SECRETORY DIARRHEA

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CASE I:

J.K.: This 73-year-old man began having watery diarrhea and episodes of hypokalemia in March 1974. Serum potassium concentration was 1.8 mEq/L. He lost 40 pounds of weight. An extensive workup, including barium contrast x-rays, small bowel biopsy and proctoscopy, revealed no evidence of gastrointestinal disease. Basal gastric acid secretion was 1 mEq/hr and maximal acid output after histamine was 3 mEq/hr (normal > 15). Stool fat was less than 5 gm per 24 hr. Urinary 5HIAA was normal.

There was thus no evidence that disease of the gastrointestinal system per se was responsible for the watery diarrhea, and Zollinger-Ellison syndrome and malignant carcinoid syndrome were ruled out. The patient was suspected of having pancreatic cholera syndrome, and the following studies were performed.

	While Eating	During Fast
a) Stool Collections:		
Stool volume, ml/24 hr	5,500	1,800
[Na] stool, mEq/L		71
[K] stool, mEq/L		77
Osmolality stool, mOsm/kg		299

The stool volumes were large, the diarrhea persisted during a fast, and electrolytes accounted for essentially all of the osmolality of stool water, i.e.:

$$(Na + K) \times 2^{*} = (71 + 77) \times 2 = 296,$$

compared to a measured osmolality of 299

*Multiplied by 2 to account for anions.

b) Angiography: This revealed no evidence of an intra-abdominal neoplasm.

c) Plasma Hormone Assays:

Gastrin
Secretin
Glucagon
GIP
Prostaglandins E and F

} Within Normal Limits

VIP:

Bloom Assay - 260-500 pg/ml (3 samples) (Normal < 100)

Said Assay - 1000 pg/ml (Normal < 200)

d) Small Bowel Perfusion Study:

Water and Glucose Movement in 30-cm Segments of Jejunum

	Water Absorption During Perfusion of Balanced Electrolyte Solution	Glucose Absorption During Perfusion of 65 mM Glucose
19 Normals	Absorbed 60 ml/hr (Range 15-104)	Absorbed 12 mmol/hr (Range 7.5-20)
J.K.	Secreted 86 ml/hr	Absorbed 13.3 mmol/hr

The perfusion study revealed that the jejunum was secreting rather than absorbing water and electrolytes during perfusion of a balanced electrolyte solution. Glucose absorption was normal.

Based on the clinical picture, the elevated plasma VIP concentration, and these perfusion studies, it was decided that the patient probably had pancreatic cholera syndrome. Exploratory laparotomy revealed a walnut-size, nonbeta islet-cell tumor in the body of the pancreas. The tumor was not malignant and was resected in toto. Islet cells which were not involved in the tumor were normal in histological appearance.

Postoperatively the patient had completely normal bowel movements and he has remained well. Plasma VIP two weeks after surgery was 23 pg/ml by Bloom and was undetectable by Said. A small bowel perfusion study done two months after surgery was normal, as shown in the next table.

Small Bowel Perfusion Study

Water and Glucose Movement in 30-cm Segments of Jejunum

	Water Absorption During Perfusion of Balanced Electrolyte Solution	Glucose Absorption During Perfusion of 65 mM Glucose
19 Normals	Absorbed 60 ml/hr (Range 15-104)	Absorbed 12 mmol/hr (Range 7.5-20)
J.K., Pre-op	Secreted 86 ml/hr	Absorbed 13.3 mmol/hr
J.K., Post-op	Absorbed 112 ml/hr	Absorbed 10.9 mmol/hr

Clinical Features of Pancreatic Cholera Syndrome

Required for Diagnosis:

Profuse watery diarrhea
Absence of gastric hypersecretion
Hyperplasia or tumor of pancreatic islets (nonbeta)

Almost Always Present:

Hypokalemia

Often Present:

Basal achlorhydria (60%)

Sometimes Present:

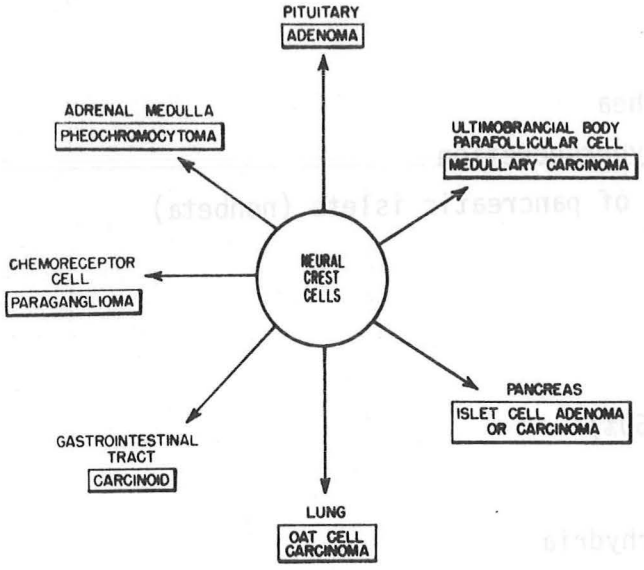
Histamine fast achlorhydria
Hyperglycemia
Hypercalcemia
Skin flushing
Steatorrhea
Metabolic acidosis
Distended gallbladder (10%)
Diarrhea improves with steroid therapy
Tetany (with normal or elevated serum [Ca])
Psychosis

Synonyms for Pancreatic Cholera Syndrome

1) Verner-Morrison syndrome
2) WDHA syndrome (watery diarrhea, hypokalemia, and achlorhydria)
3) WDHH syndrome (watery diarrhea, hypokalemia and hypo-achlorhydria)

None of these names is entirely appropriate, and it should be noted that the same syndrome can arise from tumors other than islet cell origin. In fact, tumors in many of the neural crest tissues can give rise to watery

diarrhea, i.e., medullary carcinoma of the thyroid, pheochromocytomas, ganglioneuromas, carcinoid tumors, and oat cell tumors of the lung.



Schein et al.
Ann. Int. Med. 79:239, 1973

PATHOGENESIS:

It is currently believed that diarrhea is mediated by abnormal amounts of hormones released from hyperplastic or neoplastic neural crest tissues.

Hormones that reduce absorption or cause intestinal secretion when infused intravenously so that plasma concentrations are abnormally high:

In Animals	*In Man*
Gastrin	ADH
Prostaglandins	Prostaglandins
CCK	Calcitonin
Glucagon	Glucagon
VIP	Secretin
GIP	CCK
Acetylcholine	
Calcitonin	

Secretin and VIP stimulate pancreatic secretion. Serotonin, VIP, and CCK enhance gastrointestinal motility. VIP, GIP, calcitonin, prostaglandins and secretin inhibit gastric acid secretion.

Some patients with presumed hormone-induced diarrhea have elevated plasma concentrations of more than one hormone.

	Plasma Hormone Conc.		Tumor	
	Elevated	Normal	Elevated	Normal
Rambaud et al.	VIP	GIP	VIP	GIP
Islet cell carcinoma	PGE	Secretin		Secretin
	Calcitonin	CCK		CCK
		Gastrin		Gastrin
		Glucagon		
		PTH		
Schmitt et al.	Serotonin	Gastrin	VIP	
Islet cell carcinoma	VIP	Insulin	Calcitonin	
	Secretin		Secretin	
	Glucagon			
	GLI			
Isaacs et al.	Calcitonin	PGE		
Medullary carcinoma, thyroid	Gastrin			

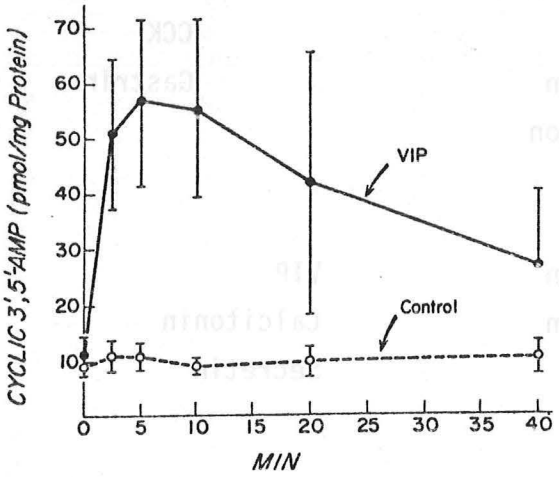
High plasma concentrations of a hormone could originate from the tumor per se, or might be released secondarily from normal tissue in response to high blood concentrations of another hormone (i.e., gastrin release from a tumor could cause calcitonin release from the thyroid).

Since the concentration of several hormones in plasma may be elevated, it follows that not all manifestations of the clinical disorder need be mediated by a single hormone.

Nevertheless, recent work suggests that in the majority of patients most of the manifestations of the syndrome are caused by VIP. In animals, VIP stimulates intestinal secretion, inhibits gastric acid secretion, is a weak stimulant of pancreatic secretion, stimulates glycogenolysis and causes hyperglycemia, relaxes the gallbladder and causes hypercalcemia. Even though VIP has not been given to man, these effects of VIP infusion in animals closely simulate many of the manifestations of pancreatic cholera syndrome. Most of the patients with the syndrome who have been reported in the past two years have had elevated plasma and/or tumor concentration of VIP. This applies mainly to pancreatic tumors, but also to at least some

other tumors associated with diarrhea (Fausa et al., patient with ganglioneuroma). Several workers refer to such tumors as "vipomas".

The mechanism of intestinal secretion induced by VIP is believed to involve the stimulation of adenylate cyclase in small intestinal mucosal cells, resulting in an increased cellular concentration of cyclic AMP. Cholera toxin and prostaglandins are known to act in this way (other hormones that cause intestinal secretion do not stimulate cyclic AMP).



Schwartz et al.
JCI 54:536, 1974

Effects of VIP (20 μg/ml) on cyclic AMP levels in rabbit ileal mucosa expressed as a function of time. Each point is the mean±1 SEM (brackets) for five complete and separate experiments

MAJOR FEATURES OF WATERY DIARRHEA SYNDROME

I. DIARRHEA:

A. Mechanism:

Six patients (three with pancreatic tumors, one with pancreatic hyperplasia, one with medullary carcinoma of the thyroid, and one with a ganglioneuroblastoma of the adrenal gland) have been studied by gastrointestinal intubation methods in order to elucidate the cause of diarrhea. Excessive pancreatic secretion was present in one (Schmitt et al.), and this was attributed to high plasma secretin concentration. Reduced small bowel absorption and/or small bowel secretion was present in the other five patients. Three of these patients were studied by our group (Walsh, Morawski, and Fordtran) and all showed jejunal secretion ± reduced ileal absorption.

B. Clinical Features of the Diarrhea:

Some of them are summarized in the next table, comparing the findings in this disease with those in Z.E. and carcinoid syndrome. Note that no patient with proven pancreatic cholera syndrome (WDHA) has been reported who had less than 1 liter stool/24 hr at the height of the diarrheal disease. It is important to emphasize, however, that the severity of the diarrhea may fluctuate. One recently reported patient (Schmitt) was diagnosed when stool volume was 0.7 L/24 hr (average over 3 days); later, however, this patient had fulminant diarrhea.

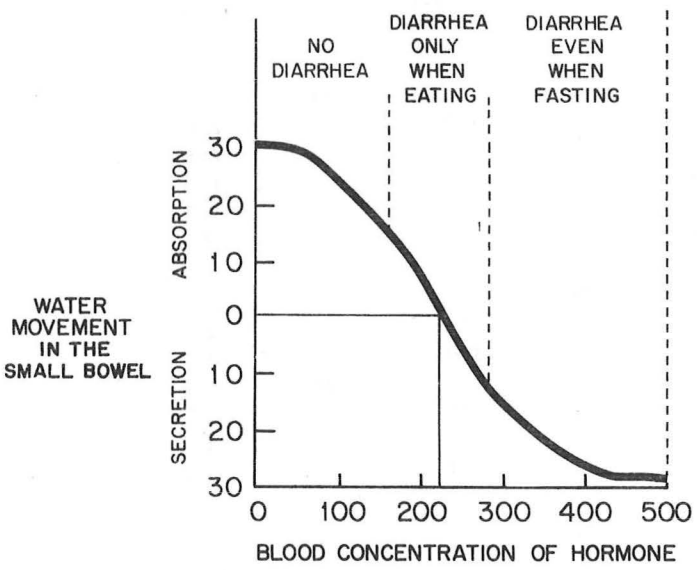
Clinical Data Taken from the Review by Rambaud and Matuchansky

	Zollinger-Ellison syndrome		WDHA syndrome		Carcinoid syndrome	
	Available	Present (per cent)	Available	Present (per cent)	Available	Present (per cent)
Course of diarrhea						
Duration before diagnosis (yrs)	60		35		63	
< 1		28.3		31.4		20.6
1-3		33.3		31.4		20.6
3-5		18.3		11.4		17.5
5-10		17.7		20.0		15.9
> 10		8.4		5.7		7.9
Type of diarrhea						
Evolution	12		23		59	
permanent		25.0		47.8		52.5
intermittent		75.0		52.2		57.5
Aspect of stools	42		39		23	
watery		66.6		100.0		91.3
fatty		28.6		0.0		8.7
watery + fatty		4.8		0.0		0.0
Highest daily volume of stools	4		30		4	
< 1000 ml		75.0		0.0		75.0
1000-3000 ml		25.0		16.7		25.0
3000-5000 ml		0.0		36.7		0.0
> 5000 ml		0.0		46.6		0.0
Serum potassium	20		34		13	
< 3.5 mEq/L		50.0		76.5		15.4
Fecal fats	44		22		9	
normal		15.9		86.3		0.0
increased						
6-14 g/24 h		22.7		9.1		22.2
15-30 g/24 h		13.6		4.6		55.6
>30 g/24 h		22.7				11.1
Duodenal or jejunal biopsy	22		11		5	
normal		40.9		91.0		100.0
villous atrophy		31.8		9.0		0.0
inflammatory changes		27.3		0.0		0.0

Thus, high volume diarrhea is a feature of all reported cases of pancreatic cholera syndrome where the tumor involved the pancreas. Stool volumes have not been frequently reported in most other presumed hormone-mediated diarrheal diseases, such as medullary carcinoma of the thyroid (MCT). From reading case reports, the diarrhea of MCT is not as severe as in pancreatic cholera syndrome.

In most cases in whom it has been tested, the diarrhea of pancreatic

cholera syndrome persists during fasting. There is, however, no a priori reason to assume that this would be true in all patients. A hypothetical scheme to illustrate the variety of patterns that might be encountered is shown in the next figure.



In most cases in whom stool electrolyte concentrations have been measured, almost all of the osmolality of stool water can be explained on the basis of sodium and potassium and their anions, i.e., there are no unaccounted for solutes in stool water.

II. HYPOKALEMIA:

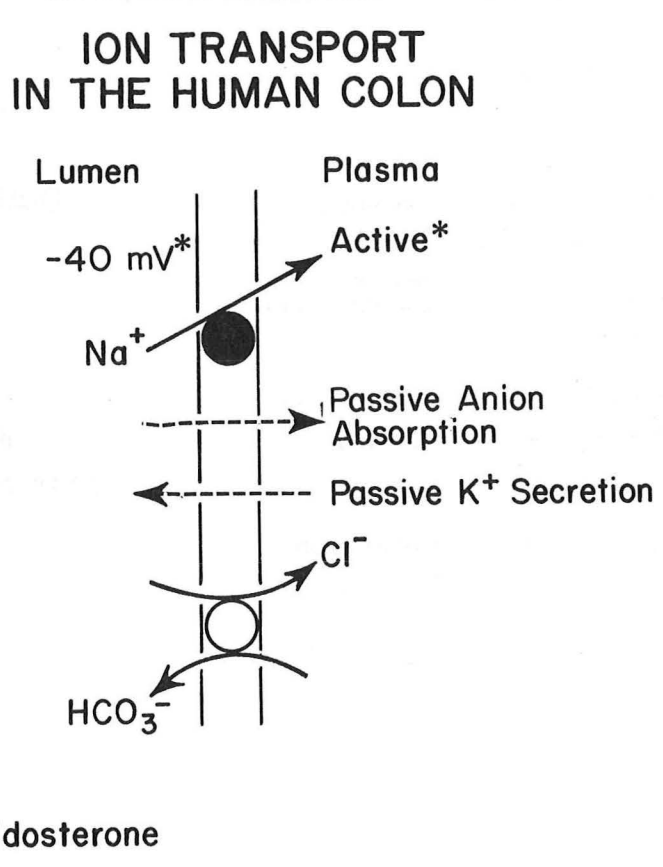
Severe hypokalemia is a clinical feature in many patients with pancreatic cholera syndrome. Verner and Morrison say that hypokalemia is a constant finding during attacks of diarrhea with a mean serum K of 2.2 mEq/L (range 1.2-3.6).

Rambaud et al. studied a patient who had a double-barrel ileostomy. Over a 10-day period, the contents of each ileostomy bag was immediately and gently injected into the cecum (6-7 instillations of 340-730 ml/24 hr). Colonic absorption or secretion was deduced from the difference between cecal inputs and anal outputs, and the results are shown in the next table.

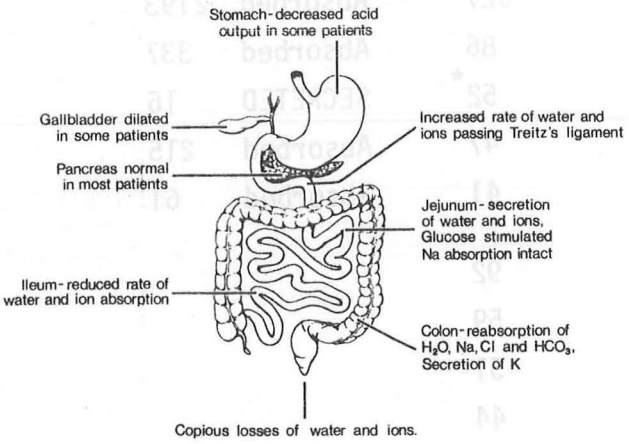
	Ileal Fluid	Feces	Effect of Colon	
Volume, ml/24 hr	3080	927	Absorbed	2193
Na, mEq/24 hr	423	86	Absorbed	337
K, mEq/24 hr	36	52*	SECRETED	16
Cl, mEq/24 hr	262	47	Absorbed	215
HCO_3, mEq/24 hr	102	41	Absorbed	61
[Na], mEq/L	140	92		
[K], mEq/L	12	59		
[Cl],mEq/L	85	51		
[HCO_3], mEq/L	33	44		

*Fecal K losses were much greater at other times in this patient (up to 256 mEq/24 hr). In some patients fecal K losses were as high as 300 mEq/24 hr.

This unique case study illustrates the importance of the colon in conserving water, Na, Cl and HCO3, and in accelerating the loss of K. The mechanisms of these colonic effects are shown in the next figure.



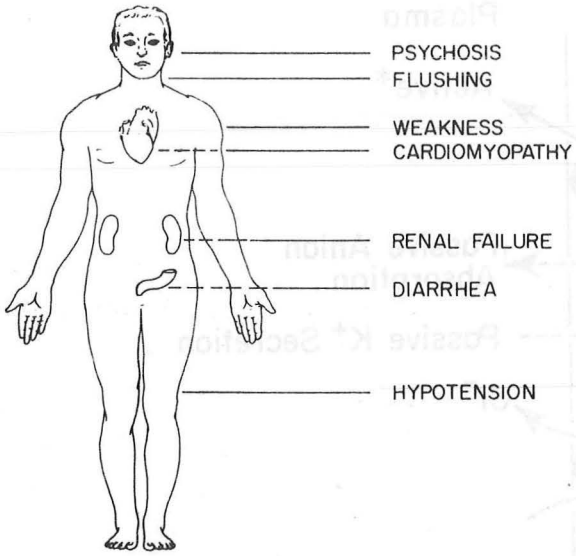
III. Pathogenesis of diarrhea and hypokalemia in three patients we have studied is summarized in the next figure:

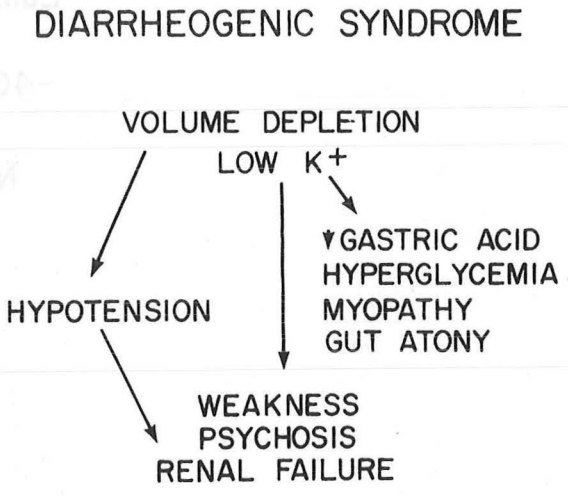


Although results in our three patients were qualitatively the same, other patterns have been reported (Schmitt - pancreatic hypersecretion; Rambaud - decreased small bowel absorption, decreased glucose-stimulated Na absorption and normal fluid flow at ligament of Treitz). Probably these differences are due to different hormone concentrations, to the presence of different hormones, and perhaps because of different durations of illness.

IV. Other Manifestations:

Some of these are summarized in the next two figures and in the next table.





Finding	*Frequency*	*Explanation*
Basal achlorhydria	59%	Hypokalemia, inhibition of gastric secretion by hormone. Rebound hypersecretion of acid may occur after tumor removed.
Hypercalcemia	About 25%	? 2° to tumor secretion and/or to volume depletion. [Ca] may rise after hydration. No evidence of parathyroid tumor has ever been found; therefore don't explore the neck before the abdomen.
Flushing	13 Cases	Unknown cause. Patchy, erythematous, sometimes urticarial. May be intermittent.
Glucose intolerance	50%	Hypokalemia and/or diabetogenic effect of tumor secretion.
Tetany	Rare	? Mg deficiency
Response to steroids	About 30%	? depresses hormone release from tumor and/or stimulates intestinal absorption (↑ Na-K, ATPase). Requires large doses. Nonspecific.

PANCREATIC CHOLERA SYNDROME CAUSED BY ISLET CELL HYPERPLASIA

The reported cases are summarized in the next table. We have studied one patient who is not included in this table; hemipancreatectomy had no effect on the diarrhea, but the entire syndrome was cured by a total pancreatectomy.

Note that one patient (the last in the table) had pancreatic cholera apparently cured by partial pancreatectomy, even though the pancreas was histologically normal.

Eight Cases of Pancreatic Cholera Syndrome Due to Islet-Cell Hyperplasia and One Case Associated with a Normal Pancreas

Sex/ Age (Yr)	Symptoms (Duration)	Oral Glucose Tolerance Test	Serum		Gastric Acidity	Laparotomy and Result	Cell Type
			Potassium	Calcium			
F/57	Watery diarrhea (9 yr)	No data	Low	Normal	Normal	Islet hyperplasia; cured	Nonbeta
F/57	Watery diarrhea (not stated)	Diabetes	Low	High	Low	Islet-cell hyperplasia, subtotal pancreatic resection; cured	Nonbeta
F/24	Watery diarrhea (4 yr)	Normal	Low	Normal	No acid	Islet cell hyperplasia subtotal pancreatectomy; cured	Nonbeta
F/43	Watery diarrhea (5 weeks)	Negative	Low	No data	Low	Islet hyperplasia; subtotal pancreatic resection; cured	Nonbeta
F/47	Watery diarrhea (14 yr)	Negative	Low	High	Low	Islet-cell hyperplasia; died of heart failure	Nonbeta
F/33	Watery diarrhea (2 yr)	Negative	Low	No data	Low	Islet-cell hyperplasia died of heart failure	Nonbeta
F/60	Watery diarrhea (1 yr)	Not done	Low	Normal	Low	Hemipancreatectomy for hyperplasia; cured	Nonbeta
F/34	Watery diarrhea (6 yr)	Diabetes	Low	Normal	Low	Total pancreatectomy, islet-cell hyperplasia; cured	Nonbeta
F/26	Watery diarrhea (10 mo)	No data	Low	No data	Normal	Subtotal pancreatectomy; pancreas "normal"; cured	Normal

Data from Arch. Int. Med. 133:492, 1974

Results in 53 Patients with Pancreatic Cholera Syndrome

Reviewed by Verner and Morrison

20 (37%) - Malignant with metastasis

16 (30%) - Cured by surgical removal of benign islet cell tumor.

7 (13%) - Benign islet cell tumor
Undiagnosised during life
Fatal diarrhea

11 (20%) - Diffuse hyperplasia
8 cured surgically

1 - Pancreas completely normal, diarrhea cured by subtotal pancreatectomy.

Summary of Status of VIP According to Current Literature

1) Probably the hormone responsible for most of the manifestations of pancreatic cholera syndrome.

2) The advent of immunology for VIP in plasma should allow earlier diagnosis of this syndrome before tumors have metastasized.

3) May mediate the diarrhea in patients with several other tumors.

Case II:

C.G.: This 25-year-old woman began having severe diarrhea and hypokalemia in 1974. She lost about 25 pounds. X-rays and other routine diagnostic studies revealed no abnormalities. Proctoscopy showed inflammatory changes suggestive of early ulcerative colitis. She was treated with prednisone, Azulfidine, Lomotil and codeine, but the diarrhea continued. In February 1975, she underwent exploratory laparotomy, which revealed no abnormal findings.

In the summer of 1975, she had an extensive workup at a medical center which revealed no evidence of gastrointestinal disease. However, the serum VIP concentration (Said) was 6,200 pg/ml, which was markedly elevated. The diagnosis of pancreatic cholera syndrome or one of its variants seemed likely. There was no evidence of any extra pancreatic tumor.

Because of the severe diarrheal disease, the markedly elevated VIP, and the previously negative exploratory laparotomy (including a negative examination of the pancreas), the absence of evidence of any other tumor, it seemed likely that the patient had pancreatic cholera syndrome due to pancreatic hyperplasia or due to a small pancreatic adenoma.

Prior to pancreatectomy the patient was referred to Dallas for intestinal perfusion studies, hopefully to elucidate the mechanism of diarrhea.

Stool Collection

3-day fast, i.v. fluids:	No diarrhea			
Eating normal food:	Volume	Na	K	Osmolality
Day 1	490	126	27	315
2	490	126	27	315
3	425	101	44	312
4	200	122	30	310
5	270	106	35	345
6	665	131	19	392
7	200	122	26	300

Thus, the patient had diarrhea, and fecal electrolytes accounted for all of the fecal osmolality. But the highest stool volume was 0.7 liters per 24 hours, and it did not persist during fasting. This would be unusual insofar as the reported cases of pancreatic cholera syndrome are concerned, but this might be explained by the fact that the diagnosis had been reached much earlier than usual in this case, because of the availability of the VIP assay.

A small bowel perfusion study was performed, and the results were entirely normal, as shown in the next table (which compares the finding in C.G. with a group of normals and with a patient with known pancreatic cholera). Ileal absorption (not shown) was also normal in C.G.

Small Bowel Perfusion Study:

Water and Glucose Movement in 30-cm Segments of Jejunum

	Water Absorption During Perfusion of Balanced Electrolyte Solution	Glucose Absorption During Perfusion of 65 mM Glucose
19 Normals	Absorbed 60 ml/hr (Range 15-104)	Absorbed 12 mmol/hr (Range 7.5-20)
Pancreatic cholera syndrome	Secreted 86 ml/hr	Absorbed 13.3 mmol/hr
C.G.	Absorbed 113 ml/hr	Absorbed 7 mmol/hr

Based on these results, a defect in small bowel function seemed an unlikely cause of this patient's diarrhea. Her stools were tested for

phenolphathalein and each was strongly positive. The final diagnosis was surreptitious laxative ingestion.

This patient illustrates the importance of ruling out laxative abuse in patients suspected of having pancreatic cholera syndrome and shows that high VIP concentrations, at least by current assay methods, are not specific for pancreatic cholera syndrome and related diseases.

Case III - A Case Illustrating Diagnostic and Therapeutic Hazards:

B.C.: This 33-year-old woman was apparently well until 1969 when she developed diarrhea. A sigmoidoscopy revealed mild proctitis and a barium enema was interpreted as mild ulcerative colitis. Rectal biopsy showed chronic nonspecific inflammation. A small bowel series showed early jejunitis.

Over the next two years the diarrhea was severe and persisted in spite of many different diets and drugs, including prednisone. Salt depletion and hypokalemia occurred frequently, requiring innumerable hospitalizations for fluid therapy. The patient was explored surgically on 9-3-71, but no definite abnormalities were found.

In 1972 colonoscopy showed colitis. X-rays showed ileitis and colitis. In 1974 she again was operated, and only minimal changes were noted in the colon and small bowel. A loop ileostomy was performed two feet above the ileocecal valve, without bowel resection. Postoperatively, she had severe diarrhea from the ileostomy, with little or no diarrhea per rectum.

She developed aseptic necrosis of both hips, presumably because of prednisone therapy, and later in 1974 she had a total left hip replacement.

Diarrhea continued and repeat x-rays in 1974 were interpreted as regional enteritis of the colon and small bowel. She was operated on in December 1974, at which time all of the colon, except the rectum, were resected. A short segment of terminal ileum was removed, and a standard ileostomy was performed. Ten cm of mid-jejunum were reversed. The pancreas appeared grossly normal. Examination of the resected colon revealed "increased cobblestoning" of the mucosa in places, but in other broad areas the mucosa was grossly normal. No ulcerations were seen. Microscopically, the colon showed "quiescent chronic transmural colitis". The resected ileum showed chronic inflammation with mucosal gland hyperplasia.

Postoperatively, severe ileostomy diarrhea continued. Her x-rays and histological material were reviewed, and it was concluded that the diagnosis of regional enteritis could not be substantiated. Pancreatic cholera syndrome was suspected. Gastric acid secretion, secretin test, small bowel biopsy and serum concentrations of calcitonin, serotonin, gastrin, prostaglandins E and F and VIP (Bloom and Said) were normal. Urinary 5HIAA and catecholamines were normal.

The patient was referred to Dallas for small bowel perfusion studies

in May 1975. Ileostomy specimens contained no phenolphthalein, and the patient denied any use of laxatives since the onset of her diarrhea.

Ileostomy Output - B.C.:

	Volume	Na	K	Osmolality
Fasting:				
Day 1	2217	122	13	288
Day 2	2160	125	14	285
Eating:				
Day 1	2520	116	19	328
Day 2	2445	99	18	300
Day 3	2718	92	17	270

Thus, this was a large volume diarrhea, which persisted during fasting and all of the osmolality of stool was accounted for by Na, K, and their anions. These findings were highly suggestive of a secretory diarrhea and easily compatible with pancreatic cholera syndrome.

Small bowel perfusion study was performed and revealed completely normal results, as shown in the next table.

Small Bowel Perfusion Study:

Water and Glucose Movement in 30-cm Segments of Jejunum

	Water Absorption During Perfusion of Balanced Electrolyte Solution	Glucose Absorption During Perfusion of 65 mM Glucose
19 Normals	Absorbed 60 ml/hr (Range 15-104)	Absorbed 12 mmol/hr (Range 7.5-20)
J.K. Pancreatic cholera	Secreted 86 ml/hr	Absorbed 13.3 mmol/hr
B.C.	Absorbed 58 ml/hr	Absorbed 13 mmol/hr

This patient's findings may be summarized as follows:

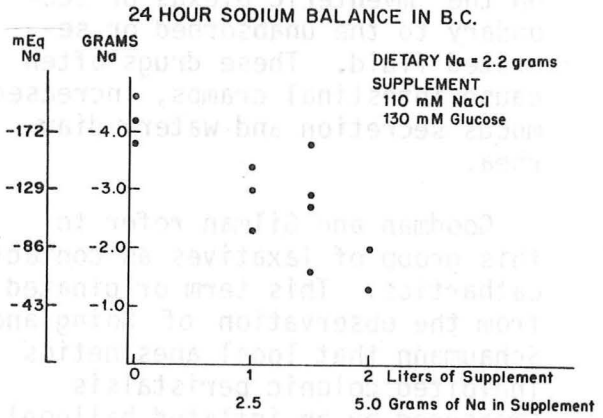
1) Severe "secretory"diarrhea
2) Normal plasma hormone assays
3) Negative previous laparotomies for tumors
4) No phenolphthalein in stool
5) Normal small bowel perfusion study
6) No diagnosis evident

The diarrhea was so severe that the patient had to receive i.v. fluids every 2-3 days, and she was in hospital for about 50% of the time in 1974-1975. The small bowel perfusion study had shown that glucose absorption was normal and that glucose enhanced sodium absorption, as illustrated in the next table.

Sodium Absorption in a 30-cm Segment of Jejunum in B.C.

Sugar	Sodium Movement
65 mM Mannitol	Secreted 8 mEq/hr
65 mM Glucose	Absorbed 12 mEq/hr
	[Na] perfused = 105 mEq/L

Thus, we attempted to correct her negative sodium balance by giving oral solutions of Na-glucose (NaCl 110 mM, glucose 130 mM, osmolality 350 mOsm/kg). The results are shown in the next figure. Although negative sodium balance was reduced by the solutions, large volumes were required and the patient was still in negative sodium balance. i.v. fluids were still required q. 3 days during the stay in the C.R.C. when these studies were done.



Because no adequate solution could be found for this problem, the patient was evaluated for an A-V shunt so that i.v. fluids could be given easily at home by her family.

Before she left Dallas, her room was searched, and an empty box of Carter's Little Pills and Lasix tablets were discovered. Analysis of ileostomy fluid revealed high concentrations of aloin. In retrospect it seems likely that the entire illness resulted from surreptitious laxative ingestion which resulted in the x-ray, surgical and pathological findings and in inappropriate and harmful medical and surgical therapy. Review of her records revealed that a rectal biopsy in 1969 showed melanosis coli.

A Tentative Classification of Laxatives

Bulk: Agar, methyl cellulose, sodium carboxymethyl cellulose, bran

Wetting Agents (Softeners): Dioctyl sodium (Colase, Surfact) — Also inhibits water and electrolyte absorption

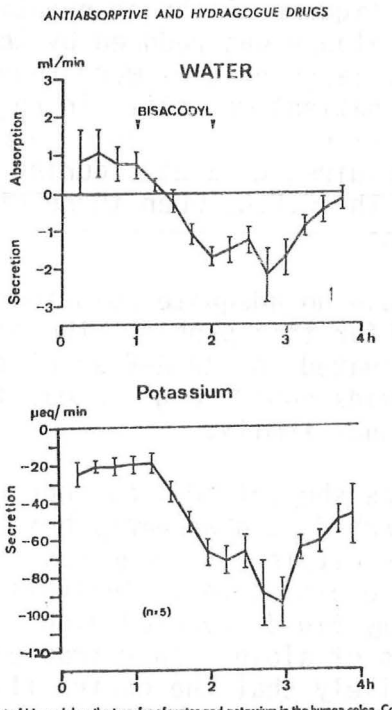
Osmotic: Salts ($MgSO_4$, Na_2SO_4)
Sugars (lactulose)

Stimulants: Anthraquinones
- Cascara sagrada
- Danthrone (Dorbane)
- Senna
- Rhubarb
- Aloe

Diphenylmethane derivatives
- Phenolphthalein
- Bisacodyl (Dulcolax)
- Oxyphenisatin

Castor oil (ricinoleic acid)
Plant resins
- Jalap, colocynth, elaterin, iponea, gambage, podophyllum

The stimulant laxatives have two general effects. First, they either inhibit ion and water absorption, or they stimulate ion and water secretion. Second, they cause mucosal inflammation (and ultimately damage to the myenteric plexus). Peristalsis is stimulated by these laxatives, either via a direct effect on the myenteric plexus or secondary to the unabsorbed or secreted fluid. These drugs often cause intestinal cramps, increased mucus secretion and watery diarrhea.



The effect of bisacodyl on the transfer of water and potassium in the human colon. Colon perfusion was performed according to the method of Devroede and Phillips (1969); values are given with the standard deviation, n = 5 (Ewe, 1974).

Goodman and Gilman refer to this group of laxatives as contact cathartics. This term originated from the observation of Going and Schaumann that local anesthetics inhibited colonic peristalsis (measured by an inflated balloon) that had been stimulated by a diphenylmethane derivative, even though the anesthetic did not

prevent colonic peristalsis stimulated by bethanechol. Goodman and Gilman use the term in a more general context to indicate that these laxative effects depend on a direct action on the intestine, rather than because of a physical force such as an osmotic pressure gradient.

The anthraquinone and diphenylmethane derivatives act mainly on the colon. After oral ingestion, a laxative effect occurs in about 6 hours. In contrast, castor oil and the cathartic resins act on the small bowel (presumably also on the colon) and cause diarrhea in about 3 hours after ingestion.

Phenolphthalein:

Fifteen per cent is absorbed and excreted in either the urine or bile (enterohepatic circulation); the latter may prolong its effect. Some authors say conjugation in the liver with glucuronide and excretion via bile is required for its laxative effect, and that phenolphthalein does not cause a laxative effect in patients with bile duct obstruction.

Bisacodyl (Dulcolax):

Decreases glucose absorption in the small bowel of man and rats, and induces secretion of water and electrolytes in the colon. Its main effect is in the colon. When given to patients with ileostomy, there is no increased ileostomy output.

Anthraquinones:

The glycosides are hydrolyzed in the lumen of the bowel by bacteria to yield free anthraquinones, which cause the laxative effect. Aloe has the reputation of being the most "irritating" of all the anthraquinones. Aloin is a mixture of active glycosides. These drugs were alleged to be cholagogues and were in many "liver pills". However, they have no effect on bile flow or formation or on gallbladder contraction. The anthraquinones are apparently the cause of melanosis coli.

Plant Resins:

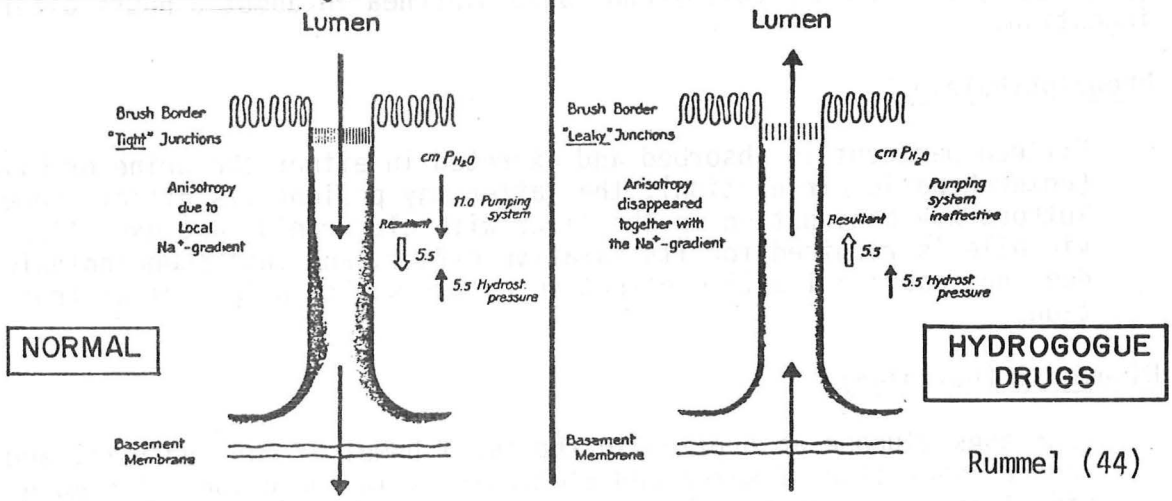
Stimulate motor activity and decrease sodium transport in the small bowel.

Thus, the anthraquinones and diphenylmethanes act mainly in the colon and the plant resins and castor oil act mainly in the small bowel. B.C., the patient with ileostomy who may have been taking Carter's Little Pills (aloe and podophyllum), probably had ileostomy diarrhea because of the podophyllum. The melanosis coli (prior to colectomy) was probably secondary to the aloe.

Mechanism of Laxative Action:

1) Decrease Na-K ATPase. This would cause reduced ion absorption, but would not cause intestinal secretion.

2) Disruption of tight junctions between epithelial cells, which decrease the effectiveness of active ion pumping and allows tissue pressure to force fluid from interstitial space into bowel lumen. See next figure.



Diarrhea in Laxative Abuse:

Usually does not exceed 1 liter per day. K losses in stool usually do not exceed 25 mEq/24 hr. Due to 2° aldosteronism, urinary losses of K often contribute to K depletion. Heizer et al. reported 2 patients with stool volume of up to 2.7 and 5.4 L/24 hr.

Surreptitious Laxative Abuse:

Major manifestations are supposed to be abdominal pain and diarrhea, hypokalemia, muscle weakness, thirst, melanosis coli, and x-ray abnormalities in the colon.

Cummings recently reported 7 patients (next table for case summaries). All were women, all concealed the laxative habit, and two concealed the fact they had diarrhea. The symptoms were diarrhea, abdominal pain, and weight loss. None had typical x-ray or sigmoidoscopic changes. Six had had exploratory laparotomy. Rectal biopsy was abnormal in three. Hypokalemia was present in four.

Diagnosis of Surreptitious Laxative Abuse

1) High index of suspicion
2) Sigmoidoscopy and rectal biopsy
3) B.E.
4) Identification of laxative by chemical testing and search, both of which must be done repeatedly.

Case	Age	Sex	Main Complaints	Length of History (Years)	No. of Hospital Admissions	No. of Days in Hospital	Type of Laxative Used	Laparotomy	Barium Enema	Rectal Biopsy	Additional Abnormalities	How Diagnosed
1)	48	F	Abdominal pain, weight loss	3	2	83	Phenolphthalein	Yes	-	-	Steatorrhoea, GTT Hb 77%, low xylose excretion, jejunal bacteriology, Personality disorder	Stool test
2)	50	F	Diarrhoea, abdominal pain, vomiting	4	6	162	Phenolphathalein	No	Diverticula	Normal	Tetany, depression	Stool test
3)	26	F	Vomiting, diarrhoea, abdominal pain	8	11	202+	Senokot	Yes x 2	Normal	Inflammation Hypertrophy of muscularis mucosae	Oedema, clubbing, hiatus hernia, low enteroglucagon, anorexia nervosa	Locker search
4)	46	F	Diarrhoea, abdominal pain	20	4	59+	Cascara	Yes	Abnormal	Inflammation Hypertrophy of muscularis mucosae	Pyelonephritis, cataracts, low B_{12}	Locker search
5)	65	F	Diarrhoea, abdominal pain, vomiting	10	6	180	Phenolphthalein	Yes	Diverticula	Normal	Gastric ulcer, alopecia artefacta	Stool test
6)	26	F	Abdominal pain, vomiting, weight loss	1	3	89+	Vegetable laxative	Yes	Normal	Normal	Pancreatic scan, serum amylase	Locker search
7)	47	F	Diarrhoea	2	8	111	Phenolphthalein + senna (Nylax)	Yes	Normal	Inflammation Melanosis	Pancreatic scan achlorhydria, oedema, raised secretion	Stool test

Case 1 Comment: This patient concealed both her dirrhoea and her laxative-taking. The steatorrhoea and Lundh test result suggested pancreatic disease, which was not confirmed at laparotomy. There was no electrolyte disturbance. Colonic function was never investigated because the diarrhoea did not become apparent until the end.

Case 2 Comment: This is a clear example of factitious diarrhoea without the characteristic radiological, sigmoidoscopic, or histological features. Apart from mild hypokalaemic alkalosis her physical condition was good but there was a background of psychiatric disturbance.

Case 3 Comment: This patient's abuse of cathartics was not associated with either melanosis coli or with radiological changes. Having been extensively investigated for vomiting she progressed to factitious diarrhoea. Despite the gross diarrhoea her plasma electrolytes remained normal.

Case 4 Comment: It took many years to arrive at the correct diagnosis in this patient. The histological changes were suggestive though there was no melanosis. Childhood impressions may well have influenced her attitude towards bowel habit and led to the fear of constipation and thus the laxative taking. She suffered severe renal damage, presumably secondary to the hypokalaemia.

Case 5 Comment: This patient spent over six months in hospital during 10 years and underwent numerous uncomfortable investigations. She has made over 80 visits to outpatients and 20 to the x-ray department. Though suspected of taking laxatives for two or three years before the final diagnosis was made, the radiology, histology, and first chemical tests of the stool did

not confirm this.

Case 6 Comment: This was a patient with a disturbed background who had many features of pancreatic disease and was willing to undergo the pain and inconvenience of investigation and laparotomy while concealing her laxative taking. Despite suspicion, the laxatives were not detected by chemical means.

Case 7 Comment: Suspicion that this patient was taking laxatives was aroused but was confounded by her denials and by negative results of radiological investigation, urine tests, and a locker search. The achlorhydria with hypokalaemia and diarrhoea suggested a pancreatic tumour but this was not substantiated. It took seven hospital admissions and a laparotomy before her laxative taking was diagnosed.

Melanosis coli:

1) Caused by anthraquinone laxatives. Anal stenosis and fecal stasis may also contribute to its causation.

2) Appears from 4 to 14 months after start of anthraquinones.

3) Goes away 5 to 11 months after stopping the anthraquinones.

4) Pigment may be distributed over the entire colon, but mainly it is in the cecum and rectum.

5) Polyps and cancer in the same region do not contain the pigment.

6) Often present on histological exam when not apparent grossly.

7) The pigment differs from melanin on EM. Probably the granules have their origin in degenerating mitochondria, after which the macrophages ingest the pigment. The granules contain lipofuscin and glycogen and perhaps anthraquinone or one of its breakdown products.

Pathology of Cathartic Colon

1) Loss of myenteric plexus
2) Atrophy of smooth muscle coats
3) Melanosis coli
4) Mucosal inflammation

Grossly the colon is thin and baggy. The transverse colon is pendulous and the sigmoid is dilated. Surgically resected specimens show gross mucosal changes, resembling the skin of a toad's back. Histologically there is a pronounced but patchy thickening of the muscularis mucosae and an excessive quantity of fat in the submucosal layer. The muscularis propria is thinner than normal.

Morrison (49) claims that the histopathology of cathartic colon is distinctive from other inflammatory bowel disorders.

X-ray Findings in Cathartic Abuse (Stimulant Laxatives)

1) Loss of haustrations
2) Smooth mucous membrane as seen in relief
3) Apparent shortening of the right colon
4) Inconsistent constrictions (pseudostrictures)
5) Marked distensibility

Changes may involve the right side of the colon and terminal ileum, or entire colon, and may closely resemble inflammatory bowel disease. On the other hand, patients with cathartic abuse may have a normal colon by x-ray.

Management of Surreptitious Laxative Abuse

Proper management is unresolved. Results in the seven patients reported by Cummings were as follows:

4 told that laxative abuse had been discovered.

- 2 of these denied it and refused further help and followup.
- 2 are under psychiatric care, and 1 has twice attempted suicide.

1 found out on her own that laxative abuse had been discovered. She is receiving psychiatric help.

2 not told that laxatives discovered. They are supported by regular outpatient visits, electrolyte therapy, etc.

Summary of Cases Referred for Perfusion Study with Tentative Dx. of Pancreatic Cholera Syndrome

Patients	Stool Volume L/24 h	Stool Electrolyte Pattern	Fecal K Loss mEq/24 h	VIP		Jejunal Perfusion	Final Dx.
				Bloom	Said		
J.K.	1.8-5.5	S	140	500	1000	Secretion	Islet cell adenoma
L.W.	8.8	S	150	13	5000	Secretion	Islet cell hyperplasia
D.S.	2.1	S	95	409	2600	Secretion	Ganglioneuroblastoma
W.D.	0.7	S	35		6500	Normal‡	Oat cell carcinoma
L.H.	1.5	S	29			Normal	Laxative
J.S.	2.7	S	98			Normal	Laxative
B.C.	2.7*	S	46	3		Normal	Laxative
C.G.	0.7	S	13		6200	Normal	Laxative
B.P.	2.1	S	68			Normal	No dx. - Autopsy neg.
B.W.	0.6	S	57			Normal	No dx. - Laparotomy neg.
R.D.	< 0.2‡					Normal‡	No dx.
C.G.	< 0.2‡				6000	Normal‡	No dx. - Partial pancreatectomy

Stool electrolyte pattern: S = secretory diarrhea (Solute gap small and diarrhea persisted during fast.)

*Ileostomy

‡At time of perfusion study patient had no diarrhea.

Suggested workup for severe diarrhea when routine GI studies demonstrate no gastrointestinal disease and fail to reveal a diagnosis:

1) R/O drug-induced diarrhea
   Laxatives, antacids, digitalis, antibiotics, antihypertensives, colchicine, paradoxical diarrhea with opiates
2) Urinary 5HIAA and catecholamines, toxic screen, serum gastrin and immunoglobulins
3) R/O endocrine disease
   Addison's, thyrotoxicosis, hypoparathyroidism
4) Small bowel aspiration - culture and giardia
5) Measure fecal volume and electrolytes during eating and fasting. In <u>osmotic diarrhea</u>, the diarrhea should stop on fasting, and there should be a large solute gap between fecal Na, K, their anions and fecal osmolality. In <u>secretory diarrhea</u>, the diarrhea will often persist on fasting, and there is a small solute gap.
6) For osmotic diarrhea, find out what is causing the osmotic gap.
7) For secretory diarrhea:
   a) Careful search for laxatives and tumor
   b) Serum calcitonin and perhaps other hormone assays, if available
   c) Small bowel perfusion, if available
   d) Angiogram - beware of false positive and negative
   e) Laparotomy - decide in advance if should do a partial pancreatectomy if a tumor not found

SUMMARY

Major Causes of Chronic Secretory Diarrhea

1) Surreptitious laxative ingestion - most common
2) Pancreatic cholera syndrome (islet cell tumor or hyperplasia)
3) Medullary carcinoma of the thyroid
4) Ganglioneuroma
5) Oat cell carcinoma of the lung
6) Secreting villous adenoma of the rectum

Note: Diarrhea due to fatty acids and bile acids may have a secretory component, but in these patients diarrhea would presumably stop upon fasting, and either steatorrhea or fairly obvious ileal disease would probably be evident. ZE syndrome and malignant carcinoid syndrome might also present as a secretory diarrhea. Patients with sprue have small bowel secretion, but it is doubtful that they would be confused with secretory diarrhea as defined above. Patients with congenital chloridorrhea would meet the criteria for secretory diarrhea; the diarrhea would have been present since childhood and fecal chloride concentration would be abnormally high.

Conclusions About VIP

1) It may be the hormonal mediator of some or many cases of diarrhea associated with neural crest tumors.

2) If so, it probably does not work by stimulating intestinal mucosal cAMP.

    a) In one of our patients (Case I) mucosal cAMP was the same before and after the diarrhea was cured by removal of the pancreatic tumor.

    b) Concentrations of VIP that are necessary to increase cAMP experimentally are much higher (100,000 pg/ml) than occur in the plasma of patients with presumed VIP-induced diarrhea (about 5,000 pg/ml).

3) Current serum assays are of no help in diagnosis of secretory diarrhea because of false-positive results in normal subjects and in patients with diarrhea due to other causes. If the assays can be improved, as it undoubtedly will be, measurement of plasma VIP concentration may become very important, assuming that VIP is a mediator of tumor-associated diarrhea.

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