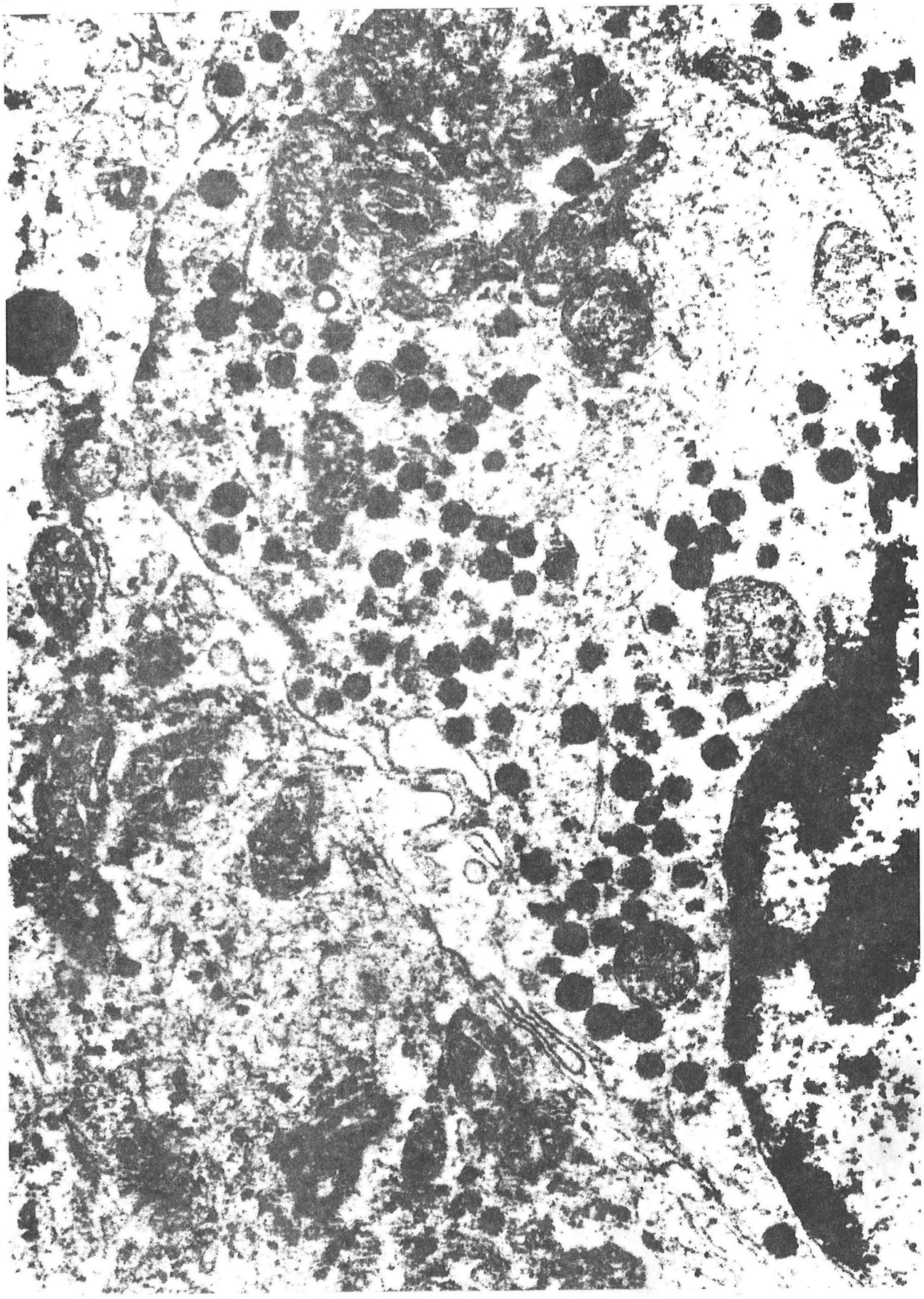
GI

VIPOMA SYNDROME



INTERNAL MEDICINE GRAND ROUNDS

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Figure 1 (Cover Page):

Electronmicroscopic picture (x 23,800) of pancreatic VIPoma cell. The tumor cell contains small, dense, haloed granules. Note the small intercellular spaces with microvilli. (Courtesy of Dr. Julia M. Polak, Department of Histochemistry, Royal Postgraduate Medical School, London, England; Ref. 1)

INTRODUCTION

In 1957 Priest and Alexander described a patient with islet cell tumor and severe watery diarrhea and hypokalemia (2). The diarrhea responded to steroid therapy for a period of one year before it became intractable and resulted in the patient's death. Since just two years earlier Zollinger and Ellison had described the association of non-insulin-secreting islet-cell tumors of the pancreas with peptic ulceration (3), this case was thought to be a variant of the Zollinger-Ellison syndrome.

However, Verner and Morrison of Duke University, North Carolina, first called attention to the syndrome of watery diarrhea, hypokalemia and death from renal failure in association with islet cell tumor (4). There are several synonyms for this syndrome (Table I).

TABLE 1

SYNONYMS

PANCREATIC CHOLERA SYNDROME

VERNER-MORRISON SYNDROME

WDHH - SYNDROME
(WATERY DIARRHEA, HYPO-
KALEMIA, HYPOCHLORHYDRIA)

VIPOMA

The name pancreatic cholera was coined by Sherman Mellinkoff, Dean of UCLA School of Medicine, (5) and was first used in a publication (without attribution to Mellinkoff) by Matsumoto and co-workers (6). Pancreatic cholera syndrome is a good name because the diarrhea results from intestinal secretion just as in Asiatic cholera. However, it fails to denote that some tumors are outside the pancreas. Bloom, Polak and Pearse first recognized that patients with this syndrome had raised plasma levels and high tumor content of vasoactive intestinal polypeptide (VIP) (7).

CASE REPORT

A.N. is a 48- year- old, white, male mechanic from Mabank, Texas. He was in good health until the summer of 1980 when his stools became loose and mushy, and over a period of several months he developed chronic watery diarrhea with up to ten bowel movements per day. He had to get up during the night to pass stool and several episodes of fecal incontinence occurred. He was seen by a gastroenterologist and had a negative work-up which included barium studies of the GI-tract, proctoscopy and stool for O & P. He was given the diagnosis of fecal incontinence and was treated with loperamide. Despite treatment the diarrhea increased slowly and the patient became progressively weaker. In December of 1981 he became unable to move his extremities and was paralyzed to a degree that he was unable to dial a telephone number. At that time he presented to Baylor Hospital in Dallas. His serum potassium on admission was 1.7 meq/l.

Stool analysis revealed secretory diarrhea. Abdominal sonography and angiography were negative but CT scan suggested liver metastases. Peritoneoscopy with directed liver biopsy revealed islet cell tumor. Plasma VIP concentration was elevated (750 pg/ml, normal <170, Laboratory of Dr. T.O'Dorisio, Columbus, Ohio). A diagnosis of VIPOMA was thus established.

The patient was subsequently admitted to the General Clinical Research Center at The University of Texas Health Science Center at Dallas and additional studies were performed (see below).

VIP
(VASOACTIVE INTESTINAL POLYPEPTIDE)

In 1968 Dr. Sami Said, a Dallas pulmonologist had been interested in the occurence of vasoactive peptides in lung tissue (8,9). He went to work on such peptides in the laboratory of Dr. Viktor Mutt at the Karolinska Institutet in Stockholm, Sweden. In this laboratory large amounts of porcine small intestinal tissue are routinely processed and it was only logical to determine if extracts of intestinal tissue, like lung tissue, contained vasoactive peptides. It was found that tissue extracts from porcine intestine

contained considerably higher concentrations of vasoactive substances than did extracts of lung tissue. Therefore, Said and Mutt planned to isolate at least one vasoactive peptide from intestinal tissue before continuing with the work on lung tissue. VIP was isolated in pure form in 1972 (10). Interestingly,the amino acid sequence had been secretly conveyed by V. Mutt to M. Bodanszky. Thus, publication of the synthesis of VIP (11) preceded publication of the amino acid sequence (12).

VIP is a 28-amino acid polypeptide with a molecular weight of 3326. The amino acid sequence shows similarities to secretin and glucagon(13) (Table 2).

TABLE 2 AMINO ACID SEQUENCES OF VIP, SECRETIN AND GLUCAGON (13)

VIP	
Porcine/bovine	H S D A V F T D N Y T R L R K Q M A V K K Y L N S I L N [a]
Chicken	H S D A V F T D N Y S R F R K Q M A V K K Y L N S V L T [a]
Secretin	
Porcine	H S D G T F T S E L S R L R D S A R L Q R L L Q G L V [a]
Chicken	H S D G L F T S E Y S K M R G N A Q V Q K F I Q N L M [a]
Glucagon	
Mammalian	H S Q G T F T S D Y S K Y L D S R R A Q D F V Q W L M N T
Turkey/chicken	H S Q G T F T S D Y S K Y L D S R R A Q D F V Q W L M S T
Duck	H S Q G T F T S D Y S K Y L D T R R A Q D F V Q W L M S T

The one-letter notation for amino acid residues (*Eur. J. Biochem.* 5:151–153, 1968) is used.

The concepts and understanding of the physiological role of VIP have undergone considerable evolution in the past 10 years. While VIP was discovered by Said as a vasoactive substance (8-10) it was viewed as a candidate GI-hormone by the late Morton Grossman (14). When in 1976 the peptide was demonstrated in neurones of the central and peripheral nervous system it soon became apparent that the major function of VIP may be that of a neuropeptide, neurotransmitter or neuromodulator (16-18).

VIP AS NEUROTRANSMITTER

Soon after cross reaction of a material in mammalian central and peripheral neurons with antisera to porcine VIP had been observed, efforts were concentrated on establishing VIP as a neurotransmitter.

Figure 2 schematically shows the action of a neurotransmitter among the other modes of peptide delivery (19).

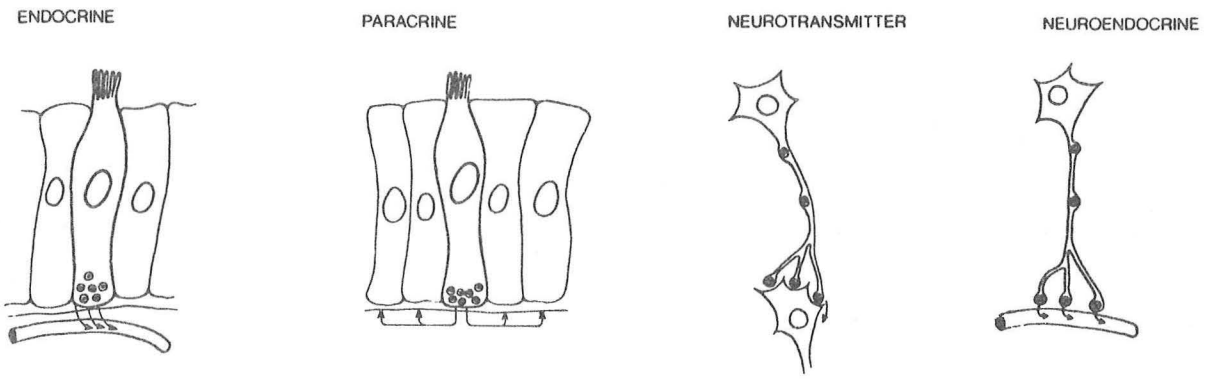


Figure 2 *Diagrammatic representation of the mode of delivery of peptides acting as hormone, paracrine messenger, neurotransmitter and neurohormone. The same molecule could function in each of these systems in a single organism. (From Dockray, 1979, Ref. 19)*

In order to establish the identity of a neurotransmitter several criteria must be fulfilled (Table 3) (20,21).

TABLE 3

NEUROTRANSMITTER:

1. SUBSTANCE MUST BE PRESENT IN NEURONS
2. NEURONS MUST POSSESS MECHANISMS FOR SYNTHESIS OF NEUROTRANSMITTER
3. PRESENCE OF PRECURSORS IN NEURONS
4. SYSTEM FOR INACTIVATION
5. MUST BE RELEASED DURING STIMULATION
6. EFFECT MIMICKED BY EXOGENOUS APPLIC.
7. INTERACTIONS WITH PHARMACOLOG. AGENTS
8. SPECIFIC POSTSYNAPTIC RECEPTORS

Neurotransmitter Criterion #1: (Substance must be present in neurones)
VIP has been demonstrated in the neurons of the central nervous system (see above) and in several peripheral autonomic nervous structures such as the enteric nervous system (22) and in autonomic nerves supplying the lungs (23) and genital tract (24). VIPergic nerves form a major part of the newly recognized class of non-adrenergic non-cholinergic (purinergic or peptidergic) nerves.

Fig. 3 shows a complex VIP-immunoreactive nerve network in human colonic mucosa. A dense mesh of interconnecting, highly varicose fibers can be seen in the muscularis mucosae extending in between and around the crypt spaces and in the core of ileal villi (25,26).

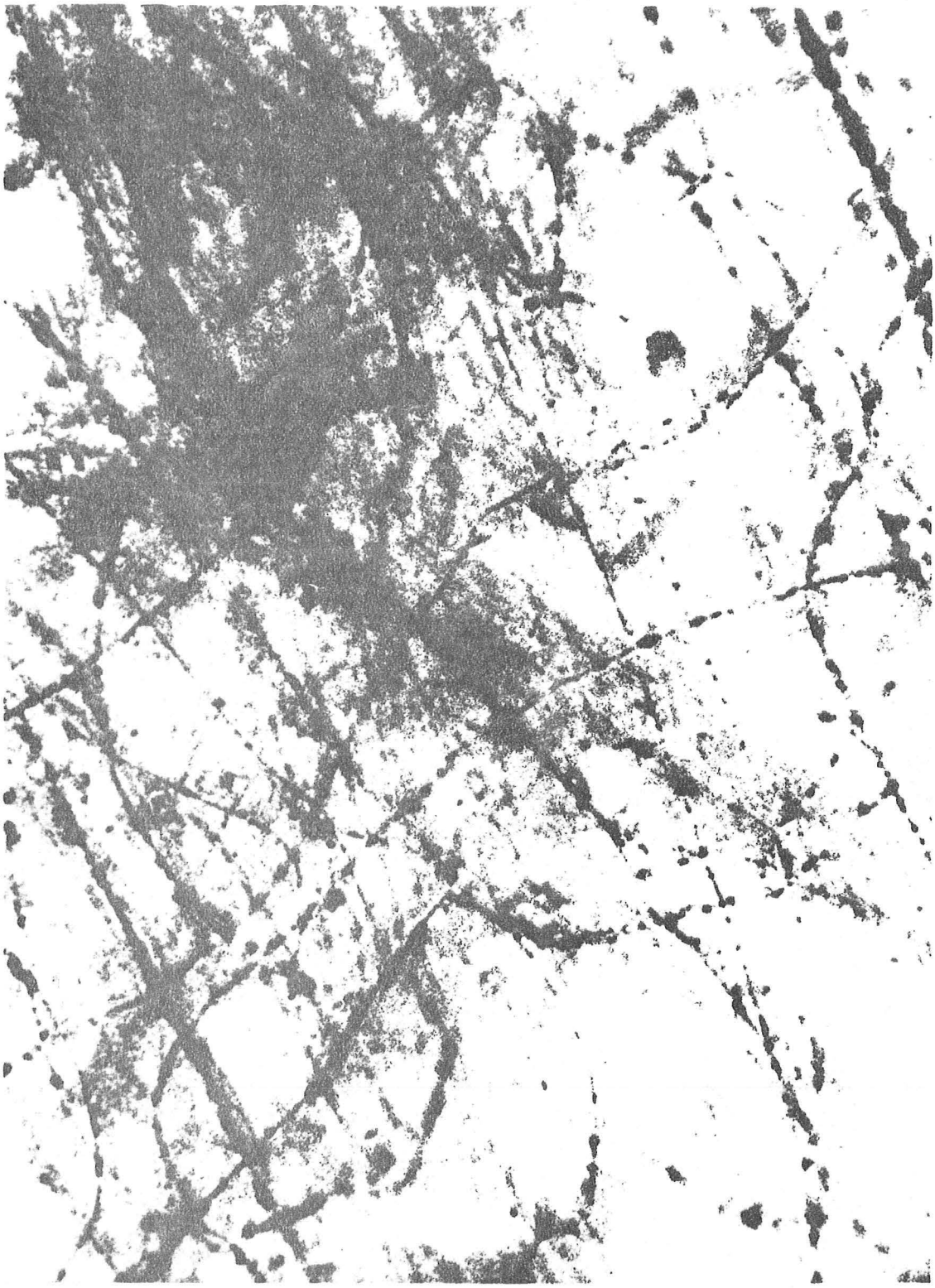


Figure 3 *A network of VIP immunostained fibers present in the submucosa of human colon, at a level just below the muscularis mucosae (x 1100). (Courtesy of Dr. Julia M. Polak, Department of Histochemistry, Royal Postgraduate Medical School, London, England; Ref. 25, 26).*

In the genital tract VIPergic nerves are found in high concentration. Dr. Julia Polak recently studied thirty surgical specimens of male external genitalia. Using immunocytochemistry and radioimmunossay VIP was found exclusively in fine autonomic nerves. VIPergic nerves were most densely concentrated on the penis around pudendal arteries and in the erectile tissue of the corpus cavernosom (27).

Neurotransmitter Cirterion #2: (Neurons must possess mechanisms for synthesis of neurotransmitter) At present no information exists on the biosynthesis of VIP in neurons.

Neurotransmitter Criterion #3 (Presence of precursors in neurons) So far no definite VIP precursors have been found. The relationship of different molecular forms of VIP in different tissues (28), and particularly the large molecular forms demonstrated in brain extract (18) to the biosynthesis, storage and secretion of VIP has not yet been established.

Neurotransmitter Criterion #4 (System for inactivation) This could include enzymatic inactivation or a specific uptake mechanism for the transmitter into the pre and postsynaptic structures. In rabbit brain a protease with a high degree of specificity for VIP has been found (29).

Neurotransmitter Criterion #5 (Substance proposed as neurotransmitter must be released from neurons). A release of VIP has been demonstrated after electrical stimulation of the pelvic and vagal nerves (30-32) and has also been observed in the central nervous system after depolarization (33).

Neurotransmitter Criterion #6 (Effect of transmitter mimicked by exogenous application) VIP has, for instance, been demonstrated to relax the smooth muscles of the stomach (31). The effects of administered VIP are similar to those observed after electrical activation of nerve fibers with release of VIP into the concomitant circulation (34).

Neurotransmitter Criterion #7 (Interaction with pharmacological agents) Pharmacological agents which interact with the synaptically released transmitter should interact with the suspected transmitter in an identical manner. So far no drugs are known which affect the response to exogenously applied VIP. Somastatin has recently been shown to cause a concomitant inhibition of both the vagally induced pancreatic bicarbonet secretion and VIP release in pigs, while the effect of applied VIP on the exocrine response from the isolated, perfused porcine pancreas was unaffected by somatostatin (35). Somatostatin however, inhibits several secretory functions in the body and the mechanism of action of this peptide is not known (see below).

Neurotransmitter Criterion #8 (Specific postsynaptic receptors) This last criterion, which has sometimes been proposed is the demonstration of specific receptors for the transmitter substance on postsynaptic membranes. Receptors for VIP have been demonstrated in the pancreas (36), liver (37), intestine (38) and in preliminary studies in the brain (Jan Fahrenkrug, personal communication, June 1982).

Thus VIP fulfills at least five of the above listed criteria for establishing it as a neurotransmitter substance.

PATHOLOGY OF GUT PEPTIDERGIC INNERVATION

Some information is now accumulating on altered morphology and distribution of the gut peptidergic nerves in several disease states. It is difficult, at present, to understand what the changes mean in terms of etiology or consequence of diseases (Table 4).

TABLE 4

DISEASE	SPECIMEN EXAMINED	VIP-CONTAINING NERVES	REF.
Hirschsprung's	Colon (aganglionic, proximal and distal segment)	Reduced number, reduced intensity of immunostaining	39
Chargas'	Rectal Biopsy	Same as in Hirschsprung's	40
Crohn's	Resected Colon	Increased number, densely immunostained thickened fibers	41
Equine grass sickness	Resected Ileum	Marked reduction (or absence) in all layers	42

In Hirschsprung's disease immunocytochemical and radioimmunoassay studies have shown a significant decrease of VIP content of gut autonomic nerves. The decrease was found in proximal (ganglionic), middle (hypo/aganglionic) and distal (aganglionic) areas of diseased colon (39). These findings suggest that VIPergic nerves have an intrinsic origin in the gut. Loss of peptidergic nerves is a consequence of loss of ganglion cells in this disease.

The findings in Chargas' disease are similar to those in Hirschsprung's (40).

In Crohn's disease, on the other hand, VIP nerves are increased in number. Densely immunostained, thickened fibers are replacing the fine, varicose fibers seen in normal bowel (41). Such changes were not found in ulcerative colitis and in colon resected adjacent to a cancer or obtained at intestinal by-pass surgery. A possible reason for the different responses of VIP innervation in Crohn's disease and ulcerative colitis may reside in the nature of the inflammatory process. In Crohn's disease this is transmural while in ulcerative colitis usually only the superficial layers of the gut are involved.

Grass sickness is a fatal disease of horses for which the etiology has yet to be ascertained. The disease has many features, e.g. severe constipation and bowel dilatation in common with Chargas' disease. In certain grossly affected areas like the ileum VIP immunoreactive fibers were found to be reduced or absent in each layer of the gut wall (42).

BIOLOGICAL ACTIONS OF VIP

The biological actions of VIP have recently been summarized by Said (43) and are listed in Table 5. It is not possible to separate physiological from pharmacological actions among the effects listed in Table 5. Many of the experiments which provided the listed results were performed with exogenously administered VIP resulting in much higher plasma levels of the peptide than are ever encountered during normal life. In *in vitro* experiments VIP concentrations were likewise very high in the bathing solutions. Since, however, tissue concentration of VIP at synapses and other receptor sites under normal conditions are not known, it is possible that some of the experiments indeed mimicked physiological situations.

TABLE 5 BIOLOGICAL ACTIONS OF VIP

Cardiovascular system	Vasodilation (including peripheral, splanchnic, coronary, extracranial, and cerebral vessels), hypotension, moderate inotropic effect on myocardium.
Respiratory system	Bronchodilation, pulmonary vasodilation, augmented ventilation, stimulation of adenylate cyclase activity in airways.
Digestive system	Increased blood flow to salivary glands.
Esophagus	Relaxation of lower sphincter.
Stomach	Relaxation of fundic smooth muscle, supression of acid and pepsin secretion.
Pancreas, liver	Stimulation of water and bicarbonate secretion (secretin-like action), increased bile flow.
Gallbladder	Relaxation of isolated smooth muscle, inhibition of contractile effect of CCK-PZ.
Small and large intestine	Inhibition of absorption, stimulation of water and ion secretion, stimulation of adenylate cyclase activity, relaxation of smooth muscle of colon.
Metabolism	Stimulation of glycogenolysis, lipolysis, and adenylate cyclase activity (in liver, pancreatic acini and adipocytes), hyperglycemia.
Endocrine function	
Pancreas	Release of insulin, glucagon, and somatostatin.
Pituitary-hypothalamus	Stimulation of release of prolactin, GH, LH, inhibition of release of somatostatin. and LH, inhibition of release of somatostatin.
Adrenal	ACTH-like action (stimulation of steroidgenesis and adenylate cyclase activity).
Central nervous system	Arousal, excitation of cerebral cortical and spinal cord neurons, hyperthermia, regional stimulation of adenylate cyclase activity.

VIP AND INTESTINAL SECRETION

Makhlouf and Said (44) were the first to observe that VIP was capable of inducing intestinal secretion in dogs (their publication was, however, chronologically not the first to report intestinal secretion in response to VIP). Dogs equipped with Thirty-Vella loops of the proximal jejunum showed a dose dependent increase in fluid secretion when VIP was given intravenously (Figure 4).

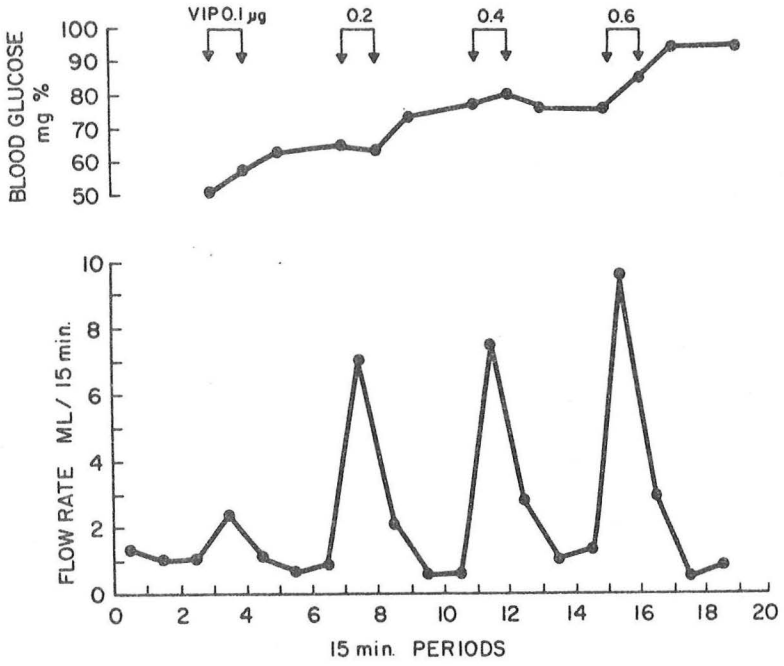


Figure 4 *Effect of increasing doses of VIP on intestinal secretory rate and blood glucose levels. VIP was infused for the first 15 minutes of every hour. From Makhlouf and Said, 1975 (44)*

Numerous other investigators expanded these observations in *in vivo* and *in vitro* models in different animal species (Table 6).

TABLE 6 *

Animal experiments examining the effect of VIP on intestinal transport

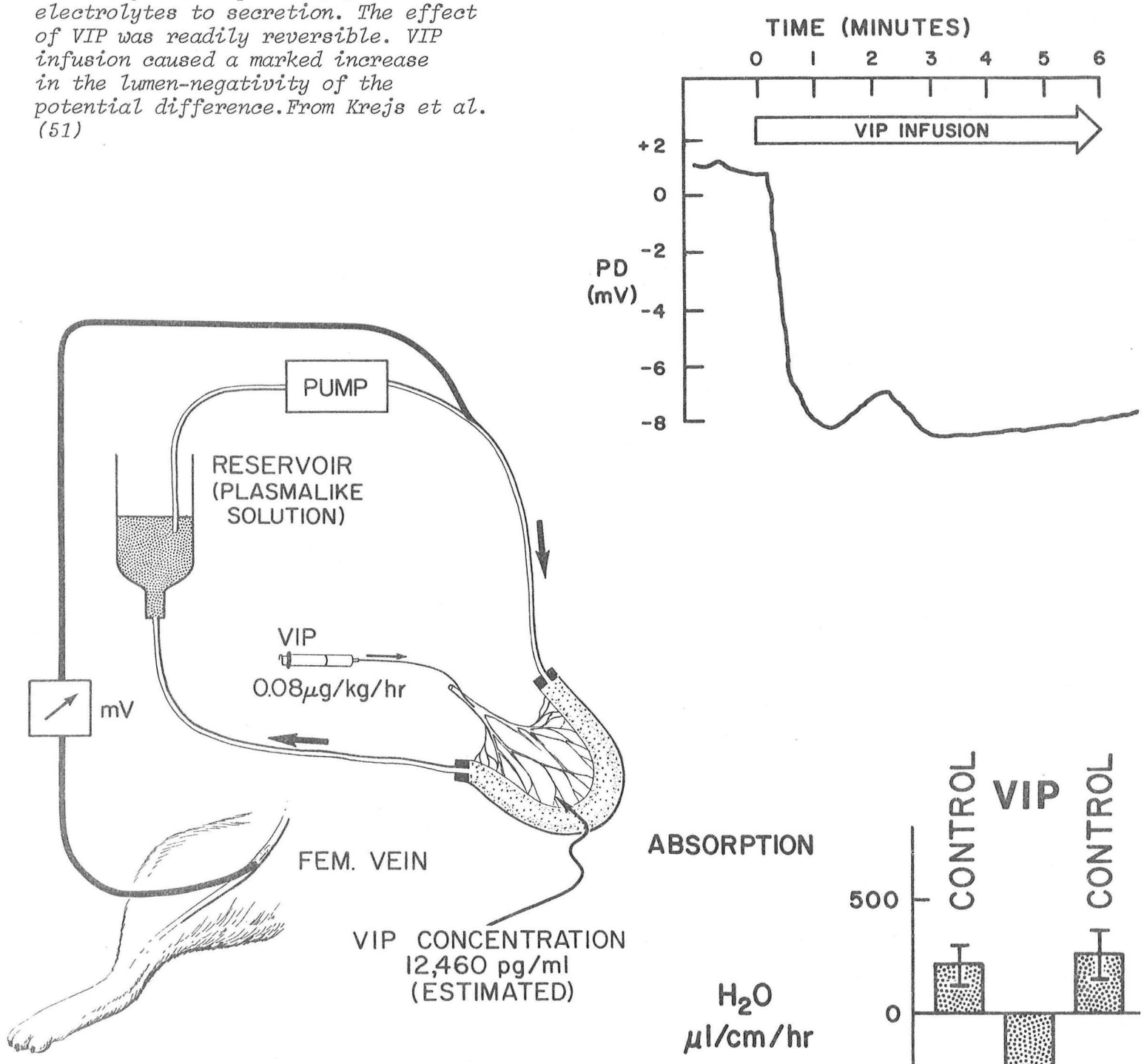
Author, year, ref.	Species	Intestine	Experimental conditions	Observations in response to VIP	Comments
Barbezat, 1973 (46)	Dog	Jejunum, ileum	*In vivo* (Thiry-Vella loop)	H_2O secretion	Marked effect in jejunum; little effect in ileum
Schwartz et al., 1974 (47)	Rabbit	Ileum	*In vitro* (Ussing chamber)	Net Cl and Na secretion	Five-fold increase in mucosal cAMP levels
Makhlouf and Said, 1975 (44)	Dog	Jejunum	*In vivo* (Thiry-Vella loop)	H_2O secretion	Potentiation of glucagon-induced secretion
Coupar, 1976 (48)	Rat	Jejunum	*In vivo* (*in situ* perfusion)	H_2O and Na secretion	No change of superior mesenteric artery perfusion pressure; no effect on glucose absorption
Waldman et al., 1977 (49)	Rat	Colon	*In vitro* (everted sac)	H_2O secretion	Increase in mucosal adenylate cyclase activity
Racusen and Binder, 1977 (50)	Rat	Colon	*In vitro* (Ussing chamber)	Cl secretion, reduced Na absorption	Increase in mucosal cAMP content
Krejs et al., 1978 (51)	Dog	Jejunum	*In vivo* (perfusion of isolated loop)	H_2O, Na, K, Cl, HCO_3 secretion	Active anion secretion
Mailman, 1978 (52)	Dog	Ileum	*In vivo* (perfusion of isolated loop)	H_2O and Na secretion	Absorptive site blood flow reduced in proportion to changes in H_2O and Na fluxes
Modlin et al., 1978 (53)	Pig	Entire gastrointestinal tract	*In vivo* (collection of diarrheal stool)	Gross watery diarrhea	VIP-induced hypokalemia
Wu et al., 1979 (54)	Rat	Ileum, colon	*In vivo* (*in situ* perfusion)	Reduced absorption or secretion of H_2O, Na, K, Cl, HCO_3	Simultaneous pancreatic polypeptide administration did not change effect of VIP
Eklund et al., 1979 (55)	Cat	Jejunum	*In vivo* (perfusion of isolated loop)	H_2O secretion	Reduced absorption at lower dose
Albuquerque et al., 1979 (56)	Rat	Jejunum, ileum	*In vivo* (intestinal segments tied off *in situ*)	H_2O secretion	Effect blocked by indomethacin

* *From Krejs, 1982 (45)*

In experiments in dogs in our laboratory (51) we demonstrated active anion secretion in response to VIP. Water and ion secretion in perfused jejunal loops was associated with an increase in transmucosal potential difference (Figure 5). Chloride and bicarbonate were secreted against an electrochemical gradient. VIP-induced secretion was readily reversible when infusion of the peptide was discontinued. In vitro experiments have suggested that cyclic AMP is the second messenger mediating the secretory process induced by VIP (47,49,50).

Figure 5

In vivo perfusion experiments in canine jejunal loops. VIP was infused directly into the superior mesenteric artery. VIP changed absorption of fluid and electrolytes to secretion. The effect of VIP was readily reversible. VIP infusion caused a marked increase in the lumen-negativity of the potential difference. From Krejs et al. (51)



VIPOMAS

After the first description of two cases by Verner and Morrison (4), the association of watery diarrhea and pancreatic tumor was discovered in other patients and led to the report of several series (57,58).

It was possible to distinguish these cases from the diarrhea seen in a number of patients with pancreatic gastrinomas by the presence of low gastric acid secretion. Indeed it was clear that the mechanism was different; in gastrinoma patients it was found that prevention of acid hypersecretion also prevented the diarrhea. In search for a humoral mediator Bloom, Polak and Pearse in 1973 found VIP containing cells in these tumors as well as high VIP concentrations in the patients' plasma. Said and Faloon (59) confirmed these findings in thirteen patients with pancreatic islet cell tumor. There have been a number of case reports since, but given present diagnostic methods, the condition is distinctly uncommon. We have seen 5 cases within the last 10 years (60,61 and present Grand Rounds).

CLINICAL FEATURES OF THE VIPOMA SYNDROME

The key feature of the illness is large-volume secretory diarrhea, with only about 20% of cases recorded as having less than 3 liters of stool per day (62). (In secretory diarrhea stool water is isotonic to plasma, stool electrolytes account for all the osmolality and diarrhea persists on fasting; 63). For practical purposes, a stool volume of less than 700 ml per day rules out the syndrome (64). Large amounts of potassium and bicarbonate are lost in the stool resulting in hypokalemia, acidosis and volume depletion. Steatorrhea is usually not present.

Stool analysis in patient, A.N. (case report, see above) is given in Table 7.

TABLE 7: STOOL ANALYSIS IN PATIENT A.N.

Diet	Weight g/24h	Osmolality mosm/kg	Na meq/l	K meq/l	Cl meq/l	HCO_3 meq/l	pH
Regular	3722	293	124	35	81	55	7.4
Fasting	2034	268	73	74	80	58	8.0

Stool fat on regular diet 11g/24h

In the few patients that have been studied appropriately (60,61,65,66) small intestinal water and ion secretion has been demonstrated by perfusion methods.

The triple-lumen tube perfusion technique was used to investigate water and ion transport in our patient with VIPOMA syndrome. With this technique net water and electrolyte absorption or secretion can be measured in a segment of intestine per unit time. The results of patient A.N. are given in Table 8.

TABLE 8: JEJUNAL PERFUSION STUDY WITH PLASMA-LIKE ELECTROLYTE SOLUTION IN PATIENT A.N. COMPARED TO THE MEAN VALUES OBSERVED IN HEALTHY CONTROLS. PERFURATE: PLASMA-LIKE ELECTROLYTE SOLUTION (PEG AS NON-ABSORBABLE VOLUME MARKER) NUMBERS ARE ml OR meq PER 30 cm PER HOUR (-) DENOTES ABSORPTION, (+) SECRETION

	H_2O	Na	K	Cl	HCO_3
A.N.	+93	+11	+.1	+1.4	+14.1
HEALTHY CONTROLS	-129	-17	-9	-11	-5.5

Other clinical features of the VIPOMA syndrome are listed in Table 9.

TABLE 9: VIPOMA SYNDROME CLINICAL PRESENTATION

CONSTANT FEATURES

WATERY DIARRHEA, HYPOVOLEMIA, HYPOKALEMIA, ACIDOSIS

VARIABLE FEATURES

ACHLORHYDRIA OR HYPOCHLORHYDRIA

HYPOCALCEMIA, HYPOMAGNESEMIA, TETANY

LARGE GALLBLADDER

MYOPATHY OR NEPHROPATHY (HYPOKALEMIC)

RASH, FLUSHING

HYPERGLYCEMIA

Achlorhydria and hypochlorhydria are often but not always present. Out of 43 patients reviewed by Verner and Morrison (58) only 14 had histamine-fast achlorhydria while another 16 had hypochlorhydria. Since gastric mucosal biopsies have invariably revealed normal parietal cells even in achlorhydric patients and since gastric hyposecretion has been corrected by resection of diarrheagenic tumors (67) it is likely that the tumor releases a gastric inhibitor. While VIP infusion inhibits pentagastrin and meal-stimulated acid secretion in the dog (68,69), acute experiments in man failed to show any suppressive effect of VIP on pentagastric-induced acid secretion (70). The effect of VIP on meal stimulated secretion is, however, not known in man. The species differences of VIP's action on gastric secretion are further emphasized by the observation that in cats VIP stimulates acid and pepsin secretion (71).

Hypercalcemia has been reported in 50% of cases (58) but the mechanism is not clear. There appears to be a negative calcium balance with increased bone resorption (72). Tetany is thought to be due to hypomagnesemia and may occur in the presence of hypercalcemia.

Flushing is occasionally observed in these patients. (In our VIP infusion experiments in healthy subjects (see below) flushing is invariably observed). Some patients have circulatory disturbances with hypotension due to peripheral vasodilation and severe hypertension may follow tumor removal (73).

Glucose intolerance is also seen in about 50% of patients with the VIPOMA syndrome. The diabetogenic effect of the secreted agent is also suggested by the observation that operative manipulation of an islet cell tumor resulted in pronounced hyperglycemia in one patient (74).

In patients with the VIPOMA syndrome a family history for the disease is usually absent. However, the report of a father with multiple islet cell adenomas and Zollinger-Ellison syndrome and his son with VIPOMA syndrome and a parathyroid adenoma suggests that VIP producing tumors may occur as part of the multiple endocrine neoplasia type I syndrome (75).

VARIANTS OF VIPOMA SYNDROME

I) ISLET CELL HYPERPLASIA

In Verner and Morrison's own later series several patients without pancreatic tumor were included (58). It was stated that 20% of cases have islet cell hyperplasia. In Said's series 14% of patients with watery diarrhea syndrome had islet cell hyperplasia (76). Several experts in the field refuse to accept pancreatic islet cell hyperplasia as part of the spectrum of the VIPOMA syndrome. S. Bloom did not find elevated plasma VIP levels in any patient with islet-cell hyperplasia (77) and J. Fahrenkrug (Copenhagen, Denmark, personal communication) doubts that this combination exists. Many of the reports about such cases are hard to interpret since the diagnosis of islet cell hyperplasia, is always poorly documented (How much is normal? How much is abnormal?) A morphometric or other quantitative approach has not been used, and the diagnosis is based on the subjective judgement of a pathologist (who, like the clinician, is disappointed for not having found an islet cell tumor and might want to come up with a positive diagnosis). A further problem arises from the fact that in the early days of the VIP radioimmunoassay false positive results were not uncommon. For instance, Said had cautioned about the interpretation of plasma VIP levels since 2 out of 25 healthy controls had elevated VIP levels at that time (78). Today it is open

to question whether such an entity as islet cell hyperplasia and elevation of plasma VIP concentration really exists. (For Pseudopancreatic cholera syndrome, see below).

2) GANGLIONEUROMA, NEUROBLASTOMA, NEUROFIBROMA & PHEOCHROMOCYTOMA

Neural crest tumors are the fourth most common type of neoplasm in the pediatric age group (8% of cancers under the age of fifteen) (79). Many of these tumors secrete catecholamines which do not cause diarrhea (hypertension flushing, fever). However, some thirty cases have now been described in which diarrhea was the presenting symptom. In these children high circulating levels of VIP were found, the ganglioneuromas or neuroblastomas were shown to contain the peptide (immunofluorescence and tissue extract) and the diarrhea resolved after tumor removal (80-82).

Secretory diarrhea and high plasma VIP concentration have also been found in a child with neurofibromatosis (83) Pheochromocytomas rarely cause diarrhea (84). VIP production and release by such tumors has been demonstrated in rare cases that are indeed associated with diarrhea (85). Since the adrenal medulla is of neural crest origin (86) it is not at all surprising that a tumor of this organ would be capable of producing a neurotransmitter such as VIP.

3) CUTANEOUS MASTOCYTOMA

Recently, a case of cutaneous mastocytoma secreting VIP has been reported in an 8-month-old child. The child did not have diarrhea, but had generalized flushing and apnea which may have been related to manipulation of the tumor (87).

4) VIP IN OTHER DISEASES

Mild plasma VIP elevations are found in patients with hepatic failure (88,89) and probably result from decreased peptide metabolism by the ailing liver. In dogs with hepatic failure a high VIP concentration can be found in CSF (90) suggesting increased CNS release of VIP in the encephalopathic state.

VIP is also released during intestinal ischemia in experimental animals (91,92). It is unknown whether this observation bears any clinical relevance (such as impairment of the cardiovascular condition by VIP in such patients).

On the basis of the report by Said and Faloona (59) in which six patients with primary bronchial carcinoma and watery diarrhea are described (5 having high plasma VIP), the American College of Physicians Medical Knowledge Self-Assessment Program IV included bronchogenic carcinoma as a cause of persistent watery diarrhea. Although the combination of watery diarrhea and lung cancer has been observed by others (93) it has very much been questioned whether the VIPOMA syndrome exists in association with bronchogenic carcinoma (64). Such cases have not been seen in other large series (77,94). On the other hand since VIP is found in autonomic nerves of the lung (23) and since VIPOMAS could also be viewed as tumors of the peptidergic nervous system it is not unlikely that some bronchogenic carcinomas may contain VIP. Further observations are needed to clarify this issue (By the same token, it may only be a question of time to find a VIPOMA in the genital tract where VIPergic nerves are present in large numbers).

IS VIP THE TRUE MEDIATOR OF THE VERNER MORRISON SYNDROME ?

The correct answer, I believe, is yes. VIP appears to be the major mediator of this syndrome. However, a lively discussion on this question has continued until today (95).

The controversy (96) has several reasons:

1) Not all patients with pancreatic islet cell tumor and watery diarrhea have elevated plasma VIP levels. For instance, in Fischer's series only one out of three patients had a high VIP concentration (97).

2) High VIP levels were reported in healthy subjects (59) and were found in other diarrhea patients such as chronic laxative abusers (60). Chronic laxative abuse has been found (on one occasion) to be associated with islet cell hyperplasia (98). However, since reanalysis of some of the samples previously reported as having high VIP concentration yielded normal results with an improved assay no definite conclusions are possible (99,100).

3) Many of the pancreatic VIPOMA's produce other pancreatic peptides. According to Bloom's experience, pancreatic polypeptide (PP) is found elevated in 75% of patients with islet cell tumors (101). In experimental animals (102) PP does not have a secretagogue function. There is, however, at least one well documented case in which the watery diarrhea syndrome was attributed to a PPoma (103) and one case with islet cell hyperplasia exclusively composed of PP cells (104). Neurotensin production has also been shown in VIPOMA's resulting in high plasma concentrations of the peptide in such patients (105). A pure neurotensinoma has not yet been described (Hopefully the title of my next GRAND ROUNDS). Occasional tumors also produce gastrin, glucagon, insulin, and somatostatin (106,107). Of interest is also the association of calcitonin production with islet cell tumors. One of our VIPOMA patients also had hypercalcitoninemia (61) and so did a patient with somatostatinoma studied at this Health Science Center (108). Since calcitonin itself is an established secretagogue (109,110) secretory diarrhea may be due to high circulating concentration of this peptide. Furthermore, since indomethacin provides for successful treatment in single cases (111) a role of prostaglandins in causing diarrhea in this syndrome is possible (112).

The evidence for VIP as the responsible secretagogue comes from:

1) the fact that many of the symptoms in the VIPOMA syndrome (see above) can be explained by the biological action of VIP observed in experimental animals (see above).

2) Clinical observations in patients with high circulating levels of VIP prior to removal of a tumor and normal VIP levels after surgery with disappearance of the diarrhea (60,113).

3) VIP infusion experiments in humans carried out in our laboratory showed intestinal water and ion movement changing from absorption to secretion while VIP plasma levels were achieved that are comparable to VIP concentration seen in patients with the VIPOMA syndrome.

In these studies (114,115) the triple lumen tube technique was used and a plasma-like electrolyte solution served for perfusion of 30cm segments of jejunum or ileum or the entire colon. Polyethylene glycol was used as a nonabsorbable volume marker. Net water and ion movement across the mucosa is calculated according to standard marker perfusion equations

When VIP was infused at a rate of 400 pmol/kg/h, plasma concentration in the healthy volunteers rose to levels well within the range observed in patients with pancreatic cholera syndrome (Figure 6).

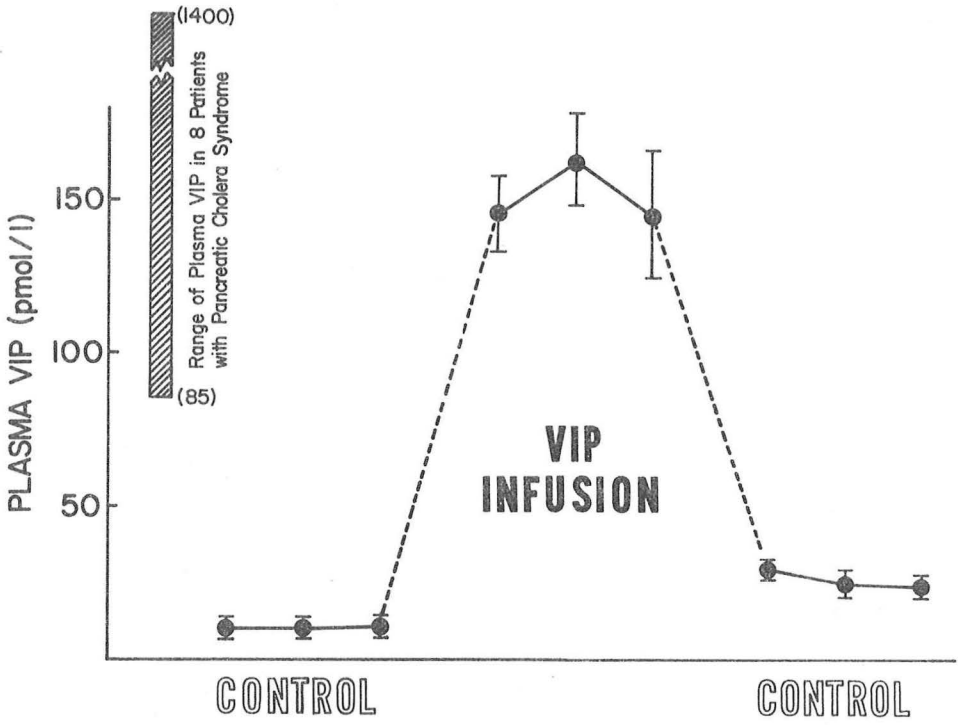


Figure 6 *VIP plasma concentration in 6 healthy subjects before, during and after VIP infusion. Measurements within the test and control periods are 30 min apart and 45 min of equilibration lie between the test period and the control periods. VIP rose from about 10 to 150 pmol/l and lay well within the range of VIP levels observed in patients with VIPOMA (hatched bar). (Radioimmunoassay results of Drs. J. Fahrenkrug and O.B. Schaffalitzky de Muckadell, Copenhagen, Denmark) From Krejs, 1981 (115)*

VIP infusion abolished water absorption in all three areas tested (Figure 7) (net secretion was observed in individual subjects).

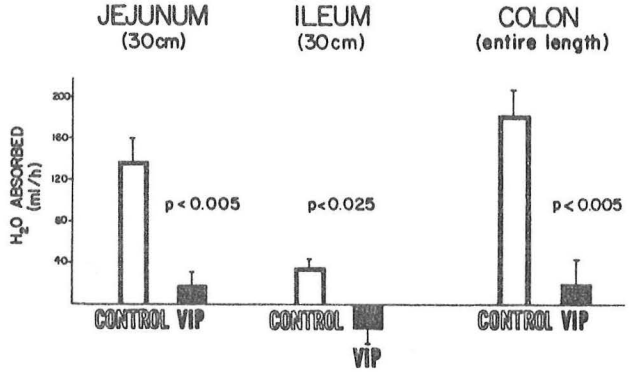


Figure 7 *Net water movement in the jejunum (n = 6), ileum (n = 10), and colon (n = 8) during control period and VIP infusion. VIP abolsihed water absorption in all three areas tested From Krejs, 1982 (45)*

In the jejunum a dose response curve was obtained (114). With increasing VIP dose (100,200, & 400 pmol/kg/hr) there was a progressive decrease of water and sodium absorption. Chloride was secreted (Figure 8). This anion secretion was active since it occured against both an electrical and chemical gradient.

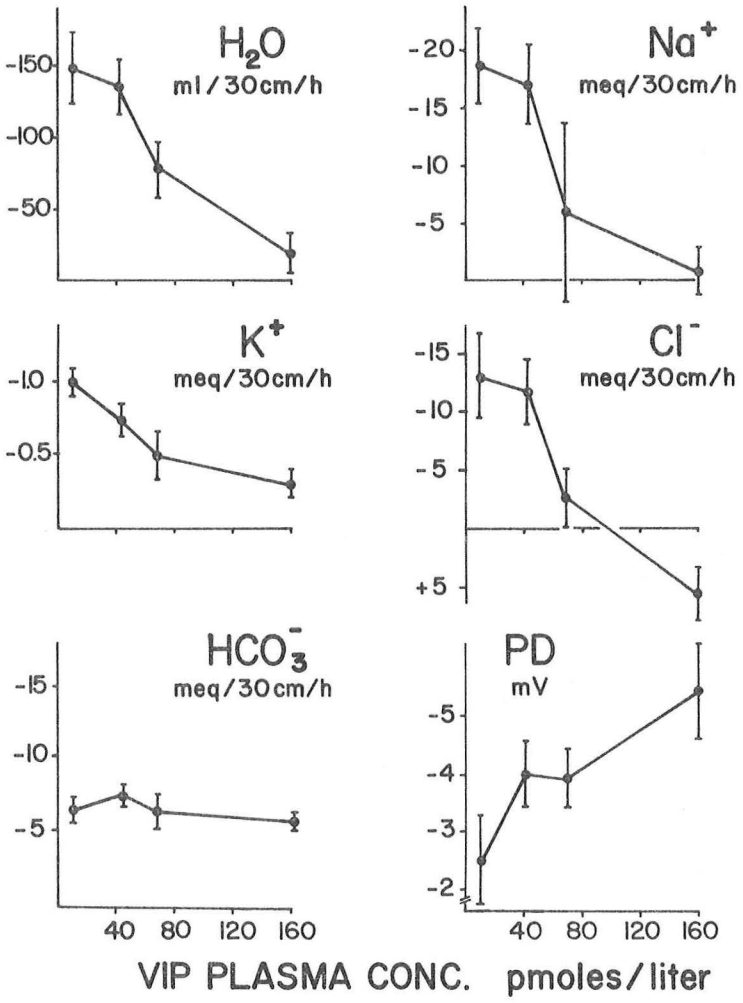


Figure 8 *Dose response curves for VIP plasma concentration and water and ion movement and PD in the jejunal test segment of 6 healthy volunteers (Radioimmunoassay of Drs. J. Fahrenkrug and O.B. Schaffalitzky de Muckadell, Copenhagen, Denmark) From Krejs, 1980 (114)*

These studies in man demonstrated that VIP is capable of reducing intestinal absorption of water and ions by inducing an active secretory process (active anion secretion). Most likely this is the pathophysiologic mechanism causing secretory diarrhea in the VIPOMA syndrome.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF VIPOMA SYNDROME

1. Stool Analysis

Stool volumes are usually in excess of 1 liter per day and diarrhea persists on fasting (60), stool osmolality is equal to plasma and stool electrolytes account for all the osmolality of stool water [(Na+K)x2=measured osmolality] (63). Table 10 gives a comparison of typical stool data in osmotic and secretory diarrhea.

DIARRHEA	OSMOTIC	SECRETORY
DAILY STOOL VOLUME	<1000 ml/kg	>1000 ml/kg
DURING FASTING	Stops	Continues (often↓)
pH	4.5	7.0
OSMOLALITY (mosm/kg)	350	290
Na^+ (meq/l)	30	100 (>70)
K^+ (meq/l)	30	40
$Na^+ + K^+$	60	140
$(Na^+ + K^+) \times 2$	120	280
SOLUTE GAP	230	10

TABLE 10
STOOL ANALYSIS IN OSMOTIC & SECRETORY DIARRHEA

The differential diagnosis of secretory diarrhea is given in Table 11.

TABLE 11

MAJOR CAUSES OF CHRONIC SECRETORY DIARRHEA

SURREPTITIOUS DRUG INGESTION

VIPOMA SYNDROME

PSEUDOPANCREATIC CHOLERA SYNDROME

GANGLIONEUROMA

MEDULLARY CARCINOMA OF THE THYROID

CARCINOID

SPRUE (IN SOME CASES)

ALCOHOLISM & FOLATE DEFICIENCY

ZOLLINGER-ELLISON SYNDROME

FATTY ACID AND BILE ACID MALABSORPTION

SECRETING VILLOUS ADENOMA (RECTUM)

CONGENITAL CHLORIDORRHEA

Two of the diagnoses listed are often very difficult to separate from VIPOMA synmdrome. These are surreptitious laxative abuse and pseudopancreatic cholera syndrome. Both conditions are discussed in detail below. Surreptitious laxative abuse is the most frequent diagnosis that we have made in patients who were referred with a tentative diagnosis of VIPOMA syndrome or with diarrhea of unknown origin after an extensive previous work-up elsewhere had been unrevealing (60,116).

2. Search for Tumor

In search for a pancreatic or retroperitoneal tumor (ganglioneuroma, etc.) sonography, CT scanning and angiography can be used. If a liver-spleen-scan, or any of the other imaging procedures suggests liver metastases then peritoneoscopy should be performed to obtain tumor tissue. In addition to a regular histological examination immunocytochemical and immunofluorescence studies allow identification of the peptides that are contained in the secretory granules seen on electronmicroscopy (108). For these special studies tissue specimens must be fixed in Bouin's solution. Tissue specimens are also frozen in liquid nitrogen to allow radioimmunoassay of tissue extracts.

3) Plasma levels of intestinal secretagogues

The radioimmunoassay for VIP is certainly one of the more difficult assays. Particularly in the mid 1970's technical imperfection with some of the assays had led to false positive results. Subsequently, some patients had unnecessary exploratory laparotomy or partial pancreatectomy (60).

The VIP assay, like virtually all other radioimmunoassays does not measure the concentration of VIP in plasma directly. The assay measures the ability of a patient's plasma to inhibit binding of ^{125}I-VIP by an antibody. A plasma concentration of 500 pmol/l actually means that the plasma sample inhibited antibody binding of ^{125}I-VIP to the same extent as 500 pmol/l of native VIP. One key issue is what besides VIP can inhibit binding of ^{125}I-VIP, or how specific is the assay? By now all major VIP-radioimmunoassay laboratories have published information on the specificity of their assays (16,117). It appears that the assays have been refined to a degree that they provide reliable information . It must be kept in mind, however, that even an extremely low false-positive or false-negative rate would severly dimish the value of such an assay since the VIPOMA syndrome is such a rare disease while chronic diarrhea is common.

We have assessed the validity of 6 currently available radioimmunoassays by sending to the laboratories coded plasma samples from VIP infusion experiments and control samples from the same subjects before VIP infusion was commenced. This validation and comparison of laboratories was performed three times, namely in 1978, 1979 and 1981. When we looked at the basal samples prior to VIP infusion only one laboratory had consistently reported normal results in 1978 and 1979 (Jan Fahrenkrug and Ove B. Schaffalitzky de Muckadell, Copenhagen, Denmark). All others read 10 to 33% of samples above the upper limit of normal reported for the individual laboratory. Furthermore, the assay in some laboratories fluctuated markedly between 1978 and 1979. In 1981 (and 1982 for Dr. Said's laboratory) all laboratories reported low values in all control samples (and high values during VIP infusion).

Thus, for 1981 (and 1982, respectively) we can report that highly reliable radioimmunoassays for VIP are available in the following laboratories:

Stephen R. Bloom, London, England
Jan Fahrenkrug & Ove B. Schaffalitzky de Muckadell, Copenhagen, Denmark
Thomas M. O'Dorisio, Columbus, Ohio
Sami I. Said, Dallas, Texas (since 1981, Oklahoma City, Oklahoma)
Josef Fischer & Richard F. Murphy, Cincinnati, Ohio and
John H. Walsh, Los Angeles, California

Assays are also available from; Dr. V.L.W. Go (Rochester, Minnesota) and James McGuigan, Gainsville, Florida) but we have no experience with these two laboratories.

In search for other secretagogues we routinely have plasma assayed for calcitonin and prostaglandins. Since many of the pancreatic islet cell tumors contain other peptides, such agents may serve as markers of endocrine pancreatic malignancy. Therefore, we obtain radioimmunoassay results on our patients' plasma for pancreatic polypeptide, glucagon, insulin, gastrin, neurotensin, somatostatin, GIP, motilin, secretin and PHI (peptide [P] having N-terminal histidine [H] and C-terminal isoleucine [I] amide).

Some investigators have reported that selective venous sampling with anatomical mapping of peptide concentration may be helpful in the work-up of patients with biologically active islet cell tumors (118). While we have not utilized this method we doubt that the benefit outweighs the invasiveness of the procedure and the fact that it is technically very difficult to perform. The venous sampling procedure can also be misleading as abnormal tumor veins can drain in an unexpected direction producing false localization.

4) Intestinal Perfusion Studies

Intestinal perfusion studies may be helpful in the differential diagnosis of secretory diarrhea (see Table 11). Net luminal gain of water and electrolytes (secretion) can be demonstrated in segments of perfused small bowel (absorption in control group)(60,61,65). This method is particularly useful to separate surreptitious laxative ingestion from VIPOMA syndrome. Perfusion studies show normal results in laxative abusers (60,61).

SELF-INDUCED AND FACTITIOUS DIARRHEA

Patients may induce or simulate diarrhea in several different ways, including ingestion of laxatives that produce secretory diarrhea, ingestion of laxatives that produce osmotic diarrhea, or addition of water, urine or other liquid to their feces. Almost all patients reported to have self-induced and factitious diarrhea have been women. In a variant of this syndrome, mothers induce diarrhea in their children (Red Diaper Syndrome due to phenolphthalein, Polle Syndrome, Munchausen Syndrome by proxy) (119,120). Surreptitious laxative ingestion is the most common cause of chronic diarrhea of unknown origin in patients that we studied.

After the diagnosis of surreptitious laxative abuse has been established, it becomes obvious that such patients are severly neurotic. However, in many instances this was not evident to the physicians who were taking care of the patients before the diagnosis was established. The lack of obvious emotional disturbance is one of the reasons why there is usually such a delay in correct diagnosis. The diagnosis is usually as shocking to the referring physician as it is to the patient and her family.

The underlying psychological factors that lead patients to this behavior are not understood. From our own experience, we believe there are two distinct groups of patients who surreptiously ingest laxatives. The first consists of women from about 18 to 40 years of age who have a variant of anorexia nervosa and a severe preoccupation with body weight. They may be thin, normal or overweight, but they see themselves as obese. Prior to using laxatives, many will have self-induced vomiting as a method of weight control (bulemia). They then begin to take laxatives under the assumption that laxatives will cause food to be flushed through the gut, unabsorbed. They often take an enormous number of laxative tablets (usually Correctol in our patients), up to 100 at a time. Although this behavior seems logical to the patient, they seemingly deny the relationship between laxatives and their diarrhea, hypokalemia, lassitude, abdominal discomfort, etc. At last they present to a physician with these problems and fail to mention that they are taking laxatives. Furthermore, they submit to any requested diagnostic test and/or surgical procedure, in hopes of regaining their health. However, when confronted with evidence that they are ingesting laxatives, they admit it. When the laxatives are discontinued, they may become quite edematous, possibly due in part to persisting hyperreninemia and hyperaldosteronism (121). This edema may cause them to return to laxatives or to start using diuretics. If not, the edema will subside spontaneously in 3-6 weeks.

The second group consists of older women, usually 40 to 60 years of age, who have no features suggestive of anorexia nervosa, and who totally deny laxative ingestion as the cause of their diarrhea, even when confronted with undeniable evidence. The underlying psychological factors that motivate these women are complex. Secondary gain of attention is probably a factor. Some authors believe that surreptitious laxative ingestion in these patients represents one of the presentations of hysteria (122). Many features of hysterical behavior are present, including the capacity for self-deception, lack of insight, and manipulation of relatives, friends and physicians, often in the absence of an obvious motive for gain. The denial that they make when presented with evidence that they are taking laxatives is not simply deliberate lying. They do not admit this, even to themselves. This allows them to continue to take purgatives even after being told of their physician's conclusion, and it helps explain why they suffer such severe symptoms and undergo prolonged and uncomfortable diagnostic tests or surgical procedures.

In addition to chronic diarrhea, the clinical picture of surreptitious laxative ingestion includes abdominal discomfort, sometimes pain and vomiting, muscle weakness, lassitude, hypokalemia (sometimes with its attendant nephropathy), abnormalities on barium enema (cathartic colon) (123) and rectal biopsy that may simulate inflammatory bowel disease (124,125) and cyclical edema (121). The colonic x-ray changes are probably due to laxative induced degeneration of myenteric plexus (126). These symptoms and findings may have persisted for years, without specific diagnosis in spite of multiple admission for diagnostic studies, fluid therapy and surgical procedures. The latter consists of almost anything, including exploratory laparotomy, gastric resection, vagotomy, cholecystectomy, hysterectomy, reversal of intestinal loops, partial pancreatectomy, adrenalectomy and colectomy.

Melanosis coli develops as a consequence of anthracene laxative ingestion (senna, cascara, aloe). The pigment is not melanin, but probably is derived from lipofuscin an anthraquinone. It is recognized at sigmoidoscopy as a dark discoloration of the mucosa, sparing lymphoid follicles and polyps. Less severe cases may only be seen on histological examination. Melanosis coli starts to develop as early as four months after starting laxatives and goes away within one year of stopping (127).

Diagnosis depends on a high index of suspicion, chemical tests of stool and urine, and, if necessary, a search of the patient's hospital room, home, and belongings. Chemical tests include analysis of stool in search of nonphysiological (and, therefore suspicious) constituents, and analysis of stool and urine for specific laxatives (122,128).

The simplest test, that should be part of the routine examination in any patient with chronic diarrhea, is alkalinization of stool and urine. This will result in a pink or red color if phenolphthalein is present. Phenophthalein is colorless up to pH 8.5, whereas the pink to red color develops above pH 9 (129). A large excess of alkali will result in the formation of the trisodium salt which again is colorless. Thus, if too much alkali is added one might fail to detect the presence of phenolphthalein. The absorption maximum of phenolphthalein is 550-555 μm. So far, we have never seen a red color develop upon alkalinization that did not prove to be phenolphthalein, although it is possible that a BSP test might result in a false-positive test. Aloes and aloin are said to also turn alkaline urine red. (122). To specifically test for phenolphthalein, we add one drop of 1 N NaOH to about 3 ml of fecal supernatant or urine. If a pink or red color develops, we measure absorption in a spectrophotometer to see if maximum absorption occurs at 550-555 μm, and we add 10 N NaOH to see if the color disappears at very high pH levels.

Fecal fluid should also be analyzed for osmolality and electrolytes. If findings are suggestive of secretory diarrhea, one of the laxatives capable of causing secretory diarrhea and sodium sulfate ingestion (see below) should be suspected. If findings are suggestive of osmotic diarrhea, a magnesium salt laxative should be ruled out. Magnesium can be measured in fecal water by atomic absorption spectrophotometry; diarrhea stools should contain no higher magnesium concentration than 12 mM (61) unless the patient is taking a magnesium-containing drug. If the osmolality is lower than the osmolality of plasma, water in some form has been added to the stool. For example, if stool osmolality is 100 mosmol per kilogram, the stool has been diluted at least threefold with water. If the osmolality is far above that of plasma, urine may have beed added to stool. This can be confirmed by finding a high monovalent cation concentration ($Na + K >> 140$) and urea in stool.

Additional tests that can be done include a qualitative test for senna in urine, chromatography for bisacodyl and measurement of sulfate (normal less than 4.5 mM) and phosphate (normal less than 12 mM) in diarrhea stool (122,128,130). If a patient caused diarrhea by sodium sulfate or sodium phosphate ingestion, it would be an osmotic diarrhea (due to sulfate and phosphate) but it would appear to be secretory since there would be no solute gap by analysis of Na, K and osmolality. Therefore, sulfate and phosphate need to be considered when diarrhea is apparently secretory in type.

Measurement of urine volume and electrolytes is also helpful since a sodium and potassium diuresis associated with diarrhea suggests the possibility of surreptitious ingestion of diuretics. Diuretics can, of course, also cause hypokalemia; if they are ingested surreptitiously, the physician may think the hypokalemia is caused by the diarrhea and consider VIPOMA syndrome.

Some physicians think it is unethical to search a patient's room in search of laxatives and diuretics (131). We disagree since, if the diagnosis of surreptitious laxative ingestion is missed, the patient will likely be subjected to needless hazardous tests and therapies. Three patients in our series had previously undergone partial pancreatectomy and one had undergone total colectomy. In some series, a room search had a higher diagnostic yield for surreptitious laxative ingestion than any other test (132).

If a diagnosis of surreptitious laxative ingestion is made, should the patient and family be confronted with the discovery? In most instances, we think the answer is yes. The main thing to hope for is prevention of useless and harmful tests and therapies in the future. With the anorexia nervosa type patient, the confrontation usually goes relatively well, she is thankful that this habit is now out in the open, but she nevertheless frequently continues to take laxatives anyway. With older women who do not take laxatives for weight control, one should expect vehement denial and early self-discharge from the hospital. We have not had a patient become violent or attempt suicide after confrontation, but such events have been recorded (132), and one needs to consider and be ready to prevent such occurrences. Every effort is made to be gentle and considerate with the patient and her family.

PSEUDOVIPOMA SYNDROME, PSEUDO-VERNER MORRISON SYNDROME, PSEUDO-PANCR.CHOLERA, CHRON. IDIOPATH.SECR.DIARRHEA

By our arbitrary definition, these patients have had diarrhea for greater than four weeks, the stool volume must be greater than 750 g per 24 hr, fecal analysis must be typical for secretory diarrhea, the diarrhea must persist on fasting, surreptitious laxative ingestion must be ruled out, and there must be no evidence of the diseases that are known to cause chronic secretory diarrhea (Table 11). In many instances, the patients will have had a negative exploratory laparotomy. Although some of our patients had elevated

serum concentrations of VIP on one occasion, this probably represented laboratory errors as the assays were being perfected. Recently, all patients we have classified in this catagory have had normal serum concentrations of VIP and calcitonin. One had a slight elevation of serum concentration of prostaglandins (she did not respond to indomethacin).

The pathophysiology of this syndrome has not been studied extensively except in a few patients. In these, reduced absorption or intestinal secretion has been noted by segmental perfusion of the small and/or large intestine (133). By definition, of course, the cause of these abnormalities is unknown; abnormal neuroendocrine function that was not tested, or an undiscovered infection are two possibilities. It seems unlikely that this syndrome could be caused by deranged intestinal motility, but this possibility has not been adequately studied. Crude clinical tests of transit time have not suggested a motility disturbance in any of our patients. The severity of this syndrome varies widely. The prognosis is also highly variable. Some patients have seemingly endless severe chronic diarrhea, some have persistent diarrhea of moderate severity, and still others have a complete resolution of diarrhea after several months to a few years. Some patients are remarkably benefited by opiates. We have tried several patients (the more severe ones) on prednisone in doses of 60-80 mg per day, with a benefit seen in only one out of five patients. One of our patients died and the autopsy was negative.

Decisions about angiography and laparotomy in these patients are difficult. We would tend to do them in patients with more severe diarrhea, and to avoid them in patients with less severe diarrhea. We do not advocate reversal of segments of small intestine, but we do seriously consider (in patients who require i.v. fluids) insertion of a jejunostomy feeding tube that can subsequently be used for infusion of glucose-containing electrolyte solutions.

In our opinion, the major lesson to be learned from our case studies is that patients may have severe secretory diarrhea that mimics most, if not all, of the clinical features of the VIPOMA syndrome, and yet have no evidence of an endocrine tumor, surreptitious laxtive ingestion, or of any other known cause of secretory diarrhea. This syndrome is much more common than VIPOMA syndrome itself. The prognosis is variable, from a severe but self-limited illness of 6 weeks to a severe protracted illness that may last years and end fatally.

Verner and Morrison have recommended that if all diagnostic measures (including laparotomy) fail to reveal an endocrine tumor in patients with chronic severe diarrhea, at least 75% of the pancreas should be resected (58). The rationale behind this policy is that the cause of the diarrhea may be hyperplasia of the pancreatic islets rather than an overt neoplasm, and that if the pancreas is left unresected, hyperplasias might develop into a neoplasm. However, this progression from hyperplasia to neoplasm has never

been observed, and as discussed above islet cell hyperplasia is a very controversial entity. In three of our patients pancreatic resection had no influence on the diarrhea. Furthermore, the spontaneous remissions noted in some patients (133) suggest that some of the good responses to partial pancreatectomy (58) may have been fortuitous.

On the basis of our experience with pancreatic cholera syndrome (61) and these patients with chronic secretory diarrhea of unknown origin (133), we would suggest the following scheme of management in patients with large volume (1 liter per day or more) and chronic (greater than 4 weeks) secretory diarrhea, but no evidence of laxative ingestion or of an endocrine tumor by radiological or sonographic techniques. If the plasma concentrations of endocrine tumor markers (VIP, calcitonin, prostaglandins, etc.) are normal or only mildly and inconsistently elevated, we would recommend treatment with nonspecific remedies such as opiates for a period of up to six months. Only if they fail to respond adequately to these remedies or if severe diarrhea recurs when symptomatic therapy is withdrawn at six months, should exploratory laparotomy be performed. On the other hand, if the plasma concentration of endocrine tumor markers are consistently and definitely elevated, it seems reasonable to carry out exploratory laparotomy regardless of the response to nonspecific medical therapy. If a tumor is not found at surgery, then our tentative recommendation would be to do a "blind" distal pancreatectomy only in those patients in whom preoperative plasma concentrations of endocrine tumor markers were markedly and repeatedly elevated.

NATURAL HISTORY OF VIPOMA SYNDROME

The average duration of symptoms is three years prior to diagnosis (57) and may range from 2 months to 4 years (134). Metastases (liver, lymphnodes) are present in one third of patients at the time of diagnosis. Death occurs from renal failure or cardiac arrest in the setting of water and salt depletion and acidosis. The survival of patients with islet cell tumor used to be less that one year from the time of diagnosis (135,136). It appears that better understanding of the pathophysiology resulting in better treatment design and the introduction of cytotoxic chemotherapy have markedly improved the survival time. In our own series of 5 patients we have two cures (see treatment below).

TREATMENT

The most effective method of treating a VIPOMA is total excision. Unfortunately this is often not possible due to either metastases or due to the fact that a benign tumor has grown too large and involves vital structures. Approximately half of the pancreatic tumors are resectable, whereas only a third has evidence of metastases at the time of diagnosis. Debulking of the tumor may be beneficial and hepatic arterial embolization may be applicable in the setting of liver metastases. Ligation of the hepatic artery was unseccessful due to formation of anastomoses. The slow embolization with fine particles first followed by larger particles seems to damage the metastases while liver function remains unimpaired (metastases seem to rely on arterial source of perfusion)(134).

VIPOMAS are often sensitive to streptozocin (formerly called streptozotocin). The remission rate is higher than 90% and may last for years (137-141). 5-Fluorouracil has also been found effective (142).

Individual case reports have suggested that indomethacin (143) lithium (144), trifluoperazine (145), phosphate buffer (113), clonidine (146), metoclopramide (147), loperamide (148) and steroids (61) may stop or improve the diarrhea.

Of interest is the observation that somatostatin is capable of inhibiting pathological secretion in the human intestine (115). Rambaud's group has recently shown a beneficial effect of somatostatin in a patient with VIPOMA syndrome (149).

When our patient A.N. received somatostatin i.v. (4 µg/kg/h) stool volume dropped from 3094 to 819 g per day and he passed semi-formed stool for the first time in many months. On perfusion studies we could demonstrate a change from intestinal secretion to absorption while somatostatin was given.

This effect was mainly due to a drop in plasma VIP levels during somotostatin infusion (decreased release of VIP from tumor, VIP level were within the normal range during somatostatin infusion). In healthy subjects, when we infused VIP and somatostation simutaneously, we did not find an effect of somatostatin on the secretory action of VIP in the human jejunum (145).

In our patient A.N. chemotherapy has so far been ineffective (streptozocin, 3 courses and DTIC, one course). 5- Fluorouracil therapy is now considered.

Indomethacin, lithium bicarbonate and lopeamide did not change the diarrheal volumes. Further therapeutic trials going on during this week will include clonidine, metoclopramide, trifluoperazine and steroids. Together with Dr. Raskin, we plan to evaluate the use of subcutaneous somatostatin administration with a mini insulin pump. The patient's oral intake of 300 meq of potassium has to be supplemented by parenteral potassium to bring his serum level up to 3.0 meq/l.

SUMMARY

Since the description of the watery diarrhea syndrome by Verner and Morrison 14 years ago, clinical and experimental observations have elucidated the pathophysiology of this disease. Vasoactive intestinal polypeptide is produced and released by a tumor of the pancreatic islets or by a tumor of neural crest origin (e.g. ganglioneuroma). Under normal conditions, present evidence suggests that VIP is a neurotransmitter in the central and peripheral nervous system and particularly in the peptidergic nervous system. The low VIP plasma concentration seen in healthy subjects is viewed as a neuronal overflow since it has been impossible to ascertain any endocrine role for circulating VIP. Markedly elevated VIP plasma levels in the VIPOMA syndrome lead to intestinal secretion with severe secretory diarrhea resulting in hypovolemia, hypokalemia and acidosis.

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THE -OMA GRAND ROUNDS
OF DR. G.J. KREJS:

1979 SOMATOSTATINOMA

1981 CALCITONINOMA

1982 VIPOMA