CHRONIC DIARRHEA IN AN ADULT WITH HYPOKALEMIC NEPHROPATHY AND OSTEOMALACIA DUE TO A FUNCTIONING GANGLIONEUROBLASTOMA

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MONTREAL

A syndrome of catechol-secreting neural tumor and diarrhea has been recognized in children since 1952.[1] Twenty-six such cases have been reported.[1-20] We have observed and studied what we believe to be the first instance of the syndrome in an adult. A 54 year old white normotensive woman with von Recklinghausen's disease developed severe diarrhea, hypokalaemic nephropathy and thin bones, all of which were reversed when a ganglioneuroblastoma was removed surgically from the right adrenal. The tumor secreted and contained large amounts of catechol amines. Furthermore, a smooth-muscle active substance was recovered from the tumor.

Case Report

In 1948 a diagnosis of neurofibromatosis in this patient was made on biopsy of a subcutaneous nodule. Her major symptom, diarrhea, began in 1949 and continued through many attempts at diagnosis and therapy until 1963. From its onset, the diarrhea was copious, watery and precipitous with frequent incontinence and soiling of undergarments. The patient showed no striking signs or disability for five years, and she worked regularly as a charwoman until skeletal and renal complications crippled her in 1957. She was admitted then because of incapacitating bone pain, weakness and polyuria.

A complete investigation of the gastro-intestinal tract did not reveal the cause of the diarrhea. The usual x-rays of the upper and lower gastro-intestinal tract, stool cultures, search for parasites, endoscopies, gastric analysis, jejunal mucosal biopsy and hematological examinations were all normal. There were excessive losses of calcium and potassium in the stool but no steatorrhea. Stool fat ranged from 4 to 7 grams per day and was considered compatible with severity of the diarrhea (4 litres per day).

The kidney dysfunction was interpreted as hypokalaemic nephropathy

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TABLE 1. A

Metabolic Complications of Diarrhea (1957)

a) Hypokalaemic Nephropathy
   i. Serum K: 2.0–2.3 mEq/L
   ii. Pyelography: normal parenchyma
   iii. Urine Specific Gravity Range:
      1952: 1.006–1.022 dehydration
      1957: 1.004–1.006 dehydration
      1963: 1.010–1.020 random
b) Osteomalacia
   i. Demineralized, tender bones
   ii. Spontaneous fractures
   iii. Atypical chemistry
      Ca normal, P down, alk. phos. normal
   iv. Bone biopsy—normal

TABLE 1. B

Pre-Op. Investigations, 1963

1. Hemogram: normal
2. Urinalysis: normal (Sp. G. 1.010–1.020, random)
3. Serum Chemistries:
   K—3.7 mEq/L (2.3 mEq/L) Ca—9.7 mgm %
   P—1.7 mgm % FBS—72 mgm %
   Alk. Phos.—6 KAU
4. Faecal Chemistry:
   Stool Fat—4.7 gm/day
   Stool K—70 mEq/day
   Stool Vol.—3–4 L/day
5. Gastric Analysis: histamine and 12 hour—normal
6. Balance Studies:
   Ca—negative (33 mgm /day)
   P—positive (215 mgm/day)
7. Renal Function: creatinine clearance 66L/day
   tubular re-absorption P—87% F.L.
8. Adrenal Function: 17-OH corticoids 7.2 mgm/day
   17-ketosteroids 1.8 mgm/day
9. Urinary 5HIAA: qualitative tests negative × 5

on the basis of depressed serum potassium levels, faint visualization of the kidneys on intravenous pyelography and an inability to concentrate the urine, which had developed during the course of the diarrhea and which was reversed with potassium supplements. (Table 1-A) A renal biopsy was not done. However, the urine was sterile, and retrograde pyelography showed a normal collecting system. (Fig. 1) The superior pole of the right kidney was depressed by a mass, localized to the right adrenal (Fig. 2). Urinary corticoids were normal, and the mass was considered to be a visceral neurofibroma.

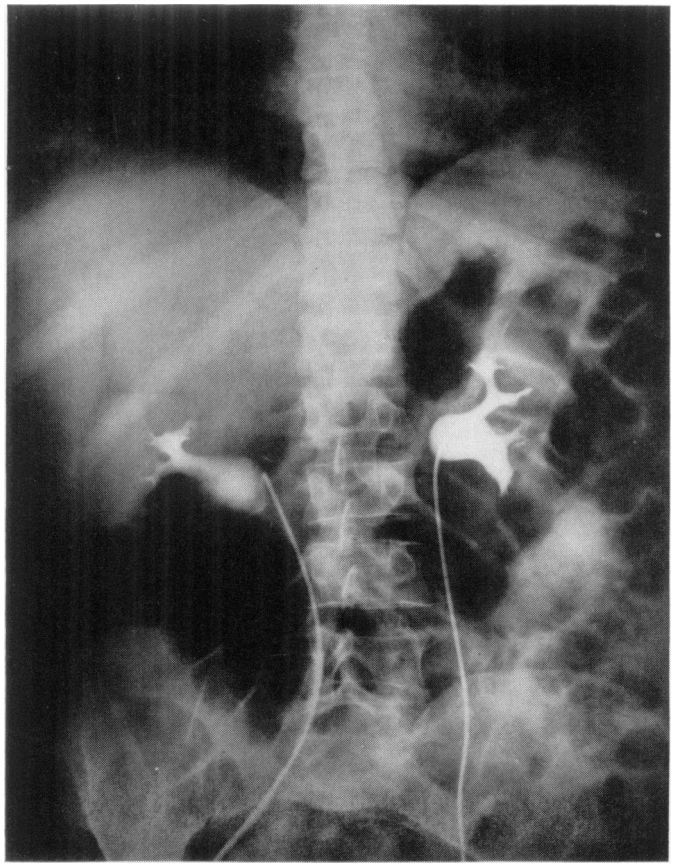

FIG. 1. Retrograde pyelogram showing well-preserved conducting system.

Her bones were thin by x-ray, and showed several spontaneous fractures (Fig. 3). Osteomalacia seemed the likely cause. The striking improvement which followed symptomatic therapy with calcium and vitamin D is shown in the pre-and post-treatment x-rays of the spine (Fig. 4).

As no cause had been established for the diarrhea which persisted, mecamylamine, a ganglion-blocking agent, was given in an attempt to reduce gut motility. She was discharged on a regimen of calcium, potassium and vitamin D supplements and mecamylamine and she was able to resume work within five months. Precipitous diarrhea continued to occur but with reduced frequency.

In 1963, on reviewing our patients with Von Recklinghausen's Disease in search for undiagnosed phaeochromocytomas, the nature of the mass in this patient's right adrenal gland was questioned. It was recalled that

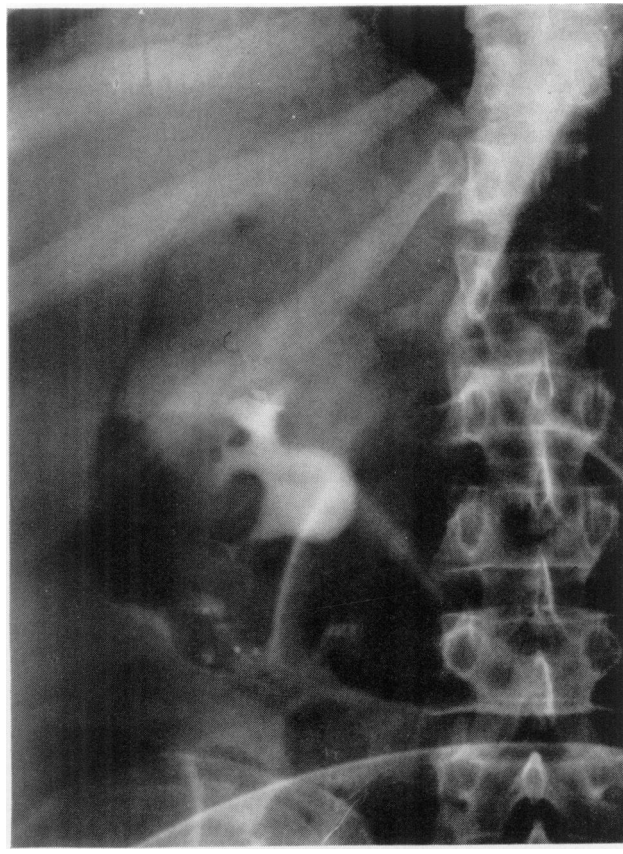

FIG. 2. Nephrotomogram, showing soft tissue mass in right adrenal.

among the many investigations done previously, several elevated blood sugars and basal metabolic rates had been recorded, which might indicate hypersecretion of catechol amines. Despite her consistently low blood pressures, admission for measurement of catechol amines was arranged. She was having three to four bowel movements per day. These were often precipitated by meals. The movements were still copious and watery. She had no symptoms of sweating, palpitations, nervousness, apprehension or headache, and no bone pain or urinary complaints. She had been working regularly up to the time of admission. Physical examination disclosed a short, slight, lantern-jawed woman with flushed complexion. The pulse and blood pressure were normal, and she was afebrile. The examination was completely normal except for the cafe-au-lait spots on the arms and trunk and palpable subcutaneous neurofibromata in the neck.

Of the many radiological, hematological and biochemical investi-

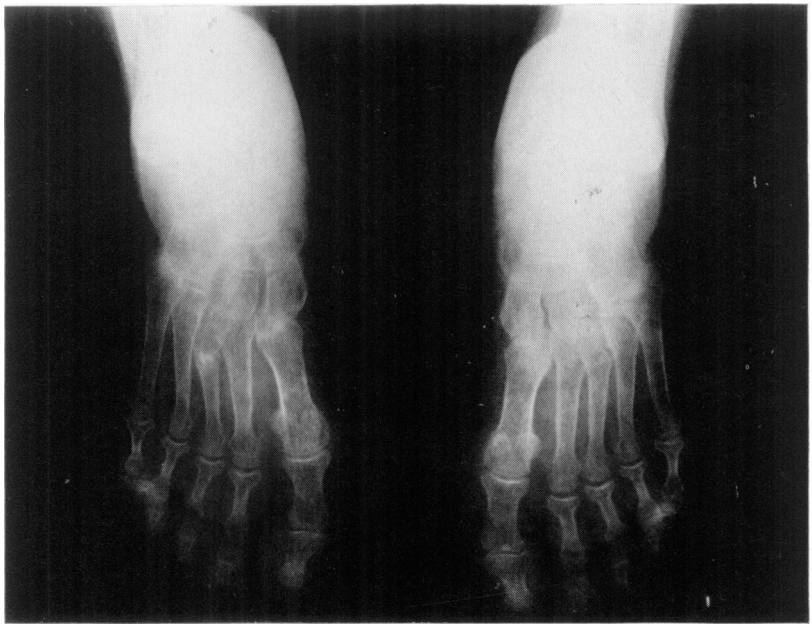

FIG. 3. X-ray of bones of feet showing spontaneous fracture of metatarsal and extreme demineralization of bone.

gations carried out, most were normal. (Table 1-B). She continued to pass three to four litres of watery stool per day, and to waste potassium and calcium. However, serum values for these electrolytes were normal on admission. Tests of renal function demonstrated a restored concentrating mechanism; endogenous creatinine clearance was slightly reduced, and tubular reabsorption of phosphate was 87% of filtered load. The serum phosphorus remained low, but serum calcium was normal and the bones were improved as shown by x-rays.

A provocative test with histamine acid phosphate, 0.1 mgm, resulted in a blood pressure change from 100/60 mm Hg to 160/90 mm Hg. It was accompanied by severe headaches and the appearance of ventricular ectopic beats on the electrocardiogram. The large amounts of epinephrine, norepinephrine, dopamine, vanilmandelic acid and homovanilic acid excreted in 24 hours are shown in Table 2.

The patient underwent resection of a right adrenal tumor on October 16, 1963. During dissection, blood pressure peaks up to 270/170 mm Hg occurred and were controlled with intravenous phentolamine. Vasopressor infusions were required for 48 hours post-operatively. The patient developed post-operative pneumonia which cleared uneventfully.

The diarrhea disappeared promptly post-operatively, and the patient

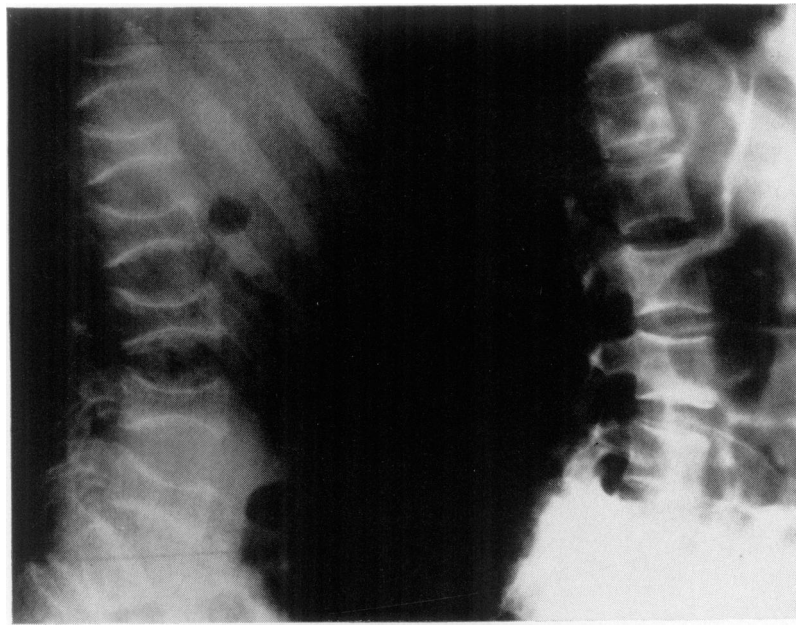

FIG. 4. X-rays of spine before and five years after treatment with vitamin D and calcium.

has had one formed motion per day since. Calcium, potassium and vitamin D supplements were discontinued. Serum values for calcium, phosphorus and potassium are now normal, and she had no skeletal problems. Excretion of VMA and total catechol amines has remained normal. The patient has been seen regularly and remains perfectly well and symptom free.

PATHOLOGY OF THE TUMOR

Grossly, the tumor was an orange-sized, irregular, lobulated mass fully encapsulated. The cut surface was whitish and firm, but disclosed a cyst containing about 15 mls of yellow fluid. The microscopic picture was typical of ganglioneuroblastoma (Fig. 5). There were masses of fibrillary glial or neurilemnal substance, scattered throughout with large ganglion cells. Focal areas showed increased cellularity and contained aggregates of atypical polyhedral cells and stellate forms, with granular and vacuolated cytoplasm (Fig. 6).

The ganglionic cells contained cytoplasmic granules which were brown in formalin-fixed and bichromate-fixed sections. The cystoplasmic granules were blackened by silver salts in the Fontana reaction, and some

TABLE 2

24 Hour Excretion of Catecholamines and Their Metabolic Products Before and After Removal of Ganglioneuroblastoma*

	Pre-op.				Post-op.			
	Sept. 63			Oct. 63	Nov. 63	Nov. 64		Dec. 65
	Normal Range	17–18	26–27	28–29	29–30	8–9	20	13
Vanilmandelic Acid†	Less than 15 mg	6.6	13.5	20.5	7.5	5.5	2.8	7.8
Epinephrine‡	9–34 μg		329	372	25			
Norepinephrine‡	11–69 μg		499	513	109			
Dopamine‡	197–413 μg		2520	3057	460			
Homovanillic Acid‡	4.56–13.61 mg		11.42	19.42				
Creatinine	1–1.5 g		0.5	0.65	0.41			
Total Catecholamines†	Less than 120 μg	242				98.5		

* Date of operation: October 16, 1963.

† Determinations done at the M.G.H., Endocrinology Laboratory.

‡ Determinations done at the Allan Memorial Institute Research Laboratory.

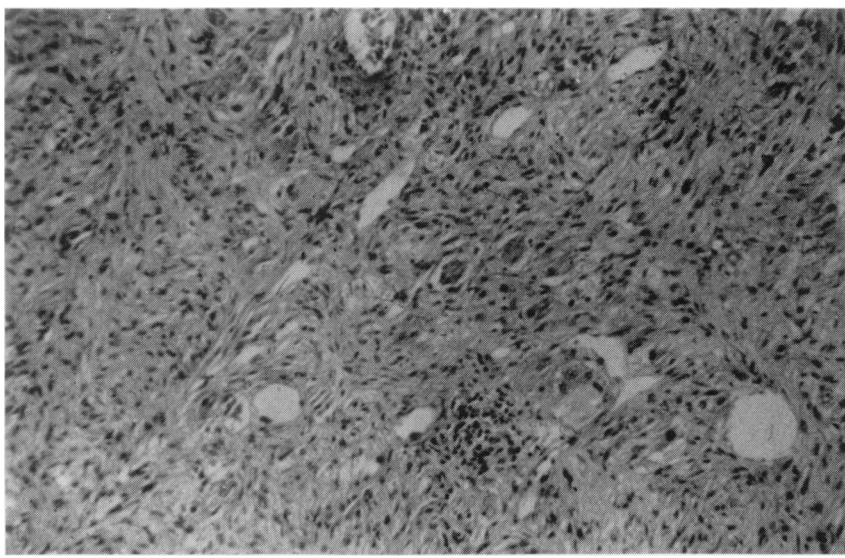

FIG. 5. Whirling pattern of small cells and fibrillar material in an adrenal medullary ganglioneuroblastoma. Hematoxylin and eosin stain, × 35.

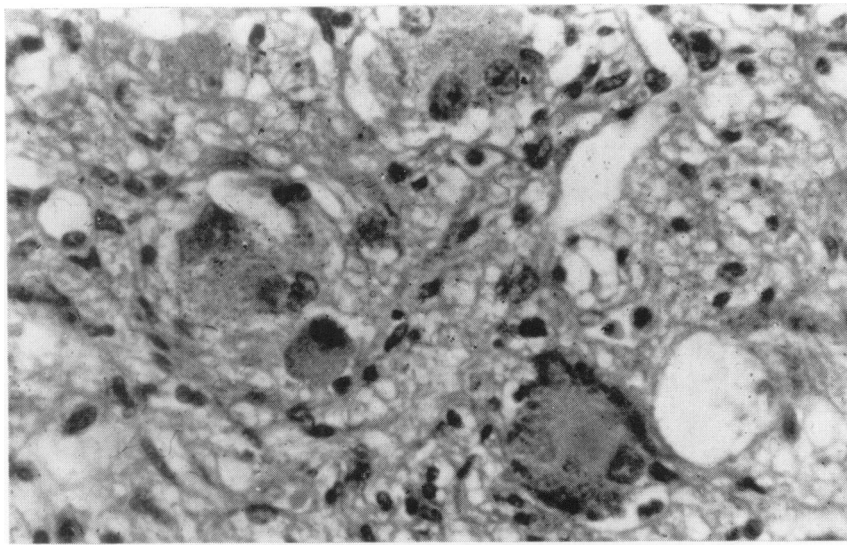

FIG. 6. Large cells of ganglionic origin surrounded by the fibrillar tissue illustrated in Figure 6. Hematoxylin and eosin stain, × 150.

stained positively with the performic and periodic acid Schiff reactions. They gave negative reactions with the Wiesel technique for chromaffin cells after chromate fixation. The pigment in the brown granules bleached when treated with hydrogen peroxide. Some of the cells contained Nissl blue granules, as well.

Active Substance Extracted From the Tumor

1. Catechol Amines: Analysis of the tumor for catechol amine content was performed by Professor T. L. Sourkes at the Allen Memorial Institute Research Laboratory, by techniques previously described.[21] The tumor contained 151.1 micrograms epinephrine, 566.8 micrograms norepinephrine and 10.5 micrograms dopamine per gram wet weight of tissue (Table 3).

2. "Smooth Muscle Active Substance": Extraction of homogenized tumor tissue by the Rocha e Silva method for plasma bradykininogen was performed by Miss L. Marlene Stotland in the laboratory of the Department of Pharmacology, McGill University.[22, 23] The tumor contained 0.54 units of bradykinin-like activity by this technique. (Table 3).

DISCUSSION

This patient demonstrated clinical and biochemical aberrations consistent with protracted severe diarrhea. Hypokalaemic nephropathy was

TABLE 3

Active Substances in Tumor Extracts

1. Catechol Amines*
   Norepinephrine, 556.8 micrograms/grams
   Epinephrine, 151.1 micrograms/grams
   Dopamine, 10.5 micrograms/grams
2. Smooth Muscle Active Substance**
   "Bradykinin Activity" 0.54U/100 grams

* Dr. T. L. Sourkes, Allan Memorial Institute Research Laboratory.
** Miss L. M. Stotland, Department of Pharmacology, McGill University.

reversed by potassium supplementation. She seemed to have osteomalacia but the exact nature of the bone lesion is not entirely clear. There was no evidence of renal phosphaturia, which sometimes occurs in neurofibromatosis,[24] nor for parathormone-like activity of the tumor. Moreover, the clinical and x-ray improvement in her bones following administration of calcium and vitamin D is compatible with the diagnosis of osteomalacia.

She exhibited no clinical evidence of increased catechol amine production, except with histamine provocation and following manipulation of the tumor at the time of surgery.

The tumor, a ganglioneuroblastoma, was of a type encountered in neurofibromatosis,[25] and histologically like tumors in children known to secrete catechol amines.[26]

Her syndrome becomes unique when viewed as an association of these phenomena, known previously in children, but not in the adult.

The twenty-six cases of functioning sympathetic nervous system tumors and diarrhea previously reported are summarized in Table 4. In twelve cases, removal or destruction of the tumor resulted in control of diarrhea. No instance was recorded where diarrhea persisted following successful removal of the tumor. This had been held to indicate that the tumor in some way causes the diarrhea.

The catechol amines themselves have not been indicted as a humoral cause of diarrhea. Except in a few instances,[27, 28] catechol amine secreting phaeochromocytomas have not been associated with diarrhea.[29] Many neural tumors in children secrete catechol amines[30] but only a fraction of them are associated with diarrhea.[31-35] Diarrhea does not result from the administration of catechol amines.

In a single case report by T. C. Hunt, diarrhea was associated with carotid body tumor, a paraganglioma, in an adult.[36] Resection of the tumor cured the diarrhea. There was no measurable increase in urinary catechol amines. Also, as in the present case, the urine contained no excess of serotonin.

TABLE 4

Summary of 26 Cases with Sympathetic Nervous System Tumors & Diarrhea

Case No.	Sex	Age (Mos.)	Histology	Catecholamines or Metabolites	Therapy	Diarrhea Improved	Ref
1	F	54	GNB				2
2	F	1	NB				3
3	M	2	NB				3
4	F	13	GN		Surgery	Yes	1
5	M	10	NB		Radiation		4
6	F	36	NB				4
7	M	27	GNB		Radiation	Yes	5
8	M	18	GN		Surgery	Yes	5
9	F	30	GN		Surgery	Yes	5
10	M	19	GNB	Elevated	Radiation	No*	6, 7
11	M	19	GN		Surgery	Yes	8
12	M	19	GN		Surgery	Yes	
13	F	30	GN	Elevated	Surgery	Yes	9
14	F	13	NB	Elevated	Chemo-therapy		10
15	F	13	GNB	Elevated	Surgery	Yes	10
16	M	8	NB	Elevated	Radiation		11
17	M	42	GN	Elevated	Surgery		12
18	F	31	GN	Elevated	Surgery		13
19	M	96	GN	Elevated	Surgery		14
20	F	36	GN	Elevated	Surgery	Yes	15
21	M	10	SB	Elevated			16
22	M	15	GN	Elevated			16
23	F	32	GNB	Elevated	Surgery	Yes	17
24	F	36	GN		Surgery	Yes	18
25	F	96	GN				19
26	M	2	NB	Elevated	Surgery	Yes	20

* Improved on corticosteroids.

Abbreviations: GN, ganglioneuroma; NB, neuroblastoma; GNB, ganglioneuroblastoma; SB, sympathoblastoma.

No additional humoral agent has been demonstrated in previous cases which might explain the diarrhea although several attempts had been made to demonstrate such a substance. Hallenbeck et al submitted saline tumor extracts to the guinea pig ileum preparation.[7] No motor effect was noted. Greenberg et al reported relaxation of chicken cloaca with tumor extract.[37] Relaxation of chicken cloaca is a property common to several smooth muscle active substances, among them bradykinin.[38]

Using Rocha e Silva's technique for plasma bradykininogen assay, we have been able to recover trace amounts of "bradykinin-like activity" from the homogenized tumor tissue. Neither the source of the material nor its chemical nature is clarified by this manoeuvre. Extra-cellular or

cellular components of the tumor tissue may have yielded the substance. Its motor effect on the guinea pig uterus, following "trypsin activation", cannot be held to identify the substance as bradykinin, though this is at least possible. Binding of serotonin, another smooth muscle active hormone, by sub-cellular particles in chromaffin tissue has now been reported.[39] While definitive exclusion of serotonin as the active substance yielded by this technique was not carried out, multiple qualitative tests for 5-hydroxy-indolacetic acid in the patient's urine were negative. Similarly, the possibility that the substance was histamine was not excluded. However, the anoestrus guinea pig uterus is relatively insensitive to histamine.[40] Also, Greenberg et al assayed histamine content in a comparable tumor. They demonstrated 0.261 micrograms per gram of tumor tissue,[37] a concentration unlikely to affect the uterus preparation.

The identity of the smooth muscle active substance remains, nevertheless, unknown to us.

A role in the regulation of gut motility has been inferred for one of the peptide tissue hormones (substance P).[41, 42, 43] The possibility that the smooth muscle active substance extracted from the tumor in this case represents one of the peptide tissue hormones suggests a possible relationship between tumor secretion and disturbance of gut motility.

While it would be premature to assign any functional importance to the smooth muscle active substance extracted from the tumor, the record of its presence may be of interest.

Summary

A 58 year old white woman with von Recklinghausen's disease developed severe diarrhea and dramatic biochemical complications. The diarrhea was cured by surgical excision of a catechol-amine-secreting ganglioneuroblastoma from the right adrenal medulla. This appears to be the first recognized instance of the syndrome of catechol-amine-secreting tumor and diarrhea in the adult. Analysis of the tumor yielded trace amounts of a smooth muscle active substance, in addition to the anticipated catechol amines.

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DISCUSSION

Dr. William C. Thomas, Jr. (Gainesville): Prior to the administration of Vitamin D to this patient, were the urinary calcium values normal or low? Did you make those measurements?

Dr. Cameron: Yes. Would you like to answer that, Dr. Warner? They were low, I believe, Dr. Thomas.

Dr. Warner (Montreal): Yes, on several occasions she was challenged with a relatively low calcium intake and seemed able to conserve her calcium by reducing her urinary calcium under this challenge. The lowest dietary intake to which she was submitted was 262 milligrams of calcium per 24 hours, and her urinary calcium under this regimen was about 90 milligrams per 24 hours.