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Secondary Hypercalcemic Hyperparathyroidism

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Summary. A search was made for patients with associated secondary hyperparathyroidism and hypercalcemia: 22 such cases were found in the literature and 22 were recorded among 92 patients operated upon because of parathyroid disease. In the remaining 70 patients the effect of the operation on the serum calcium level was investigated: persisting hypercalcemia after the operation was found in 28 per cent of the cases.

The patients reporded in the literature possessed severe renal and skeletary changes and light microscopic evidence of parathyroid adenoma (2 cases), hyperplasia (15 cases), or hyperplasia and adenoma (5 cases).

The other 22 patients had histories of long-standing renal disease, most often chronic pyelonephritis, of varying severity. Skeletary roentgenograms were often normal. Morphologic examination of the parathyroids showed adenoma (6 cases) or hyperplasia (16 cases). Postoperatively, normal serum calcium level was found in 9 cases and persisting hypercalcemia in 13 (=59 per cent) cases. One patient possessed also a malignant α-cell insuloma and Zollinger-Ellison's syndrome.

It is suggested that secondary hyperparathyroidism may develop in patients with only slight or moderate impairment of renal function, that hypercalcemia occurs more often than previously believed in secondary hyperparathyroidism, and that some cases of secondary hyperparathyroidism previously, erroneously have been classified as primary hyperparathyroidism.

Introduction

Hypocalcemia is generally considered to be the most important factor in the development of secondary hyperparathyroidism. It has even been suggested that in cases in which it is difficult to differentiate between primary and secondary hyperparathyroidism, the presence of hypercalcemia definitely speaks in favour of the primary variant (Nordin, 1958). Albright and Reifenstein (1948) proposed the following steps in the evolution of secondary hyperparathyroidism: 1. kidney insufficiency, 2. phosphorus retention, 3. tendency to a low serum calcium level as an adjustment to the high serum phosphorus level, and 4. hyperplasia of the parathyroid glands to meet this tendency. This supposed sequence of events has been accepted for many years. However, the exact mechanism of induction of parathyroid hyperplasia in chronic renal disease (Potts, 1969) and the stimulator(s) of parathormone (PTH) secretion (Reiss and Canterbury, 1971) are still poorly known. Moreover, O'Riordan *et al.* (1970) could not find any correlation between the serum levels of calcium and PTH in untreated patients with chronic

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renal failure. In dogs with experimental renal insufficiency we have observed morphologically altered parathyroid glands and hypercalcemia, but no case of hypocalcemia (Boquist *et al.*, 1972). Thus, it is possible that hypocalcemia is of less importance in the development of secondary hyperparathyroidism than previously believed.

In a review of patients operated upon because of parathyroid disease we found 22 cases with histories of renal disease and elevated serum calcium level before the operation. Most of them were initially believed to represent primary parathyroid hyperfunction because the renal affection sometimes was rather inconspicuous and because the causal relationship between the parathyroid and the kidney disease seemed difficult to settle. A thorough investigation revealed that the renal disease in all cases had preceded the development of signs of parathyroid hyperfunction. Consequently, their parathyroid disease can be classified as secondary hyperparathyroidism, and because of the presence of hypercalcemia they have been included in a group called secondary hypercalcemic hyperparathyroidism, which is suggested as a new clinical entity, apparently comprising a number of cases which previously have been tought to have a primary parathyroid disease.

The present study represents: a) a literature review of all known cases of secondary hyperparathyroidism with associated hypercalcemia and b) an investigation of the 22 new cases mentioned above; in 4 of these more extensive clinical, laboratory and histopathologic data were obtained than in the others and these 4 cases are separately reported.

Normal Values

Where nothing else is mentioned, the following abbreviations and normal values are guilty: serum calcium (Sca) 4.2–5.2 mEq/l; serum phosphorus (Sp) 2.7–4.7 mg/100 ml; urinary calcium (Uca) <300 mg/day; alkaline phosphatase (alk.phosph.) 2–8 Buch & Buch U; serum creatinine (Scr) 0.6–1.1 mg/100 ml for males and 0.4–0.9 mg/100 ml for females; BUN 10–20 mg/100 ml; NPN 25–40 mg/100 ml; "concentration test"—urinary specific gravity after thirst during 12 hours >1.025; endogenous creatinine clearance (Ccr) (corrected to 1.73 sq. meters body surface area) 85–125 ml/min; maximal histamine response (females) 17.7 ± 1.6 mEq HCl/hour—basal secretory rate (females) 2.24 ± 1.76 mEq/hour.

Cases Reported in the Literature

In the literature we have been able to find reports of 22 patients with secondary hyperparathyroidism and associated hypercalcemia (Table 1). Only cases with long-standing renal disease and microscopically verified parathyroid disease have been included in the Table. Patients with hypercalcemia appearing after the administration of vitamine D or calcium, or in association with dialysis or renal transplantation, have been excluded.

All the 22 cases possessed severe derangement of renal function and marked skeletary changes (renal osteodystrophy). Data about the serum level of alkaline phosphatases were given in 18 cases, in all of which the level was elevated. Nephro- or urolithiasis were not reported. Only 7 patients were operated upon. The number of parathyroid glands from each patient that was examined light microscopically after operation or autopsy, varied from 2 to 5. The light microscopic findings included 2 cases of adenoma, 15 cases of hyperplasia, and 5 cases of hyperplasia and adenoma.

In addition to the patients presented in Table 1, brief reports without separate documentation have been given in the literature of secondary hyperparathyroidism and hypercalcemia: Richet *et al.* (1965) found one case of hypercalcemia among 35 uremic patients: Black (1967) observed 10 cases of hypercalcemia among 53 patients with generalized renal osteitis fibrosa; in a study of 225 uremic patients, Henning *et al.* (1968) recorded one case of hypercalcemia, 60 patients with hypocalcemia, and normal serum calcium level in the remaining patients; Katz *et al.* (1969) reported 9 cases of hypercalcemia among 195 uremic patients.

New Cases

The region investigated comprises $2^1/_2$ counties with in all about 700000 inhabitants. The record files in the various hospitals in this region from the years 1958–1970 were investigated in a search for patients operated upon because of hyperparathyroidism. In all, 94 such patients were found two of them have been separately reported (Boquist *et al.*, 1971) and have not been included in the present work. Their records were reviewed and the histopathologic specimens obtained at biopsy, operation or autopsy were re-examined. The information gathered in this way indicated that signs of renal disease clearly preceded the development of hyperparathyroidism in 22 of the cases (3 males and 19 females).

Four of the 22 patients had been subjected to more extensive clinical, laboratory and histopathologic examinations than the others. These 4 patients are presented in Table 2 and in separate case reports. The remaining 18 patients had histories of long-standing, recurrent renal disease for which some of them had been hospitalized. Sufficient laboratory data on renal function were lacking in some of these cases, which are presented in Table 3.

The initial diagnosis in 20 of the 22 cases was primary hyperparathyroidism. In 13 (= 59 per cent) of the patients the parathyroid operation was unsuccessful in that the hypercalcemia remained postoperatively. Normal serum calcium level after the operation was found in 9 patients. For comparison, the number of unsuccessful operations was studied also in the 70 (out of 94) patients who had a parathyroid disease other than secondary hypercalcemic hyperparathyroidism and who had not been reported previously; 28 per cent of the operations were not successful.

Report of New Cases

Case 1. Woman, born in 1926, with histories of recurrent urinary tract infection since about 1940. From 1952–1957 she consumed large amounts of analgesics containing phenacetine. The urogram was normal in 1950. Oedema, hypertension and tiredness appeared for the first time in 1956 and during the following years signs of progressive renal failure developed.

The essential findings during the following years were: 1958: Symptoms of peptic ulcer. Blood pressure 175/105. Concentration test 1.017. 1959: Scr 1.7. Sca 5.1. Sp 2.2. Alk. phosph. 2.0. 1963: Roentgenograms showed peptic ulcer in duodenum. 1964: Sca 5.3. Sp 2.2. Alk. phosph. 3.4. 1965: Scr 4.7. Proteinuria. Anemia. Maximal histamine response was 24.0 and the basal secretory rate 2.3. Gastric resection (Billroth II) was performed because of hematemesis and melena. 1966: Relaparotomy and vagotomy were carried out because of hematemesis.

1967: At exploration on October 12, four parathyroid glands were identified, and three and a half of them were removed. Light microscopic examination showed chief cell hyperplasia (Fig. 1). Relaparotomy on October 31, because of melena, disclosed an ulcer in the stoma; the gastroenteroanastomosis was resected and a new gastrojejunostomy was performed. Maximal histamine response after the operation was 43.1 and the basal secretory rate 0.0.

Table 1. Literature review: secondary hyperparathyroidism with associated hypercalcemia

Author(s)	Sex, age	Renal disease		Blood pressure	Laboratory findings			Parathyroid morphology	Other findings
		Duration (years)	Diagnosis		Sca (mg/100 ml)	Sp (mg/100 ml)	BUN or NPN		
1. Hubbard and Wentworth (1921)	♂, 20	—	Interstitial nephritis	—	11.9–13.4	—	—	H+A	Mc
2. Duken (1928)	♂, 8	> 7	Hydronephrosis, Chron. pyelonephritis	105/75	10.1–16.0	6.0–9.0	NPN 107	H	—
3. Smyth and Goldman (1934)	♂, 14	> 2	Hydronephrosis, Chron. pyelonephritis	110/56	10.5–11.9	10.9–16.0	NPN 80–333	H	Mc
4. Price and Davie (1937)	♂, 14	>12	Interstitial nephritis	120/75	12.5–13.6	5.0–6.5	BUN 318–397	H	—
5. Herbert *et al.* (1941)	♀, 40	4	Renal sclerosis	180/110	11.7	7.8	BUN 300	H	Mc
6. Snapper (1949)	♀, 14	6	Chron. glomerulonephritis	172/110	8.3–12.8	8.0–10.0	BUN 27–100	H	—
7. Dreskin and Fox (1950)	♂, 27	21	Hydronephrosis, Chron. pyelonephritis	116/44	9.1–11.5	7.2–8.7	NPN 83–103	H	Mc
8. Richards (1951)	♀, 44	22	Chron. nephritis	200/100	10.9–13.3	8.7–11.9	BUN 158–365	H	Mc
9. Joiner and Thorne (1953–1954)	♀, 30	22	Chron. interstitial nephritis	106/55	9.8–11.4	3.6–7.4	BUN 40–400	H	Mc
10. Lee *et al.* (1955)	♂, 30	12	Interstitial fibrosis, Nephrocalcinosis	—	9.2–11.3	7.2–16.9	BUN 165	H+A	Peptic ulcer
11. Brookfield *et al.* (1955)	♂, 26	> 2	Chron. pyelonephritis, Hypoplasia of right kidney	130/70	9.0–12.0	10.0–12.0	NPN 100–350	H	Mc
12. Uehlinger (1956)	♀, 29	—	Interstitial familial nephritis	110/60	13.0	20.0	NPN 300	H	—

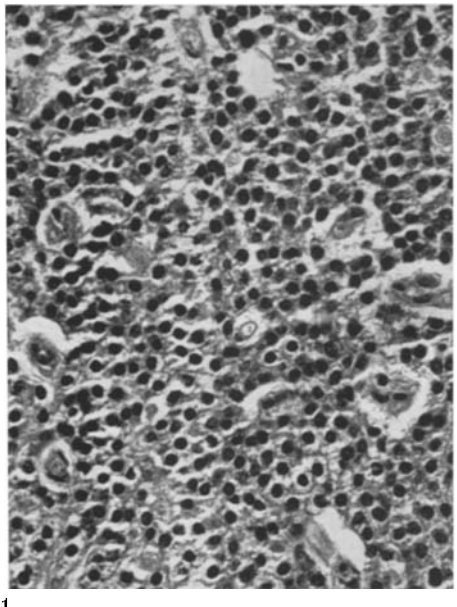
13. Chernoff and Hartroft (1956)	♀, 42	>10	Chron. glomerulonephritis, Acute and chron. pyelonephritis	210/120	9.6–11.5	5.1–21	NPN 347	H	Peptic ulcer
14. Goldberg and Torack (1960)	♀, 59	—	Chron. pyelonephritis	180/100	10.5–11.1	4.8–8.3	BUN 49–97	H+A	—
15. Case Rec. Mass. Gen. Hosp. (1963)	♀, 36	11	Chron. glomerulonephritis, Chron. pyelonephritis	150/105	10.0–13.2	6.3–6.6	BUN 144	A	Thyroid carcinoma
16. Fordham and Williams (1963)	♂, 22	19	Contracted kidneys	180/110	10.0–10.8	6.5–8.4	BUN 71–86	H	—
17. Wilson *et al.* (1965)	♂, 19	10	Small scarred kidneys	—	9.8–12.2	13.2	BUN 62–112	H	Mc
18. Golden *et al.* (1965)	♀, 49	—	Chron. pyelonephritis	—	9.2–11.0	7.2–12.0	BUN 94–147	H+A	—
19. Posey and Ritchie (1967)	♀, 28	25	Chron. pyelonephritis	Elevated	7.8–11.3	4.8–12.3	BUN 110–195	H	Mc
20. Seifert and Seeman (1967)	♀, 24	>10	Chron. pyelonephritis	—	10.8	15.5	BUN 180	H	Mc
21. Davies *et al.* (1968)	♂, 48	7	Polycystic kidneys	—	12.7	2.0	BUN 45–48	A	—
22. Gill *et al.* (1969)	♀, 49	>30	Small kidneys	136/90	10.4–11.4	9.8–11.8	BUN 111	H+A	Breast carcinoma

H=Hyperplasia; A=Adenoma; Mc=Metastatic calcification.

Table 2. Patients with chronic pyelonephritis operated (parathyroidectomy) because of parathyroid disease and hypercalcemia

Pat. No., sex, age at op. (years)	Duration of renal disease (years)	Urolithiasis	Skeleton roentgenograms	Preoperative Findings							Parathyroid morphology	Sca after op.	Other findings
				Sca	Sp	Uca	Alk. phosph.	Scr	BUN	Blood pressure			
1. 41, ♀	27	+	Normal	5.7	0.6	269	8.0	5.5	40	190/120	H	NC	Malignant insuloma; Zollinger-Ellison's syndrome
2. 38, ♀	11	+	Normal	6.5	1.5	248	4.7	0.9	13	170/110	H	HC	—
3. 55, ♂	27	+	Normal	6.1	2.0	180	7.1	2.1	48	130/90	A	NC	Peptic ulcer in duodenum
4. 62, ♀	32	—	Decreased mineralization of hands	6.3	1.5	440	17.0	1.0	—	200/120	H	HC	Pernicious anemia

H=Hyperplasia; A=Adenoma; NC=Normocalcemia; HC=Hypercalcemia.



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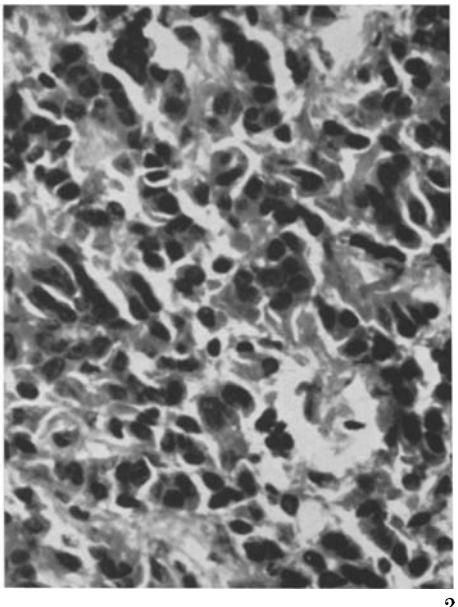

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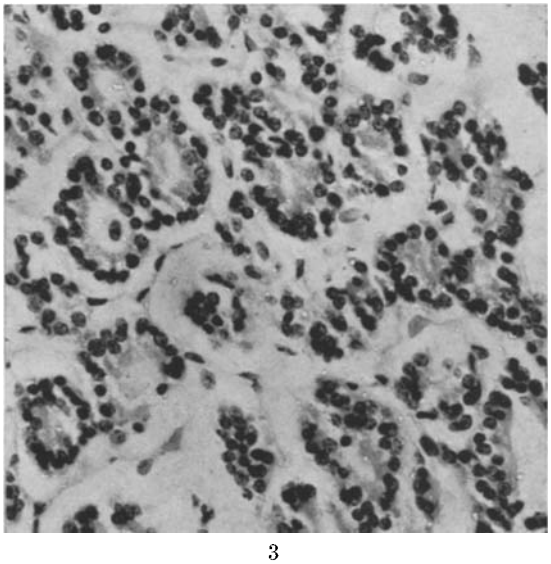

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Fig. 1. Photomicrograph of hyperplastic parathyroid gland showing monomorphous light chief cells, absence of fat cells and rich vascularization. Hematoxylin and eosin; original magnification $\times 40$

Fig. 2. Photomicrograph of malignant insuloma composed of α_1- and α_2-cells. Hematoxylin and eosin; original magnification $\times 100$

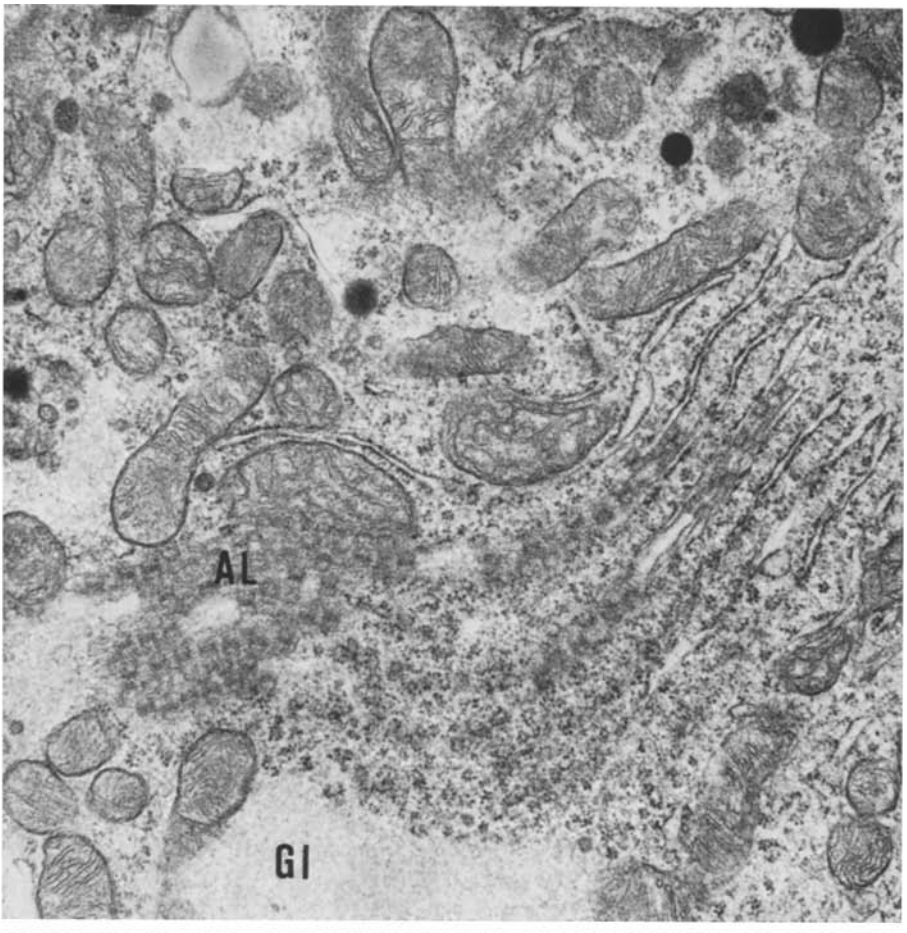
Fig. 3. Photomicrograph of hyperplastic parathyroid gland showing light chief cells in acinar arrangement. Hematoxylin and eosin; original magnification $\times 60$

Table 3. Patients with long-standing renal disease operated (parathyroidectomy) because of parathyroid disease and hypercalcemia

Pat. No., sex, age at op. (years)	Renal disease			Skeleton (biopsy, X-ray)	Preoperative findings								Parathyroid morphology	Postoperative findings	
	Duration (years)	Diagnosis (biopsy, X-ray)	Urolithiasis		Sca	Sp	Uca	Alk. phosph.	Scr	BUN or NPN	Concentration test	Blood pressure		Sca after op., follow-up	Renal function, concentration test
1. ♀, 68	—	—	+	—	7.2	1.8	—	—	1.3	—	—	—	H	HC 2 y, 1 m	—
2. ♀, 41	—	—	+	—	5.6	2.5	272	—	0.9	—	—	—	H	HC 1 y, 9 m	
3. ♀, 59	10	—	—	Osteitis fibrosa	6.6	2.7	—	12.1	—	NPN 80	1.017	240/140	A	NC 10 y, 6 m	1.010 ↓
4. ♀, 50	20	Chron. pyelonephritis	+	—	6.3	2.2	282	—	0.9	—	—	—	A	NC 4 y, 8 m	—
5. ♀, 39	—	Medullary sponge kidney	—	N	7.4	1.2	—	5.0	0.8	—	1.013	—	H	HC 2 y, 2 m	—
6. ♀, 72	>23	—	+	—	5.9	2.9	88	5.6	—	—	1.009	—	A	HC 13 y, 1 m[a]	—
7. ♀, 52	>11	Chron. pyelonephritis	+	N	6.1	1.6	510	N	0.9	—	1.027	180/80	H	HC 5 y, 4 m	1.021↓
8. ♂, 52	16	Chron. pyelonephritis	+	—	6.3	1.0	—	—	1.1	—	—	—	A	NC 2 y, 5 m	—
9. ♀, 49	>40	—	+	N	6.4	1.3	361	5.6	0.9	—	1.014	215/115	H	NC 6 y	1.018↑

10. ♀, 52	>10	Chron. pyelo-nephritis, Hydro-nephrosis	+	N	8.2	2.3	369	10.5	1.2	—	1.009	215/130	A	HC 7 y	1.013 ↑
11. ♀, 62	38	Chron. pyelo-nephritis	+	Decreased minerali-zation	6.7	2.5	350	142	1.9	—	1.017	—	H	HC 1 y, 2 m	1.017
12. ♀, 68	37	Chron. pyelo-nephritis	+	—	5.7	1.4	—	7	0.6	—	—	—	A	NC 1 y, 2 m	—
13. ♀, 34	—	Chron. phelo-nephritis	+	—	5.5	1.4	—	3	1.2	—	—	—	H	HC 10 m	—
14. ♀, 72	>13	—	+	Decreased minerali-zation	6.8	N	—	↑	2.0	—	—	—	H	HC 5 y, 5 m	—
15. ♀, 46	—	Chron. pyelo-nephritis	—	N	5.5	2.1	281	3.9	2.0	BUN 37	1.013	210/135	H	HC 5 y, 10 m	1.008 ↓
16. ♀, 48	—	—	—	N	5.7	2.2	312	4.9	—	—	1.016	—	H	NC 6 m	1.019 ↑
17. ♀, 63	8	Chron. pyelo-nephritis	—	Decreased minerali-zation	6.1	—	—	3.5	1.0	BUN 24	1.023	210/115	H	HC 1 y, 2 m	1.018 ↓
18 ♀, 49	—	—	+	N	5.5	1.6	213	4.2	—	—	1.018	210/110	H	NC 3 m	—

N=Normal; H=Hyperplasia; A=Adenoma; HC=Hypercalcemia; NC=Normocalcemia; ↑=increased; ↓=decresaed; y=years; m=months.
[a] Hypercalcemia 13 years after the operation.



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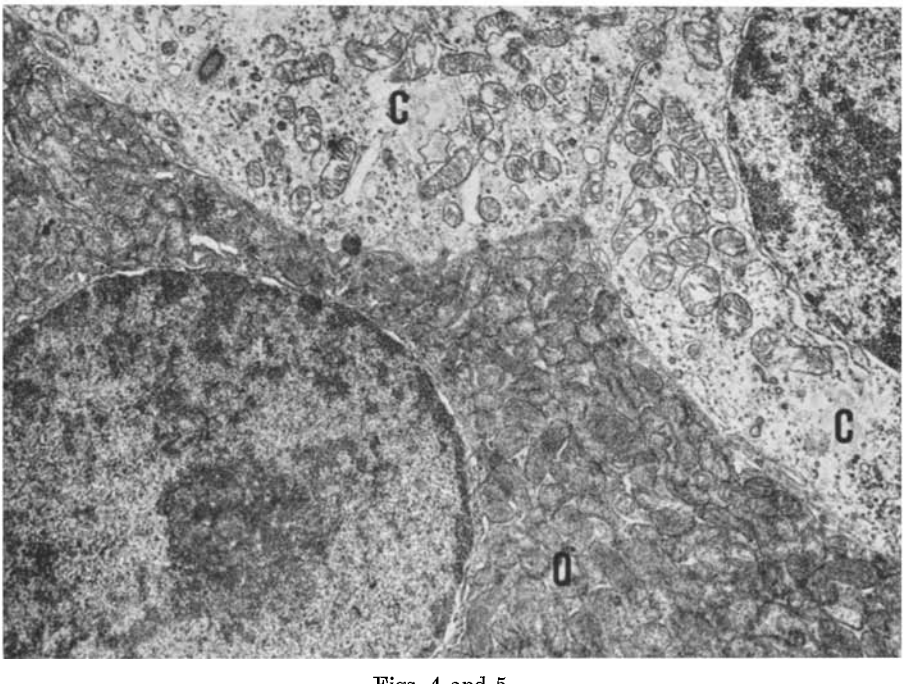

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Figs. 4 and 5

1969: Relaparotomy because of recurrent hematemesis; a tumor was removed from the pancreas; light microscopic examination showed a polymorphous insoluma composed of α_1- and α_2-cells (Fig. 2). After the operation the renal insufficiency progressed rapidly and the patient died on April 25.

Gross and microscopic postmortem findings included: Chronic pyelonephritis; peptic ulcers in duodenum and jejunum hyperplasia of thyroid, adrenals and one remaining parathyroid gland; metastases from a malignant insuloma in lymph nodes and pancreas.

Case 2. Woman, born in 1932, with symptoms of chronic renal disease since pregnancy in 1959 and constant proteinuria since 1960. A marked transitory decrease of renal function because of pyelonephritis was observed in 1969; Ccr was initially 65, two weeks later 91, and three months later 104.

Examinations in 1969 disclosed hypertension (220/140), hypercalcemia (4.8–6.5) and hypophosphatemia (1.5–2.1). Angiograms and biopsy showed chronic pyelonephritis in both kidneys and nephrocalcinosis on the right side. Concentration test was 1.015.

At operation on September 1, 1970, the lower left and right parathyroid glands were removed. Light microscopic examination showed parathyroid hyperplasia (Fig. 3). The patient is alive and Sca has been elevated at repeated determinations after the operation (5.4 in November 1971). Concentration test was 1.016 in March 1971.

Case 3. Man, born in 1914, who was hospitalized for the first time in 1942 because of renal disease; blood pressure 150/95, NPN 38–49, proteinuria, microscopic hematuria, bacteriuria, and concentration test 1.020. During the following years signs of slowly progressing renal disease were found. Roentgenograms showed irregularly contracted kidneys and hydronephrosis. In 1947 the blood pressure was 170/110. Peptic ulcer in the duodenum was diagnosed in 1952 and gastric resection (Billroth II) was performed two years later. In 1963 the concentration test was 1.012 and Ccr 64. Hypercalcemia (5.3–6.1) was recorded for the first time in January 1969. Sp was min. 2.0 and Uca max. 180. Renal angiography and biopsy were performed in 1969 and the diagnosis chronic pyelonephritis was settled. At operation on December 16, 1969, one enlarged parathyroid gland was removed. Light and electron microscopic examination showed adenoma, mainly composed of chief cells (Figs. 4 and 5). Sca has been normal (4.3–4.7) at repeated determinations after the operation. Concentration test was 1.011 in May, 1971.

Case 4. Woman, born in 1908, who had repeated periods of proteinuria during childhood and adolescence. Nephritis was recorded in 1928. In 1945 pernicious anemia was diagnosed. Since 1956 she has been treated with vitamine B 12. In 1965 the blood pressure was 200/120, Scr 1.1 and concentration test 1.021. Suspicion of hyperparathyroidism arose in 1969. The laboratory findings included: Sca max. 6.3, Sp min. 1.5, Uca max. 440, alk. phosph. max. 17, Scr 1.4, Ccr 77, concentration test 1.022. Cortisone administration had no effect on Sca.

At operation on June 30, 1969, and subsequent light microscopic examination of resected material, nodular colloid goiter and parathyroid hyperplasia were diagnosed. After the operation there was an initial decrease of Sca to 4.0 and then a slow return to hypercalcemic levels.

Discussion

The cases of secondary hyperparathyroidism with associated hypercalcemia which were reported in the literature (Table 1) possessed severe renal damage

Fig. 4. Electron micrograph of chief cell cytoplasm in parathyroid adenoma showing glycogen (*Gl*), electron dense rounded particles, mitochondria, free ribosomes, rough-surfaced lamellar endoplasmic reticulum, and annulate lamellae (*AL*). Glutaraldehyde and osmium tetroxide fixation, uranyl acetate and lead citrate stain; original magnification ×31000

Fig. 5. Electron micrograph of parathyroid adenoma showing chief cells (*C*) with low cytoplasmic electron density and a moderate number of mitochondria, and one oxyphil cell (*O*) with an abundance of mitochondria. Glutaraldehyde and osmium tetroxide fixation, uranyl acetate and lead citrate stain; original magnification ×11500

and renal osteodystrophy; the associated hypercalcemia was most often briefly mentioned and not discussed. The new cases (Tables 2 and 3) had slight or moderate renal impairment of long duration. The skeletary roentgenograms were usually normal. The serum phosphorus level was often decreased in the new patients, whereas hyperphosphatemia was recorded in most cases in Table 1. This difference is probably due to a more severe renal failure in the latter than in the former cases, since it is known that the serum phosphorus level is elevated in advanced renal insufficiency.

Although the association of secondary hyperparathyroidism with chronic renal disease is well known, less attention has previously been paid to the development of parathyroid hyperfunction in cases with mild impairment of renal function (Bilinsky, 1968). The results of the present study denote that secondary hyperparathyroidism may occur also in patients with slight or moderate renal impairment, if this is of sufficiently long duration, and that hypercalcemia is more common in secondary hyperparathyroidism than previously believed. It is probable that some patients with secondary hypercalcemic hyperparathyroidism previously, erroneously have been thought to have a primary hyperparathyroidism because of inconspicuous renal symptoms and because of difficulty to settle whether the renal or the parathyroid disease developed first.

The cause of the hypercalcemia in the cases under discussion is not clear. It is generally considered that the serum calcium level is low or normal in secondary hyperparathyroidism and that the hypocalcemia is a stimulus to hyperplasia of the parathyroid glands. No hypocalcemia could be demonstrated in our cases. When, signs of hyperparathyroidism appeared after many years of renal disease, the serum levels of calcium were clearly elevated denoting that the hypercalcemia probably was a result of hyperfunction with increased secretion of PTH. No PTH determinations were performed in our cases but increased levels of this hormone have been reported in patients with renal disease. Highman and Hamilton (1937) observed a high concentration of PTH when serum from uremic patients was injected into rabbits. Increased level of serum PTH has been found in chronic renal disease (Berson and Yalow, 1966) in secondary hyperparathyroidism (Potts *et al.*, 1969) and in 90 per cent of patients undergoing dialysis (O'Riordan *et al.*, 1970). In experimental studies on dogs with advanced renal insufficiency, a twenty-fold increase of the PTH-level was reported by Slatopolsky *et al.* (1971).

Serum calcium determinations were repeatedly performed in the new cases; no case of hypocalcemia was recorded prior to parathyroidectomy. Thus, as far as can be concluded from these determinations, it seems that the hypothesis that hypocalcemia is a stimulus to parathyroid hyperplasia, not is valid for these cases. The factor or factors responsible for the development of parathyroid hyperfunction in the new cases are not known, but it is believed that the factor or factors emanate from, or are activated by the insufficiently functioning renal parenchyma. It is worth to mention that the metabolism of vitamine D is impaired in patients with renal insufficiency (Avioli *et al.*, 1968; Potts *et al.*, 1969) which might lead to disturbances in calcium metabolism and parathyroid function, and recent evidence suggests that the kidney produces a factor of hormonal nature which is necessary for the activity of vitamine D (Lawson *et al.*, 1971).

Parathyroid hyperplasia was more frequent than adenoma in the cases collected from the literature. Among the new patients there were 16 cases with hyperplasia and 6 with adenoma. So-called light chief cells were predominating in both hyperplastic and adenomatous parathyroid glands. Annulate lamellae (Boquist, 1970) were only found in adenomatous parathyroid tissue.

A high frequency of chronic pyelonephritis was found in the present study. This conforms to what is known from other reports of secondary hyperparathyroidism (Pollak *et al.*, 1969).

Patient No. 1 had a malignant insuloma composed of α_1- and α_2-cell and a Zollinger-Ellison's syndrome. Parathyroid disease occurs rather often in association with this syndrome, usually without evidence of preceding renal failure. However, one patient with renal disease and Zollinger-Ellison's syndrome has been reported in the literature (Debray *et al.*, 1965). The role of the pancreas in the regulation of calcium metabolism has not been elucidated, but it is known that glucagon decreases the serum calcium level without interaction of calcitonin (Tanzer *et al.*, 1970). No determination of the serum glucagon level was performed in Case No. 1. Inasmuch as α_2-cells of normal pancreatic islets are known to produce glucagon, it is, however, possible that there was an increased production of glucagon in this case, which could have had a hypocalcemic effect; this might lead to secondary hyperfunction of the parathyroid glands. Paloyan *et al.* (1967a) have suggested an interaction between glucagon, PTH and calcitonin at the level of renal function. In a retrospective review of material obtained at autopsy from 15 cases of parathyroid adenoma and carcinoma, Paloyan *et al.* (1967b) observed a high incidence of islet hyperplasia.

Fifty-nine per cent of the new patients remained hypercalcemic after parathyroidectomy which may be due to a persisting stimulation from or *via* the kidneys to parathyroid hyperfunction with associated hypercalcemia. Sufficient data for an evaluation of renal function after the operation on the parathyroid glands, were available only in some of the new cases; both increased and decreased functional capacity of the kidneys were found. In primary hyperparathyroidism it has been found that the renal function often continues to deteriorate also after adequate parathyroid operation (Hellström and Ivemark, 1962; Britton *et al.*, 1971).

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