ACUTE THYRO-PARATHYROTOXICOSIS

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EVERYBODY is familiar with the dreadful "thyrotoxic storm". Very few instead know the "parathyroid storm", that is the crisis which follows the abrupt overproduction of parathormone with consequent sudden rise of the blood calcium which, in its turn, produces the characteristic syndrome of calcium intoxication.

The "parathyroid crisis" is usually the consequence of two conditions: sudden evolution of a chronic hyperparathyroidism, or a primary acute hyperparathyroidism, idiopathic or symptomatic of functional overactivity of the gland.

In the first case the diagnosis is made easier by the pre-existence of signs of bone demineralisation of the Recklinghausen type, of renal stones, of relapsing gastric ulcers or by the presence of a palpable neck mass. Lemann and Donatelli collected 46 of such cases up to 1964.

On the other hand, "primary acute parathyrotoxicosis" is much less common and much more difficult to recognise, because the acute calcium intoxication is a very complicated syndrome, with the following symptoms:

1. *Nervous symptoms* such as extreme neuro-muscular fatigue and hypotonia, personality and behaviour changes, drowsiness, lethargy and, eventually, coma;

2. *Gastro-intestinal symptoms* such as severe anorexia with aversion to food and intractable vomiting, abdominal pains and constipation;

3. *Renal signs* such as polyuria, polydipsia, renal insufficiency eventually progressing to uremia;

4. *Cardiac signs* such as tachycardia and arrhythmias, and, eventually, sudden heart failure or block;

5. *Biochemical signs* such as sudden hypercalcemia over 15-20 mg./100 ml., hypophosphatemia and, sometimes, high serum phosphatases.

By contrast we do not find the signs of chronic hyperparathyroidism, that is bone cysts and metastatic organ calcinosis, though slight signs of incipient bone demineralisation and kidney microcalcinosis may be often suspected.

There are however cases—and we had recently the fortune to describe a typical one

(Austoni, *et al.*, 1964)—in which there is a "concomitant acute and primary thyro-parathyro-toxicosis" and in such cases the resulting syndrome is even more complicated and difficult to diagnose and to treat.

This last condition is not only a rare, autonomous clinical entity which deserves to be fully described, but also a very important emergency condition, which requires outstanding diagnostic and therapeutic effort to prevent death, since it must be quickly recognized so that surgery can be immediately performed. In fact only the ablation of the hyperfunctioning glands can bring about recovery.

Case Report

A 22-year-old white male started showing some sign of hyperthyroidism and some personality changes in the autumn of 1963. In November there was a worsening of the condition: a sudden increase in nervousness, tachycardia and temperature (37.3°-37.6°) occurred. An episode of persistent vomiting called attention to the loss of weight which had been of 6 kg. in a few weeks. Polyuria, polydipsia and anorexia were also noted. At this time the picture of hyperthyroidism seemed so well defined (BMR + 32%) that the patient was treated, to no avail, with anti-thyroid drugs. There were also an enlargement of the right lobe of the thyroid and a mild right gynecomastia, but no ocular signs. In December he was admitted to our hospital as an emergency because of persistent vomiting, severe anorexia and some obsessional features.

On admission he was dehydrated and had azotemia. He had lost another 10 kg. in one month and showed severe muscular wasting and weakness, but in spite of this he showed marked restlessness and agitation. His personality and his behaviour were now clearly obsessional. The very thought of food caused him to vomit. The administration of high doses of tranquilizers, barbiturates and artificial hibernation were of no avail. Vomiting, polyuria, anorexia and fever kept on wasting his reserves.

At this point he was repeatedly treated with thiouracil mercaptoimidazole, p-oxipropiophenone and barbiturates in spite of the fact that a thyroid uptake test showed the existence of a block in the iodine trapping mechanism. There were however a BMR of + 49%, an elevated PBI (25-32 γ /100 ml.) and low blood cholesterol (103 mg./100 ml.) (see also in Table A). At this point another crisis of hyperthermia (39° C), tachycardia, agitation, vomiting, polyuria, and aching in the extremities made the situation desperate: in two months, in crisis after

TABLE A

BLOOD

	Na+ mEq./l	K+ mEq./l	Cl- mEq./l	Ca++ mg./ 100 ml.	P mg./ 100 ml.	Alk. Phos- phatase Bodan- sky Units	NPN mg./ 100 ml.	PBI γ/ 100 ml.	Cholest. mg./ 100 ml.	URINE Ca (mg./24h)
Dec. 9, 1963	144	3.75	94				88	25.2		
" 24	143	3.93	96				56			
Jan. 3, 1964	140	3.40	98	11.4	2.70	4.5	30	32.7	121	505
" 7				14	2.90					491
" 13	146	4.12		12.6	2.85					811
" 14				13.8	3.66					734
" 17		4.55		13.4	6.20					355
" 20		4.68		13.3	6.40	3.5	138			87
" 21	141	4.55	105	12.8	7.00		140			206
" 22	140	4.50	102		7.80		170			
" 22	SURGERY: Subtotal thyroidectomy and parathyroidectomy									
" 22				10.8			130			
" 23	144	3.66		11.0	4.30		82			353
" 24	145	3.47	98	10.2	4.40		59			369
" 25	144	3.66		9.8	2.90		38			252
" 27	141	4.13		9.6	2.00		20	13.0	125	288
Feb. 4	145	4.12		10.0	3.70	4.5	18	13.0	234	202
" 13	144	4.50	98	11.0	4.70			9.3	247	216
" 14	DISCHARGED with replacement therapy of thyroid and dihydrotachysterol									
" 28	144	4.31	98	8.0	4.20	2.5	12		260	
Mar. 25				10.6	4.10			8.7	159	75

FIG. 1.—Thyroid section (x57) at the border between the adenomatous nodule and an area of micro- and macrofollicular hyperplasia.

crisis, the patient had lost 30 kg. in weight; it was clear, furthermore, that anti-thyroid therapy was of no avail, if not harmful. The problem seemed to be insoluble and the prognosis was getting worse and worse.

Nevertheless, re-evaluating several diagnostic possibilities, one of the initial symptoms was taken into special consideration, namely the polyuria. This symptom had been lost sight of in the critical assessment of the illness mainly because of the large amount of intravenous fluids administered (2-3 litres/day). It was however always present together with a low specific gravity of the urine (1016). The suspicion arose that we were dealing with a polyuria secondary to hypercalcemia. A Sulkowitch test and

subsequent blood calcium determinations confirmed the suspicion. Further studies showed that, with a calcium intake approximately zero, there was a daily loss of 500-600 mg. In spite of this fact no signs of skeletal rarefaction were present except for a few, ill-defined signs of osteoporosis. The hypercalcemia was not modified by corticosteroids or by chelating agents (EDTA and high doses of citrates). The polyuria was not altered by ADH administration or by fluid restriction. It was clear that we were dealing with a case of primary hyperparathyroidism. It seemed difficult however to establish the relationship between such a condition and the hyperthyroidism particularly because of the resistance of the syndrome to antithyroid drugs.

The problem was solved spontaneously a few days later, when the picture was completed by the appearance of symptoms which betrayed the sudden worsening of the hypercalcemic intoxication.

1. At first signs of renal incompetence appeared suddenly, in spite of the generous fluid administration, diuresis and calciuria decreased. The toxic state worsened with further involvement of psyche and sensorium. Urea-clearance was only 16% and blood urea, uric acid and phosphorus suddenly rose.
2. At the same time a severe and diffuse polyneuritis appeared which was accompanied by motor and sensory changes and by paresis mainly localized in the extremities and extrinsic ocular muscles. Occasional twitches or full-fledged tonic clonic seizures were also present.
3. There was also a considerable worsening of psychic involvement; hallucinations appeared and severe agitation.
4. Tachycardic and hypertensive crisis supervened accompanied by complex ECG changes partly due to Ca and K disturbances. It was clear that the patient

FIG. 2.—Parathyroid section (x57) with clear principal cell hyperplasia (adenomatous?).

was developing uremia and that the only solution available at this point was to resort to surgery immediately.

Operation revealed the presence of a *hyperactive multinodular adenomatous goiter* accompanied by *hyperplasia (adenomatous?) of the parathyroid glands*. Surgery solved the problem in spite of an appalling post-operative thyrotoxic crisis. The patient was discharged shortly thereafter in good condition and is now receiving, as replacement therapy, small doses of thyroid and dihydrotachysterol.

Clinical and Biochemical Picture of Acute Thyro-Parathyrotoxicosis

Thyrotoxicosis is occasionally accompanied by hypercalcemia: Bauer and Krane (1962) have found only 11 cases reported in the literature. Some of these had also symptoms due to the hypercalcemia. However, since the blood calcium returned to normal after treatment of the hyperthyroidism and since in 6 such cases no parathyroid pathology was found on surgery, these authors concluded that the hypercalcemia was not due to the parathyroid hormone but to excessive bone reabsorption caused by thyroxine. On the same lines is the very recent case of Bauman and Rosen (1964) in which recurrent episodes of hyperthyroidism were always associated with hypercalcemia, but symptoms of calcium toxicity were lacking. Frame and Durham (1959) nevertheless, succeeded in gathering from the literature at least 3 cases, besides one of their own (Noble and Borg, 1936; Miller and Evans, 1942; Koenig *et al.*, 1957) in which the association between the two conditions is fully demonstrated. Another one is that of Aarseth and Bjørge (1949). In 3 other cases of Randall and Keating (1958) the parathyroid tumour was silent. In 9 other cases (Meyer-Borstel, 1929; Ball, 1930; Cooley, 1931; Bergstrand, 1931; Ballin and Morse,

FIG. 3.—Parathyroid section (x336) with lobule-like appearance of clear principal cell hyperplasia.

1931; Ponteva, 1939; Rienhoff, 1950; Hellström, 1954; Jackson *et al.*, 1961) the association seems probable, even though sufficient metabolic and histologic data are lacking. However, all these cases appeared to be chronic in type and all showed the existence of primary bone, renal or gastric involvement with, eventually, a secondary, sudden onset of acute calcium intoxication. The disease was almost always due to the presence of a parathyroid adenoma. By contrast, the signs of hyperthyroidism were usually modest and simple hyperplasia of the gland was its cause.

In our case instead we had to deal with a *primary, acute and concomitant thyro-parathyrotoxicosis which had a progressive course that led to renal uremia*. This condition, which was resistant to several antithyroid drugs, turned out to be caused by a *nodular toxic goiter* (Fig. 1) associated with an ill-defined parathyroid change consisting in hypertrophy of one gland and hyperplasia, rather close to an adenoma, of the other two glands found at operation (Fig. 2-3).

We failed to find cases similar to ours in the literature. We think therefore it may be useful to attempt to discuss in detail the nosology of this composite condition on the basis of both components: the *thyrotoxicosis*, as described by Williams and Bakke (1962) and the *acute parathyrotoxicosis*, as outlined by Lemann and Donatelli (1964).

Age and Sex: In *thyrotoxicosis* there is a definite higher incidence among females (4:1) together with a preference for the 3rd, 4th and 5th decades of life. In *parathyrotoxicosis* there is no sex preference, but greater incidence in the 5th, 6th and 7th decades of life. Our patient, on the contrary, was a 22-year-old male

TABLE 1
COMPARISON OF SYMPTOMS AND SIGNS OF ACUTE PARATHYROTOXICOSIS
AND THYRO-PARATHYROTOXICOSIS (modified from Lemman and Donatelli)

Symptoms	Para-Thyr. Storm	This Case	Signs	Para-Thyr. Storm	This Case
Muscular Weakness	80%	+	Muscle Hypotonia	44%	+
Nausea—Vomiting	80%	+	Palp. Neck Mass	42%	+
Anorexia	80%	+	Hypertension	35%	+
Weight Loss	65%	30 Kg.	Dehydration	31%	+
Fatigue	65%	+	Tachycardia	26%	+
Drowsiness—Lethargy	65%	+	Fever	22%	+
Confusion—Mental Changes	57%	+	Hyperpyrexia	?	occasional
Bone Pains	55%	+	Abd. Tenderness	15%	—
Abdominal Pains	48%	+	Band Keratopathy	9%	—
Polyuria—Polydipsia	40%	+	Trachea Deviation	4%	—
Constipation	37%	+	Neuritis	?	+
Renal Colics	22%	—	Faintness—Convulsions	?	once
Character Changes	no data	+	Renal Failure	?	reversible
			Whitish Nails	?	+

TABLE 2
COMPARISON OF SYMPTOMS AND SIGNS OF THYROTOXICOSIS WITH
THYRO-PARATHYROTOXICOSIS (modified from Williams, 1962)

Symptoms	Thyro-toxi-cosis	This Case	Signs	Thyro-toxi-cosis	This Case
Nervousness	99%	+	Tachycardia	100%	90-120/min.
Character Changes	100%	+	Widening Pulse Press	100%	150/50
Hyperhidrosis	89%	+	Goiter	100%	R. lobe nodule
Heat Sensitivity	89%	+	Skin Changes	97%	red, warm, wet
Palpitation	89%	+	Tremor	97%	+
Muscle Weakness	88%	+	Eye Signs	71%	—
Weight Loss	85%	30 Kg.	Splenomegaly	10%	—
Dyspnea	65%	+	Gynecomastia	10%	+(right)
Hyperpyrexia	65%	—	Liver Palms	8%	—
Nausea—Vomiting	9%	+	Muscle Wasting	100%	+
Eye Complaints	54%	—	Thyroid Stcrm:		
Leg Swelling	35%	—	Hyperpyrexia	100%	occasional
Diarrhoea	23%	—	Tachycardia	100%	140-260/min.
Increase in Stools	33%	—	Delirium	100%	+
Constipation	4%	+	Restlessness	100%	+
Weight Gain	2%	—	Flushing, Wet Skin	100%	+

without any history of endocrine disturbances, hereditary or otherwise. The case differed also from the proven cases of chronic hyperparathyroidism accompanied by hyperthyroidism which refer to 5 women aged 29, 33, 51, 60 and 70 years and one man aged 63.

Onset and Course: as in the separate conditions, the onset and course may be quite varied, so in our case the onset was insidious, while the course was progressive and overwhelming. The course may be divided into *three stages*:

1. *Prodromal stage:* at the beginning mild symptoms of hyperthyroidism (nervousness, tachycardia, weight loss, low grade fever) and hyperparathyroidism (anorexia, nausea, vomiting, polyuria) were present. These symptoms lasted about 30 days. The most striking feature

however, was the character and behaviour changes as emphasized by Fitz and Hallman (1952).

2. *Acute stage with recurrent crises (thyro-parathyrotoxic state):* without any evident reason crises ensued. These crises were characterized by high fever (39° C), tachycardia, restlessness, severe anorexia, vomiting, polyuria, dehydration and psychomotor agitation which was in striking contrast to the extreme weakness. Four toxic crises occurred in 45 days and during them there was a clear deterioration which could not be checked. These crises represent the most important aspect of this stage but we are unable to define better their physiopathology. In fact, both the thyrotoxicosis and the hypercalcemia were only of

TABLE 3

PATHOGENESIS OF CALCIUM TOXICITY

- 1.—Hypercalcemia causes polyuria.
- 2.—Polyuria in its turn causes hypovolemia.
- 3.—Glomerular filtration rate is then reduced.
- 4.—Hyperazotemia and retention of other toxic compounds, namely phosphorus, will follow.
- 5.—Concomitant hypercalcemia and hyperphosphoremia will cause Ca phosphate precipitation in tissues and chemical death of the cell.
- 6.—In myocardium, hypercalcemia causes block of oxidation and phosphorylation with irreversible cellular damage.
- 7.—In the kidney, microcalcinosis causes degenerative and necrotic lesions both in tubules and interstitium with subsequent pyelonephritic and proliferative changes.
- 8.—In the neuro-muscular system, hypercalcemia decreases the neuro-muscular excitability.

9. The *thyroid condition* was peculiar and baffling: on the one hand a full-fledged toxicity accompanied by high PBI and low blood cholesterol; and on the other hand a BMR not very elevated and a block of the thyroid uptake for iodine. All this is perhaps to be related to the anti-thyroid drugs used, in spite of which an elevated thyroxine output persisted. Nevertheless it could also be that the hypercalcemia potentiates the thyroxine effects.

10. The *renal picture* on the other hand offered very consistent evidence of the concomitant parathyrotoxicosis. During the first two stages there was polyuria with hypos-thenuria. It is known that this is caused by the hypercalciuria. Furthermore, it is also well established that the parathormone increases

phosphorus excretion from the distal tubule and decreases its absorption from the proximal tubule. All this leads to multiple hæmatological and urinary abnormalities accompanied by severe renal impairment. If to all the foregoing we add the special circulatory load imposed on the kidneys by the thyrotoxicosis (shortened circulation time and hypovolemia secondary to dehydration) we can easily understand why the kidneys, together with the heart, are most impaired.

In the 3rd stage the functional nephropathy ends in renal failure according to the following physiopathological pattern (Table 3).

At this point it may be useful to recapitulate the biochemical, metabolic and electrocardiographic abnormalities present in our case and to compare them with those found in thyrotoxicosis and in parathyrotoxicosis (Table 4):

It should be immediately emphasized that in our case the highest level of blood calcium encountered was 14 mg./100 ml. This is far from the values usually found in acute calcium intoxication. It is safe to assume that the thyrotoxicosis may cause a potentiation of effects. Therefore in the *thyro-parathyrotoxicosis* we need not wait for the appearance of severe hypercalcemia before taking adequate steps.

It should be also noted that the blood phosphorus was in the beginning constantly low but always within normal limits. On the other hand its sudden increase when renal

TABLE 4
BIOCHEMICAL ABNORMALITIES IN THYRO-PARATHYRO-TOXICOSIS

	Parathyro- toxicosis	Thyrotoxicosis	This Case
Hypercalcemia (over 11 mg./100 ml.)	100 %	occasional	11.4 - 14
Hypophosphatemia (under 2.5 mg./100 ml.)	30 %	no	2.7 - 2.9
Hyperphosphatemia (final stage)	no data	no	6.2 - 7.8
Hyperphosphatasemia (over 5-6 Bodansky Units)	72 %	occasional	3.5 - 4.5
Hyperazotemia (over 50 mg./100 ml.)	93 %	occasional	30 - 170
Hypocholesteremia (under 120 mg./100 ml.)	no data	70-80 %	102 - 121
PBI (over 6-8 γ /100 ml.)	no	100 %	25.2 - 32.7
Hypercalciuria (over 200 mg./day)	100 %	frequent	reached 811
Elevated I^{131} -uptake (over 40-60 %)	no data	100 %	2 %; 7 %
BMR (over 20-30 %)	no	100 %	+ 32 %; + 49 %
ECG: shortened Q-T interval	frequent	no	occasionally at lower limits

TABLE 5
RADIOLOGICAL FINDINGS

	Parathyro- toxicosis	Thyrotoxicosis	This Case
Osteitis fibro-cystica	28%	no	no
Bone demineralization	57%	rare	+ — —
Nephrolithiasis	28%	uncommon	no
Nephrocalcinosis	21%	no	no
Peptic ulcer or gastritis	21%	occasional	no
Neck or mediastinum mass	14%	100%	— — —
Hiatus hernia	+	no	no
Oesoph. diverticula	+	no	no

TABLE 6
PATHOLOGY OF THYRO-PARATHYROTOXICOSIS

	PARATHYROID				THYROID				REMARKS
	Single Adenoma	Multiple Adenomas	Hyperplasia	Carcinoma	Hyperplasia	Toxic Adenoma	Non toxic Adenoma	Carcinoma	
<i>Chronic hyperthyro- parathyroidism:</i>									
Noble-Borg (1936)	+				+				Hyperparathyroidism preceded (bone cysts) do (kidney stones)
Miller-Evans (1942)	+				+				Concomitant (nephro- calcinosis + bone changes)
Aarset-Bjorgo (1949)	+				+				Peptic ulcer before hyperthyroidism
Koenig <i>et al.</i> (1957)	+				+				Hyperparathyroidism preceded (kidney stone + peptic ulcer + bone changes)
Frame-Durham (1959)	+				+				Parathyroid adenoma asymptomatic except renal stone
Randall-Keating (1958)	+							+	Parathyroid adenoma asymptomatic
Randall-Keating (1958)	+						+		Parathyroid adenoma asymptomatic (bone a. kidney not explored)
Randall-Keating (1958)	+					+			Kidney stones preceeded
Jackson <i>et al.</i> (1961)	+				+	+			Concomitant thyroid- parathyroid toxicosis
<i>Acute Thyro-Parathyro- toxicosis: Austoni et al. (1964)</i>			+			+			

failure supervenes, is very characteristic. This, together with the increase of azotæmia, has a specific prognostic significance. Also strange

was the normal alkaline phosphatase which indicates a normal osteoblastic activity. Radiological findings: in Table 5 are shown the

main radiological changes of these conditions.
Morbid anatomy and etiology: Since no similar

TABLE 7.

THERAPY OF THYRO-PARATHYROTOXICOSIS

1. *Treating the thyroid storm:*
 - a *aetiological:* surgery, eventually DXR, I¹³¹
 - b *pathogenetic:* antithyroid drugs
 - c *symptomatic:* hibernation
2. *Treating the parathyroid storm:*
 - a *aetiological:* surgery, eventually DXR
 - b *pathogenetic:* not available
 - c *symptomatic:*—increasing *Ca* excretion with saline or Na sulphate infusions (Walsher, 1959)
—decreasing *hypercalcaemia:*
EDTA, citrates (Rasmussen, 1962), diet rich in P (Albright, 1931), Na phosphate per os or i.v. (Dent, 1962), corticosteroids (Gwinup, 1961)
—*Haemodialysis*

observations are available, we have to take into consideration the findings of known chronic cases (Table 6).

It should be, however, emphasized that, while in chronic cases the primary factor is the parathyroid tumour, in our case the principal change was the multinodular toxic goiter.

As a matter of fact, it was difficult to define the parathyroid changes: one gland, included in the thyroid, showed a simple hypertrophy of the clear principal cells, while the other two were classified as hyperplastic on the ground of their macroscopic appearance and small size and weight (about 240 mg.), but their histological picture could have been that of an adenoma. It must be pointed out that these criteria are not sufficient to differentiate the two conditions. This might be consistent with the fact that the name of "adenomatous hyperplasia" was used in the past (Rasmussen and Reifenstein, 1962) in cases of polyendocrine adenomas. But "in this condition the parathyroid tumours are always multiple and often involve all of the parathyroid tissue". Because of this, there is some difference of opinion as to whether this condition should be classified as "multiple adenomatosis" or should be given the name "primary chief-cell hyperplasia". For this reason it is perhaps better that the pathology of our case should remain under the name of chief-cell (adenomatous?) hyperplasia until new cases are reported.

Also any aetiological speculation seems useless too, except for a peculiar fact present in the history of our patient. Because of acne he had been undergoing for one year intense heliotherapy and ultraviolet radiation therapy, whose actions on the calcium metabolism could be equated to that of Vitamin D.

On the other hand it is sufficient to underline the fact that our case was not a familial multiple endocrine syndrome (Werner, 1954) and that the onset of the two diseases appeared to be coincidental. The presence of a toxic adenoma of the thyroid, which usually is not subject to a pituitary control, is against the hypothesis of a primary hypothalamo-pituitary disturbance.

Prognosis and Therapy

The experience gathered from the management of parathyrotoxicosis and of secondary calcium intoxication indicates that the main factor to be taken into consideration is the hypercalcaemia. If this is caused by an increase in parathyroid hormone production, the only therapy is the surgical removal of the parathyroid glands. Every other therapeutic measure intended to bind or remove the calcium is ineffective or only palliative. The excess parathyroid hormone switches irreversibly the equilibrium between the large bone pool of calcium and the small extra-cellular fluid pool. Prognosis is therefore fairly satisfactory in those cases which have been operated upon. In the series of Lemann and Donatelli there were 3 deaths (13%) out of 23 cases. In the 23 cases which did not undergo surgery mortality was 100%.

In the acute thyro-parathyrotoxicosis, in which the situation is worse because of the threat of thyroid crisis, the prognosis appears to be much more uncertain. This is specially true if surgery, due to diagnostic difficulties, is delayed. In such an event even symptomatic therapy becomes important (Table 7).

The modalities and the results of the symptomatic treatment of hyperparathyroidism still remain to be evaluated from a clinical standpoint. If however the excess in parathormone keeps on removing toxic amounts of calcium from the bones, these measures are only palliative and surgery appears even more mandatory.

In conclusion, our case seems to indicate that the association of thyroid and parathyroid hyperfunction produces an autonomous syndrome complex, which we must bear in mind especially in emergencies, since it implies many diagnostic problems and, above all, prompt surgical treatment.

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