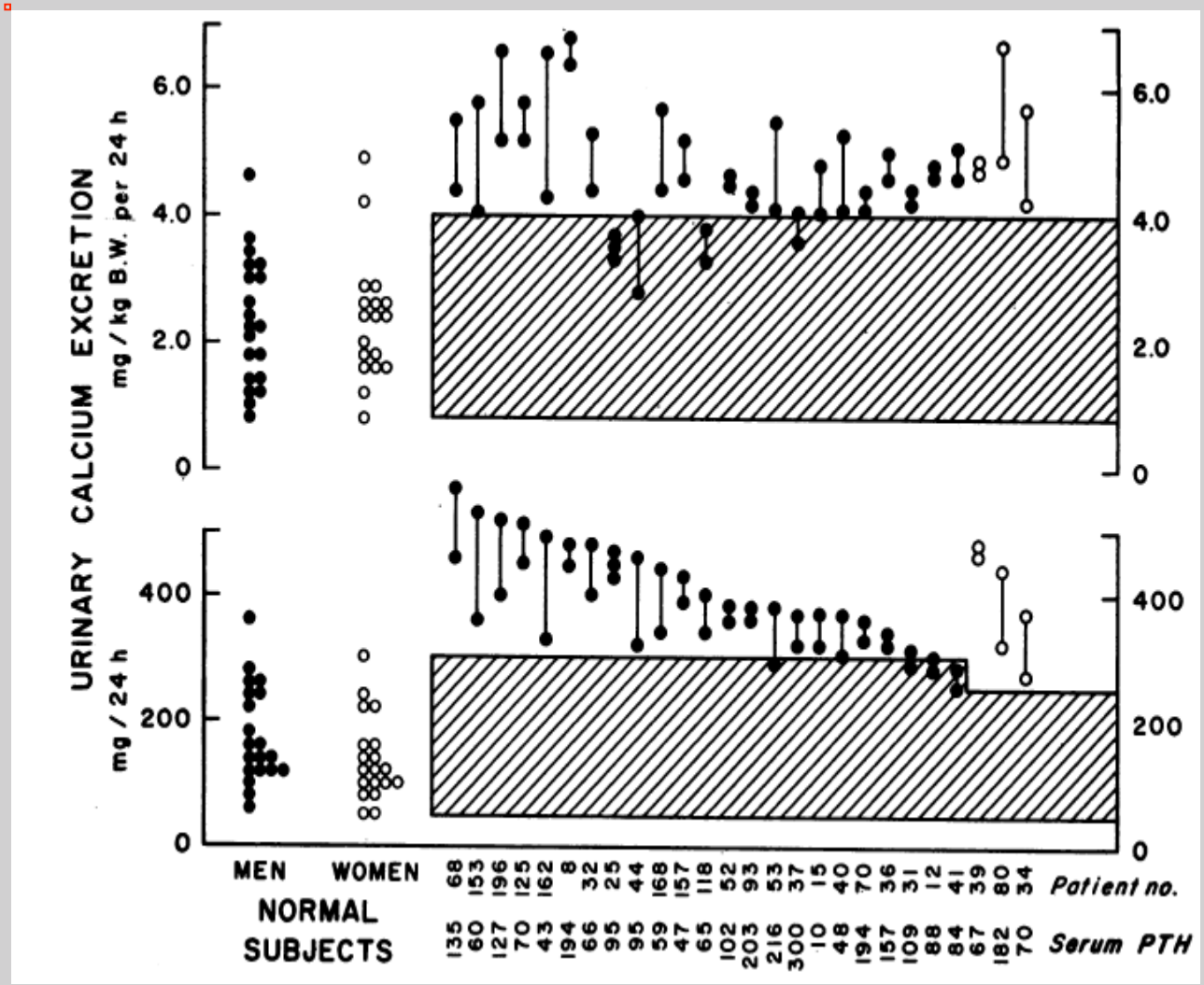
Evidence for Secondary Hyperparathyroidism in Idiopathic Hypercalciuria

FREDRIC L. COE, JANET M. CANTERBURY, JOHN J. FIRPO, and ERIC REISS

The Journal of Clinical Investigation Volume 52 January 1973



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Gastrointestinal disorders associated with calcium malabsorption

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J. Endocrinol. Invest. 31: 845-850, 2008

Role of calcium malabsorption in the development of secondary hyperparathyroidism after biliopancreatic diversion

J.A. Balsa[1], J.I. Botella-Carretero[1], R. Peromingo[2], I. Zamarrón[1], F. Arrieta[1], T. Muñoz-Malo[3], and C. Vázquez[1]

[1]Department of Endocrinology and Clinical Nutrition; [2]Department of Surgery; [3]Departemnt of Biochemistry, Ramón y Cajal Hospital, Madrid, Spain

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 14, Number 4, 1999
Blackwell Science, Inc.

Bone Loss in Celiac Disease Is Related to Secondary Hyperparathyroidism*

PETER L. SELBY,[1] MICHAEL DAVIES,[1] JUDITH E. ADAMS,[2] and E. BARBARA MAWER[1]