MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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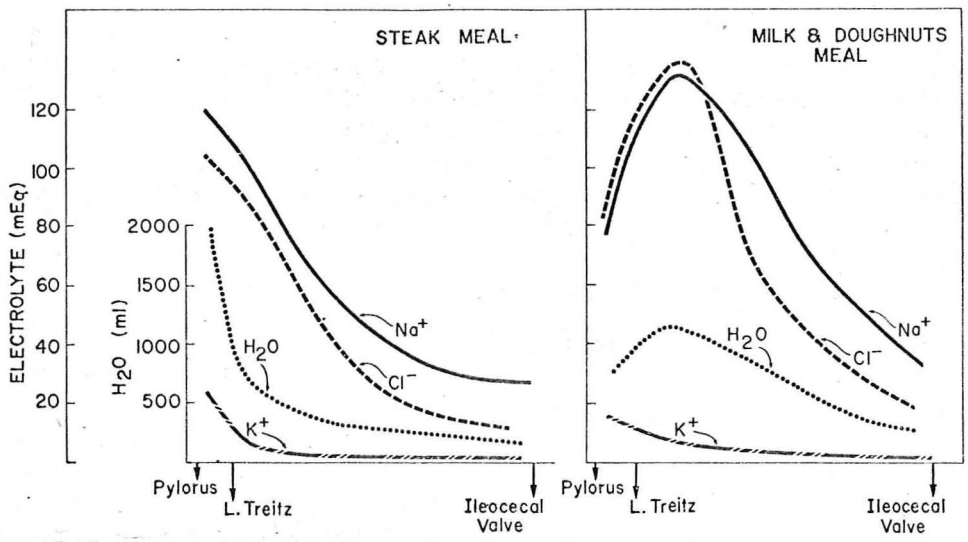
Chronic and Recurrent Diarrhea

1. PATHOPHYSIOLOGY OF DIARRHEA (See Federation Proceedings 26:1405, 1967, for a more detailed discussion)

The normal small bowel contains essentially no fluid. Following the ingestion of a meal, however, large volumes of fluid pass through the gut, as shown in the following diagram:



Note that the pattern differs with the meal ingested. After a steak meal, water and sodium chloride are rapidly absorbed in the proximal intestine; absorption continues in the ileum, but at a diminished rate. Approximately 250 ml are left unabsorbed in the small bowel, to be delivered to the colon.

After ingestion of a milk and doughnut meal, the volume of water and amount of electrolytes increases as the meal travels through the proximal intestine. Absorption commences in the mid-jejunum, and continues through the rest of the small bowel. About 300 ml of fluid is unabsorbed, to be delivered to the colon.

Obviously, the type of food ingested is a major determinant of the direction and rate of fluid movement in the proximal small intestine. The characteristics of a meal which determine what effect it will have are its osmolality, the rate of its digestion (which determines the rate at which osmotically active solutes are added to small bowel contents) and the relative concentrations of actively and rapidly absorbed versus slowly or non-absorbable solutes in the meal or in its digestive products.

Normal colon function can be appreciated by comparing the volume and composition of fluid delivered to the colon (from the ileum) and the water and electrolyte composition of stool.

	Fluid Delivered Daily to Colon		Daily Stool Composition	
	Amount	Concentration mEq/L	Amount	Concentration mEq/L
Water	600 ml		100 ml	
Na	75 mEq	125	4 mEq	40
K	5 mEq	9	9 mEq	90
Cl	36 mEq	60	2 mEq	15
HCO_3	44 mEq	74	3 mEq	30

From this table it can be determined that the normal colon absorbs about 500 ml of water, 71 mEq of sodium, 34 mEq of chloride and secretes 4 mEq of potassium per day. This represents only about 20% of the colon's capacity to absorb water and electrolytes, and if ileal delivery rate were steady, and the colon's function normal, over 2 liters of fluid would have to be delivered to the colon per day before diarrhea would ensue. This estimate assumes delivery to the colon of normal fluid, without an excess of nonabsorbable solutes.

The major mechanisms of normal absorption and secretion are shown in the following table:

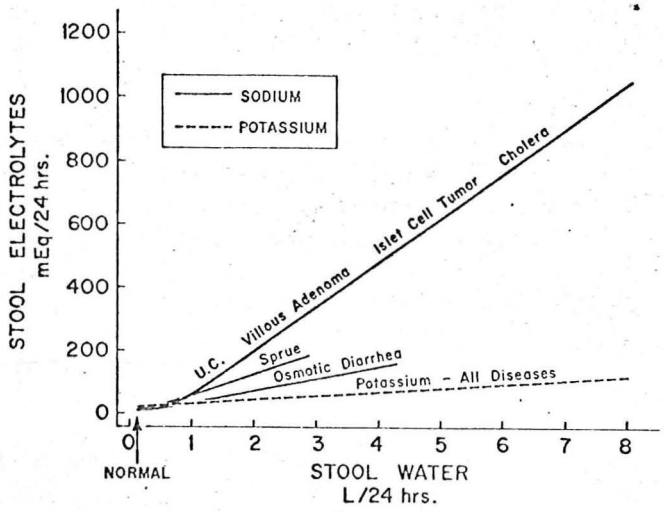
	Duodenum and Jejunum	Ileum	Colon
Permeability characteristics	Permeable to H_2O, NaCl, small solutes (urea, xylose)	"Tight"	"Tight"
Special mechanism for absorption of:	Glucose-galactose, fructose, amino acids, HCO_3^-	Na, Cl, glucose-galactose, fructose, amino acids	Na, Cl
Special mechanism for secretion of:	Hydrogen	HCO_3^-, hydrogen, ? K*	HCO_3, hydrogen, ? K*
Major mechanism for NaCl absorption:	Passive (Solvent drag)	Active transport via "carrier"	Active transport via "carrier"

* Most evidence suggests K secretion is passive, secondary to electrical gradients, but question is still open.

Water and Electrolyte Changes in Stool During Diarrhea

As noted in Table 1, normal stool water contains a higher concentration of potassium than sodium. However, as stool volumes increase during diarrhea, there is

a progressive rise in sodium and chloride concentrations and a corresponding fall in potassium concentration. When stool volumes exceed 3 liters per day, the electrolyte composition of stools approaches values close to those of plasma. This is illustrated in the next figure:



U.C. = ulcerative colitis

As shown in this figure, sodium loss relative to stool water is the same in cholera, ulcerative colitis, islet cell adenoma and villous adenoma of the rectum, even though the severity of diarrhea varies in these diseases. By contrast, in steatorrhea, and with osmotic diarrhea (laxatives, sugar malabsorption), sodium loss relative to water loss is lower. This is because osmolality of stool water in these latter diseases is made up of non-electrolytes as well as ions.

Potassium loss, relative to water loss, is fixed, regardless of diarrhea etiology.

Anion losses in diarrhea: In all diseases except chloridorrhea, the sum of [Na] + [K] is greater than [Cl].

The bicarbonate concentration of stool water is not a reliable index of net bicarbonate loss to the body in diarrhea, since organic acids (action of intestinal bacteria on unabsorbed carbohydrate) react with and dissipate bicarbonate; hence the "anion gap" in Table 1.

Chronic diarrhea may result in either systemic acidosis or alkalosis:

Acidosis: If $[Na]_{stool} + [K]_{stool} - [Cl]_{stool}$ is greater than the plasma bicarbonate, the patient is losing bicarbonate or its equivalent, and acidosis results.

Alkalosis: If $[Na]_{stool} + [K]_{stool} - [Cl]_{stool}$ is less than plasma bicarbonate, acid in some form is being lost; this tends to produce alkalosis.

Secondary effects of diarrhea, i.e., hypokalemia, starvation, shock and renal impairment, are also important in deciding the final systemic acid-base picture that will result from diarrhea. For instance, alkalosis may result not only from acid loss in stools, but also from contractions of ECF without a commensurate loss of bicarbonate, and from K deficiency. Similarly, acidosis can result from loss of

bicarbonate or equivalent in stool, as well as from renal failure and shock.

Diarrhea may be caused, at least theoretically, by four mechanisms:

I. Osmotic Diarrhea
   A. Ingestion of poorly absorbed solutes--some laxatives
   B. Maldigestion--disaccharidase deficiency, etc.
   C. Failure to transport a solute which is normally absorbed by some special mechanism (i.e., active transport, or carrier-mediated transport)
      1. Chloridorrhea, congenital or acquired
      2. Glucose-galactose malabsorption
      3. Some laxatives
      4. Diffuse inflammation

II. Abnormal mucosal cell permeability--Sprue, chloridorrhea

III. Intestinal Secretion--These diarrheas persist when patients fast, in contrast to I and II.
   Cholera, islet cell adenoma (both Zollinger-Ellison syndrome and pancreatic cholera), villous adenomas of rectum, ulcerative colitis, and probably acute infectious diseases and some laxatives.

IV. Motility Disturbance--Malignant carcinoid syndrome, neurogenic diarrheas (diabetic neuropathy), irritable colon syndrome, ? thyrotoxicosis

As already noted, the volume and composition of diarrheal fluid depends on which of these factors initiates the diarrhea, and in some instances, measurement of stool electrolytes may help in diagnosis; for example, in chloridorrhea [Cl] > [Na] + [K], and in laxative diarrhea of the osmotic type, stool osmolality > ([Na] + [K]) x 2, reflecting the presence of the unabsorbed solutes of the laxative.

II. DIFFERENTIAL DIAGNOSIS OF CHRONIC AND RECURRENT DIARRHEA

It is recognized that chronic diarrhea may be a manifestation of an enormous number of diseases. In some instances these are perfectly obvious, and there is no diagnostic problem. In the following discussion it is assumed that the patient has had a reasonable work-up and that uremia, cavitary tuberculosis, cancer of the stomach or colon, cancer of the pancreas, and diarrhea around a fecal impaction have been excluded. It is further assumed that the easily diagnosed malabsorption diseases (celiac sprue, Whipple's disease, blind loop syndrome, pancreatic insufficiency, disaccharidase deficiency), regional enteritis, ulcerative colitis and malignant carcinoid syndrome have been ruled out, and that the patient has not had abdominal surgery known to be associated with diarrhea (vagotomy, gastric resection, small bowel resection, etc.). Chronic diarrhea due to laxatives has been adequately stressed, and there is no need to review the importance of a careful examination of the stool to rule out parasitic infections, especially E. histolytica.

Even after such obvious diseases and problems have been excluded, chronic

diarrhea often remains unexplained. This, coupled with inadequate measures to control the symptom, often leads to severe disability.

Diarrhea in the face of a negative workup raises the possibility that the diarrhea is functional or psychogenic in origin, and that the patient has no organic disease. Such diseases are usually grouped under the heading of irritable colon syndrome (mucous colitis, psychogenic diarrhea, functional diarrhea, etc.).

Irritable Colon Syndrome

This term is used to embrace a group of colonic disturbances in which there may be pain of colonic origin, disordered bowel habit, with either diarrhea or constipation, and sometimes the passage of mucus per rectum (2). The disorder is about twice (some say 5 times) as common in women as in men. While the disease can occur at any age (including childhood [4]), most patients are between 20 and 50 (with an average age of about 25) when they first develop symptoms.

Two main types of the disorder are recognized (2):

1. Spastic colon group. Pain, presumably of colonic origin, is the main symptom. Bowel habit variable, sometimes normal, sometimes periodic constipation or diarrhea, or both these symptoms alternating.
2. Painless diarrhea group. Diarrhea is usually intermittent, with normal bowel action occurring in between attacks; but about one-third have more or less continuous diarrhea.

Possible predisposing causes:

1. Purgatives: Although commonly used by these patients, clearlynot the cause of the syndrome in most patients (2).
2. Post-dysentery (2): In these cases the onset of the disorder follows an episode of dysentery (amebic, shigella or possibly viral). No evidence of persisting infection. This may be the initiating cause in 20% of patients.
3. Psychological factors: Present in 80% of patients. The personality characteristics described by White and Jones (1) are depicted in the following table:

Tension	96%
Resentment	92%
Anxiety	82%
Depression	74%
Asthenia	73%
Guilt	67%
Dependency	64%
Rigidity of thought	50%

White and Jones found that 24 of 28 "less neurotic patients"(not incapacitated by their neurosis) showed a close correlation between emotion and aggravation of symptoms. In the "more neurotic group" (handicapped by their psychoneurotic symptoms) only 58% showed a close correlation between emotion and colonic symptoms.

Almy (3) states that, in general, patients with diarrhea as a reaction to stress have lacked for parental affection, either because of neurosis in the parents

or because of their death, divorce or separation. Such patients often appear immature and dependent, rigid and compulsive. Although outwardly pleasing and even apologetic, they often have deep-seated and sustained feelings of guilt and hostility, neither of which finds ready expression in words or actions. They have feelings of inadequacy when faced with personal problems.

The frequency of various psychological factors in patients studied by Chaudhary and Truelove (2) are given in the following table:

Psychological Factor	Men (44 patients)	Women (86 patients)
Marital difficulties	3	13
Anxiety over children	2	13
Related to parents	2	14
Sexual difficulties	5	4
Related to business or career	12	11
Financial anxieties	1	3
Fear of cancer	4	10
Fear of other major disease	1	2
Obsessional worrying about many trivial problems	10	28
Miscellaneous	4	13

It will be seen that women were more frequently involved in psychological stress related to their families than were the men. Specific sexual problems were apparently not common. The men were more likely to be suffering from nervous strain in relation to their careers. The absence of financial worries was conspicuous, and appeared to be because the patients, with hardly an exception, were the sort of persons who live strictly within their financial means.

Other findings: Physical examination is negative or non-contributory except for tenderness on palpation of one or more parts of the colon, which is present in about 60% of cases (2) (equally common in spastic colon and painless diarrhea).

Sigmoidoscopy may reveal hyperemia, excessive mucus secretion or abnormal motility, but no ulcerations, bleeding or abnormal friability of the mucosa.

Colonic biopsy reveals normal mucosa. Stool fat and guaiac tests are negative. X-rays negative, or barium enema may show "irritability" of the colon. White and Jones (1) state that the amount of barium suspension required to fill the colon is only 32 ounces instead of the 36 to 40 ounces usually required.

Treatment:

1. Reassure about absence of organic disease
2. Explain disease as an "abnormal reaction of the bowel" analogous to blushing, tachycardia, etc.
3. Show interest in patient's personal problems, and let the patient become dependent on the doctor
4. Sedatives and tranquilizers
5. Antispasmodics

Prognosis (2): One-third become symptom-free; majority continue to have intermittent symptoms. Those in the post-dysentery group generally have a more favorable prognosis. The presence of an identifiable psychologic factor makes the prognosis worse.

There has been speculation that irritable colon syndrome may be a forerunner of diverticulosis of the colon (9).

The preceding has been a classical account of irritable colon syndrome. It is appropriate to ask how much of this is real and how much imaginary.

Controlled studies on the psychological and emotional problems in these patients have not been carried out. Other GI diseases, often held as classic examples of psychosomatic disorders, have, however, been examined. For example, patients with ulcerative colitis were found not to differ emotionally from a control group of patients, the latter being patients without ulcerative colitis attending a GI clinic (8). Such studies are so difficult to adequately control and normality so difficult to define that a clearcut analysis of the exact role of emotion in GI disease may never become available. Even the clearest proof that patients with irritable colon syndrome were "within normal limits" emotionally would not disprove the notion that overreaction of the colon to a normal amount of stress caused the diarrhea.

Motility studies of the colon have likewise failed to establish irritable colon a distinct entity. By and large, patients with spastic colitis have colonic hypermotility, while patients with painless diarrhea tend to show hypomotility (6, 7). Chaudhary and Truelove (6) found that patients with irritable colon syndrome have a hyperactive response to IM prostigmine, suggesting an excessive reaction to parasympathetic stimuli. Interestingly, they did not find hyperreaction (i.e., greater than normal subjects) to an emotionally charged interview.

Misiewicz et al. (7) did not find a hyperreactive motility to prostigmine in patients with irritable colon syndrome.

The mechanism of diarrhea in irritable colon syndrome is unknown, but presumably is due to too rapid emptying of the colon, before normal reabsorption of salt and water is completed. Defective salt and water absorption is unlikely since intermittent constipation is often seen in some of these patients.

Assuming that irritable colon syndrome is a true entity, is there a counterpart within the small bowel? The answer is unknown.

Summary of Characteristics of Diarrhea in Irritable Colon Syndrome

1. Usually intermittent, may be constant
2. Stools usually small in volume; normal ileal fluid amounts to no more than 500 ml/day, so diarrheas of larger volume would be impossible to explain on the basis of irritable colon.

3. Stools not excessively foul
4. Negative GI work-up

References for irritable colon syndrome:

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III. CHRONIC DIARRHEA OF UNKNOWN ETIOLOGY THAT DOES NOT FIT IRRITABLE COLON SYNDROME

A "negative work-up" in a patient with chronic diarrhea that does not, for one reason or another, fit the irritable colon syndrome constitutes a major clinical problem. Two examples will illustrate this group of patients.

Case 1. This patient is a white female, a doctor's wife, who was first seen in 1964 when she was 26 years old. She began having intermittent diarrhea 3 years previously. Prior to that time her bowel movements were completely normal, or slightly constipated in type.

The diarrheal episodes start out by her having one normal bowel movement, followed by several loose ones. The stools are very foul. She believes that they contain fat. No blood has been noted.

At times she may have apparently normal stools for several days, but then the diarrhea will recur and last for several days to a week.

Associated with the diarrhea she has urgency and cramping lower abdominal pain

that is relieved by bowel movements. During the illness she lost 7 pounds, but she had no other systemic symptoms, such as fever, skin rash, or flushing. She has no symptoms of ulcer or liver disease. There was no evidence of emotional instability and diarrhea did not appear related to stress. She believes that the diarrhea was less severe during pregnancy a year before this history was taken. She had never had abdominal or pelvic surgery. She had never traveled outside the USA.

Physical examination was normal. CBC, sed rate and urinalysis were normal. Serum proteins normal. Stool culture normal; search for amebae and other parasites negative.

Proctoscopy was normal. Smear of rectal aspirate was normal. Recent upper GI, small bowel series and barium enema had been done by the referring physician and were reported normal. These were reviewed and their normality confirmed.

Initial impression was irritable colon syndrome, although three factors were somewhat against this diagnosis: (1) Absence of demonstrable emotional problem, (2) stools large in volume by history, (3) history of probable excess fat in stools.

On the next visit the patient brought in 3 random stool specimens which were guaiac negative, but which contained a moderate increase in fat content by Sudan stain.

A 3-day quantitative stool collection was then obtained. Total weight = 994 gm (331 gm/day), total fat = 149 gm (47 gm/day). Thus, steatorrhea of rather marked degree was noted. This, of course, rules out irritable colon syndrome.

A xylose test was done and revealed 7.7 gm excreted in 24 hours (normal). A jejunal biopsy was done, and was normal. The small bowel series and barium enema were repeated, looking especially for evidence of regional enteritis. Both were normal, but this does not rule out the disease.

Steatorrhea associated with normal xylose absorption, normal jejunal mucosa and normal x-rays of GI tract suggested exocrine pancreatic insufficiency. Amylase x3 was normal. A secretin-pancreatozymin test was performed, wherein duodenal contents are collected after stimulation of the pancreas by these enzymes. Analysis of these fluids for bicarbonate ion concentration and enzyme content revealed normal results. Because the test is not trustworthy, a therapeutic trial with Cotozyme was carried out for 2 weeks. This potent pancreatic replacement did not reduce the diarrhea or the steatorrhea.

Rarer causes of steatorrhea were then looked for and excluded:

1. Zollinger-Ellison syndrome (7% have diarrhea and steatorrhea without ulcer):
   Basal gastric secretion 0.4 mEq/hr
   Maximum histamine response 6.0 mEq/hr

2. a-beta-Lipoproteinemia:
   Wet smear of fingerprick blood showed no acanthocytosis.
   Fasting jejunal cells contained no fat

3. Bacterial proliferation in small bowel:
   No history of abdominal surgery. No stasis by x-ray.
   Culture of jejunal contents revealed only a few colonies of E. coli.
   No growth in anaerobic culture
   Schilling test normal

4. Malignant Carcinoid Syndrome:
   Urinary 5HIAA = 8 mg/24 hours (normal)

5. Disaccharidase deficiency (see Gut 8:373, 1967):
   Normal lactose and sucrose tolerance tests. No diarrhea induced with either sugar

6. Scleroderma:
   Esophageal motility normal
   No Raynaud's or skin changes
   Intestinal x-rays normal

Thus, the results of all these studies failed to shed any light on the etiology of her diarrhea and steatorrhea, which continued to be incapacitating. To add to the confusion, the steatorrhea was intermittent; sometimes stools contained a marked excess of fat, and other times no fat at all.

Finally, in desperation, she was started on folic acid. The rationale for doing this was ill defined, the main reason being that in the past some patients with peculiar types of malabsorption syndromes (i.e., tropical sprue) have responded favorably (see Gastroenterology 47:457, 1964). In any case, she had a dramatic improvement, and gained 15 pounds, and her lethargy and weakness completely disappeared. Unfortunately, serum folic acid levels were not measured prior to therapy.

When contacted on 11/14/68, she was 5 months pregnant, and stated she was otherwise perfectly normal. Close questioning revealed that she may have one loose bowel movement as often as once a week, but nothing that she considers diarrhea. She will return for quantitative stool fat collection after delivery.

Thus, a diagnosis was never made.

Case 2. L.P.

This 28-year-old patient considered herself perfectly well until spring of 1967, when she spent two weeks in Mexico. Toward the end of her trip she developed mild diarrhea, which persisted on return to the USA. She had not taken antibiotics or other drugs to prevent tourista diarrhea.

The diarrhea fluctuated in severity. During "bad" periods she would have 5-6 watery or mushy stools between 7 a.m. and noon, and 1-2 similar stools the rest of the day. During better times she would have 2-3 loose bowel movements per day, usually in the morning. She never had normal stools.

Associated with the diarrhea there was mild cramping pain. No blood or mucus, no perianal disease, no weight loss, and no anorexia. General health was good, with no systemic symptoms.

Diarrhea persisted, and in the summer of 1968 she was first examined. The work-up was completely negative (with negative stool tests for fat and blood), except that routine stool cultures on 4 occasions showed absolutely no growth of normal flora.

Repeated stool cultures failed to grow any pathogens and parasites could not be found. Stained smears of stool failed to show monilia or staphylococci.

Anaerobic stool cultures showed apparently normal numbers of anaerobic organisms.

The diarrhea continued through the fall of 1968, until the patient developed a thrombophlebitis which was treated with oral penicillin. After 2 days of penicillin therapy she developed, for the first time in 18 months, normal bowel movements. She has been completely well ever since.

A stool culture on 12/23/68 revealed normal flora.

"Normal bacterial flora" is discussed in detail in references 9 and 14. Abnormal flora is thought to be a cause of diarrhea in 4 clinical situations:

1. Traveler's diarrhea
2. After antibiotic therapy
3. Diarrhea associated with immunologic defects
4. Tropical sprue

By "abnormal flora" is meant abnormal types or numbers of bacteria in normal locations, as opposed to bacterial proliferation in the small bowel which also is a cause of diarrhea and steatorrhea (10).

1. Traveler's Diarrhea:

a. Duration of diarrhea: Average 2 days. Ten days is maximum duration according to Kean (1), so that the chronic diarrhea in our patient cannot be "tourista" in its usual form.
b. Prophylaxis: Attack rate can be substantially reduced by sulfathalidine (2 gm/day) (1) or by oral streptomycin (4).
c. Etiology (1): Available evidence suggests that tourista is not caused by shigella, salmonella, pathogenic E. coli, klebsiella, paracolon, amebiasis or staph toxins. Kean (1) found no evidence for a viral etiology, although others have stated, without supporting data, that virus infection is the major cause (12).
d. In the absence of other proved etiology, some abnormality in flora is the most plausible explanation for tourist diarrhea although this has never been established by quantitative bacteriologic studies, and routine cultures are usually within normal limits.
e. Attack rate:

	Incidence of Diarrhea
U.S. Travelers, according to Kean (1):	
Mexico	33%
Hawaii	8
Mediterranean area of Europe	67
Scandinavian countries	35
British Travelers, according to Turner:	
North, South and Central Europe	16
Middle East	24
Asia, including India and Pakistan	15
Africa	26
Australia/New Zealand	11
South America/Caribbean	13
Canada and U.S.	7
Foreign Students in U.S., according to Dandoy*	14

Mexican Travelers to U.S. - According to Dr. Jose Rubiloba (2), tourista attacks as high a percentage of Mexicans in U.S. as Americans visiting Mexico (data not given). One of Dr. Rubiloba's co-workers is Chief of Medicine for Mexico's Balsa Hotel Chain.

* Admittedly a poor study. Author was not sure foreign students, many of whom were Orientals, understood the questions asked them.

2. Post-Antibiotic Diarrhea

Antibiotics may theoretically cause diarrhea in 3 ways--by inducing a malabsorption syndrome (i.e., neomycin [18]), by allowing an overgrowth of staph or fungus, or by inducing some other abnormality of the bacterial flora. For reasons that are unknown, lincomycin is especially likely to cause diarrhea.

Antibiotic-induced diarrhea is only occasionally associated with emergence of an obvious staph or fungus infection, and the addition of nystatin does not substantially reduce GI symptoms produced by oral tetracyclines (13). Therefore, it generally is believed that diarrhea after antibiotics results from changes in the relative numbers of different intestinal bacteria without a specific pathogen. Everyone admits this concept lacks proof.

The changes in flora induced by antibiotics are not well studied. Smith (7) reports that penicillin suppresses or eliminates gram-positive bacteria and stimulates directly or indirectly the multiplication of gram-negative bacteria. Streptomycin tends to do the opposite. Broad-spectrum antibiotics suppress both gram-negative and gram-positive organisms with tendency for fungus proliferation. Many workers believe that abnormalities in anaerobic bacteria (numbers or types) may be important in antibiotic diarrhea, but pertinent data are nonexistent.

Breidenbach and Martin (5) briefly presented 9 case reports of chronic and severe diarrhea in which stool cultures revealed a predominant growth of either pseudomonas, proteus, paracolon, aerobacter, E. freundii or A. dispar. GI work-up was otherwise negative, including proctoscopy. These patients had usually been given antibiotics sometime in the past. Antibiotic therapy, directed against these organisms, cured the diarrhea in most cases.

Thisstudy was criticized by Donaldson (9) because variations in colonic flora might have been caused by the diarrhea itself. However, recent studies (15) have shown that chronic diarrhea (ulcerative colitis and regional enteritis) does not result in emergence of predominant organisms of the types described by Breidenbach and Martin.

3. Immunologic Defects and Abnormal Flora--See below

4. Tropical Sprue and Abnormal Flora--Inferred because some cases respond to antibiotics, yet have normal bacterial populations in small bowel (16, 17,19); colonic flora have not apparently been analyzed by quantitative methods.

Mechanism of Diarrhea When Bacterial Flora is Abnormal. This is completely unknown. Weijers and van de Kamer (8) believe that harmful amines are produced (cadaverine, putrescine, tyramine, histamine, etc., etc.) and that these are somehow related to diarrhea. Not convincing.

Tansy et al (6) have isolated a substance from Strep. fecalis cultures that they consider an "intestinal stimulant" capable of causing diarrhea.

Although intestinal bacteria have been of enormous interest to physicians since the turn of the century, the following statement by Jordan (quoted in reference 14) is still applicable:

> "Whenever a man gets the idea that he is going to work out the bacteriology of the intestinal tract of any mammal, the time has come to have him quietly removed to some suitable institution."

Nevertheless, stains of the stool for staph and monilia and stool culture looking for unusual predominant organisms has a definite place in the work-up of patients with chronic diarrhea even in the absence of a history of recent travel or antibiotic therapy.

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IV. OTHER DISEASES TO CONSIDER WHEN THE WORK-UP IS NEGATIVE IN A PATIENT WITH CHRONIC DIARRHEA

Diarrhea and Immunoglobulin Deficiency

Diarrhea, with or without steatorrhea, with or without jejunal biopsy abnormalities, and with or without thymoma, has been commonly associated with a wide spectrum of immunoglobulin deficiencies. In particular, deficiency of immunoglobulin A has been associated with diarrhea. Such patients may have normal jejunal histology, a celiac sprue-like lesion, or nodular lymphoid hyperplasia. Severe and resistant giardial infestation of the GI tract is frequently present in these patients, but eradication has usually not helped the diarrhea. One patient has had diarrhea controlled by fresh plasma infusions (Binder, New Eng. J. Med. 277:802, 1967), which contains IgA. Commercial gamma globulin does not contain IgA and did not control the diarrhea in this case. Another patient did respond to commercial gamma globulin (Conn, Ann. Int. Med. 65:528, 1966).

Mechanism of diarrhea is unknown. Antibiotics may bring transient or longer relief of diarrhea, suggesting abnormal flora. IgA is normally secreted into the intestinal tract in relatively high concentrations and may play a role in regulating intestinal bacteria. However, some patients with complete absence of IgA donot have diarrhea (Bull and Tomasi, Gastroenterology 54:313, 1968).

Other references (by no means complete) attest to the frequency ofthis syndrome; many of these describe multiple (3-8) cases:

1. Gastroenterology 52:911, 1967
2. Gastroenterology 52:121, 1967
3. Gastroenterology 51:305, 1966
4. Gastroenterology 51:641, 1966
5. Gastroenterology 51:1058, 1966
6. Gastroenterology 51:573, 1966
7. Am. J. Med. 44:168, 1968
8. Am. J. Med. 42:319, 1967
9. Am. J. Med. 40:78, 1966
10. Gut 7:119, 1966

Immunoelectrophoresis should be done in every patient with chronic diarrhea of unknown etiology and in every patient with celiac sprue (even if they respond to a gluten-free diet). See reference 10 for such a case.

Paradoxical Diarrhea With Opiates

Chronic diarrhea can result from use of opiates. Attempts at reducing the dose may make diarrhea worse. Only complete withdrawal will cure the diarrhea.

Cohen, R.A., and Pope, M.A. Paradoxical diarrhea with opiates. JAMA 205:802, 1968.

Spurious Steatorrhea

Bamforth, J., et al. Spurious steatorrhea. Brit. Med. J. 2:682, 1967.

Patient ate enormous amounts of Brazil nuts during fat balance study. These are not broken down completely, and spuriously elevate fecal fat. Thus, dietary fat may invalidate fecal fat estimation.

Allergy

Ingelfinger, F.J., et al. Gastrointestinal allergy. New Eng. J. Med. 241:303, 1949.
Handel, J., and Swartz, S. Gastrointestinal manifestation of the Schonlein-Henoch syndrome. Am. J. Roentgenol. 78:643, 1957.
Taylor, K.B. Immunological mechanisms of the gastrointestinal tract. Gastroenterology 51:1058, 1966.
Hsi-yen Liu, et al. Bovine milk protein-induced intestinal malabsorption of lactose and fat in infants. Gastroenterology 54:27, 1968.

Allergy has not been established as a cause of chronic diarrhea, although allergy to milk proteins remains a possibility, especially in children. Certainly, skin tests are unreliable as an index of gastrointestinal allergy.

Giardiasis

Giardiasis frequently is present in patients with immunologic deficiencies; see that section. In some patients giardiasis appears to be the only cause of chronic diarrhea, with or without malabsorption. Cysts may not be present in stool and diagnosis by small bowel biopsy or jejunal aspirate may be necessary. The presence of giardia does not necessarily mean this parasite is causing the diarrhea.

Hoskins, L.C., et al. Clinical giardiasis and intestinal malabsorption. Gastroenterology 53:205, 1967.

Chronic Diarrhea and Medullary Carcinoma of Thyroid

Williams (J. Clin. Path. 19:103, 1966) first noted the frequency of chronic diarrhea in patients with medullary carcinoma (12 of 41 cases). If the tumor is resected, diarrhea stops, at least until the malignancy recurs. There are certain similarities between argentaffin cells, from which carcinoid tumors develop, and the parafollicular cells of the thyroid which form medullary carcinoma (J. Clin. Path. 19:114, 1966), and one patient had a mild elevation of urinary levels of 5HIAA (see report by Bernier, et al. reviewed in Gastroenterology 54:469, 1968; original is in French).

Williams, et al. (Lancet 1:22, 1968) have recently reported that prostaglandins are present in tumor tissue, and 2 patients, both with diarrhea, had elevated blood levels of prostaglandins. Prostaglandins are known to stimulate intestinal smooth muscle (Bergstrom, S., Science 157:382, 1967, and Hydovitz, J.D., New Eng. J. Med. 278:915, 1968).

Medullary carcinoma of the thyroid and pheochromocytoma may occur in some patients, but patients with pheochromocytoma alone rarely have diarrhea (Williams, E.D., et al., Brit. Med. J. 3:295, 1967).

Chronic Diarrhea Associated With Ganglioneuroma

Massive watery diarrhea with or without mild steatorrhea; may respond favorably to adrenal steroids (reference 1). Diarrhea is cured by removal of the tumor. Hypertension, flushing, fever, etc., may be absent, in which case diarrhea and its consequences may be the only manifestations (2).

Abnormal catecholamine excretion is usually, but not invariably, present, and laparotomy may be necessary for diagnosis (2).

A smooth muscle active substance (bradykinin-like) has been extracted from the tumor in one case (1). Diarrhea does <u>not</u> result from catecholamine infusion and except for 2 cases pheochromocytoma has not been associated with diarrhea (1).

1. Cameron, D.G. Chronic diarrhea in an adult with hypokalemic nephropathy and osteomalacia due to a functioning ganglioneuroblastoma. Am. J. Med. Sci. 253: 417, 1967.

2. Peterson, H.D., et al. Chronic diarrhea and failure to thrive secondary to ganglioneuroma. Arch. Surgery 95:934, 1967.

3. Hamilton, J.R., et al. Diarrhea associated with adrenal ganglioneuroma. Am. J. Med. 44:453, 1968.

4. Hunt, T.C. Diarrhea due to carotid body tumor (paraganglioma) in adult. Proc. Roy. Soc. Med. 54:227, 1961.
Resection of tumor cured diarrhea.

Islet Cell Adenoma

A. Zollinger-Ellison Syndrome: Diarrhea is only manifestation in 7% of cases. Most, of course, have peptic ulcer, with or without diarrhea. Steatorrhea is usually associated with the diarrhea, both of which are related to high rates of gastric acid secretion. See Shimoda, Saunders and Rubin, Gastroenterology 55: 705, 1968, for studies on mechanism of steatorrhea in this syndrome. Diagnosis by acid secretory studies.

B. "Pancreatic Cholera": Watery diarrhea without steatorrhea, no gastric hypersecretion. Mechanism not clear; probably tumor secretes a diarrhogenic substance. Best references are:
   1. Matsumoto, K.K., et al., Gastroenterology 50:231, 1966
   2. Marks, et al., Gastroenterology 52:695, 1967. This report describes dramatic improvement of diarrhea with adrenal steroid therapy.

   Diagnosis by exploratory laparotomy.

Excessive Bile Salts in Colon

Following ileal resection, severe diarrhea may occur. In many cases this is secondary to steatorrhea, but in some such patients steatorrhea is mild or absent, yet they have severe diarrhea. Two authors report that cholestyramine will control diarrhea in these patients (Rowe, G.G., Gastroenterology 53:1006, 1967; Poley and Hofmann, Abstract to ASCI, 1968). If moderate or severe steatorrhea is also present, cholestyramine may make it (and diarrhea) worse. Poley and Hofmann report that these patients do well on a combination of medium chain triglycerides and cholestyramine.

Supposedly unabsorbed bile salts in these patients cause diarrhea in some way, possibly by an osmotic effect, although direct inhibition of water and salt absorption in the colon has been suggested in a preliminary study (Gastroenterology 54: 1256, 1968).

Diabetic Diarrhea

May occur with or without steatorrhea. All cases have peripheral neuropathy, but manifestations of the latter may be mild. Other diseases must be ruled out, especially celiac sprue, if the patient has steatorrhea. Some cases respond to antibiotics (see Green, et al., Diabetes 17:385, 1968) and presumably the etiology of diarrhea and steatorrhea in these cases is abnormal bacterial proliferation in the small bowel.

Many cases do not respond to antibiotic therapy; see Wruble and Kalses (Am. J. Med. 37:118, 1964). For a discussion of the neuropathologic findings in diabetic diarrhea, see Hensley and Soergel, Arch. Path. 85:587, 1968.

Other "Neurogenic" Diarrheas

Tabes dorsalis
Multiple sclerosis
Myelitis
Encephalitis
Heat stroke
Lead poisoning

Discussed in Wilson, S.A.K., Neurology, Vol. 1, Williams & Wilkins, Baltimore, 1941

Charcot-Marie-Tooth Disease
Norstand, J.F., et al. Peripheral neuropathy in association with gastrointestinal symptoms. New York J. Med. 58:863, 1958.

Orthostatic Hypotension
Wagner, H.N., Jr., Bull. Johns Hopkins Hosp. 105:322, 1959.

Dystrophia myotonica with associated sprue-like symptoms
Am. J. Med. 16:614, 1954.

Amyloidosis

Diarrhea, with or without steatorrhea, occurs in about 15% of patients with amyloidosis. Incidence much higher in "Portuguese variety". Mechanism of diarrhea is not known, but French thinks it may be due to autonomic dysfunction. Suspect when diarrhea associated with peripheral neuropathy and/or autonomic dysfunction in a non-diabetic. Of course, also suspect when diarrhea superimposed on other chronic disease. Diagnosis by biopsy rectal or jejunal mucosa or other organs.

French, J.M., et al. Peripheral and autonomic nerve involvement in primary amyloidosis associated with uncontrollable diarrhoea and steatorrhoea. Am. J. Med. 39:277, 1965.

Kyle, R. A. Value of rectal biopsy in diagnosis of primary systemic amyloidosis. Am. J. Med. Sci. 251:501, 1966.

Abdominal Lymphoma

Suspect when a patient with "celiac disease" fails to respond to gluten-free diet (in such cases lymphoma may be masquerading as celiac disease, including mucosal biopsy change) or when a patient with long-standing and/or controlled celiac disease has a relapse (celiac disease predisposes to lymphoma).

Diagnosis may be suggested by small bowel x-ray or by small bowel biopsy, but laparotomy is usually required.

Seijffers, et al. Intractable watery diarrhea, hypokalemia, and malabsorption in a patient with Mediterranean type of abdominal lymphoma. Gastro. 55:118, 1968.

Eidelman, S., et al. Abdominal lymphoma presenting as malabsorption. Medicine 45: 111, 1966.

Austad, W.I., et al. The relationship of malignant tumors of lymphoid tissue and celiac disease. Am. J. Digest. Dis. 12:475, 1967.

Scleroderma

Diarrhea and malabsorption may be the main, and at times the only, manifestations of scleroderma. In some cases malabsorption is secondary to bacterial overgrowth in the small bowel, and either antibiotics or resection of dilated segments of small bowel may result in dramatic improvement.

Hoskins, L.C., et al. Functional and morphologic alterations of the GI tract in scleroderma. Am. J. Med. 33:459, 1962.
Heinz, E.R., et al. X-ray aspects of intestinal scleroderma. Ann. Int. Med. 59: 822, 1963.
Salen, G., et al. Malabsorption in intestinal scleroderma. Ann. Int. Med. 64:834, 1966.

Cirrhosis

Severe unexplained diarrhea may be the chief complaint of patients with cirrhosis. The exact cause can rarely be pinpointed. Malabsorption due to bile salt deficiency or associated pancreatic insufficiency is often incriminated if steatorrhea is present. Passive congestion of the gut or disaccharidase deficiency (due to protein malnutrition) of the mucosal cells of the small bowel are blamed if there is no or little steatorrhea.

Diarrhea and Malabsorption in Systemic Mast Cell Disease

Cause unknown. Jejunal mucosa normal. Skin pigmentation occurs in this disease as well as sprue, and this may cause confusion.

Bank, S., and Marks, I.N. Malabsorption in systemic mast cell disease. Gastroenterology 45:335, 1963.
Jarnum, S., et al. Mastocytosis of skin, stomach and gut with malabsorption. Gut 8:64, 1967.

Addison's Disease

Diarrhea may be a serious symptom. Its cause is uncertain. In some cases it may be related to steatorrhea.

Steatorrhea is common in patients with Addison's disease, and may be an important cause for weight loss in these patients. Stool fat may be as high as 32 gm/day in these patients. Appropriate treatment of Addison's disease reverses the steatorrhea completely.

Welbourn, R.B. Proc. Roy. Soc. Med. 56:1080, 1963.
McBrien, et al. Steatorrhea in Addison's disease. Lancet 1:25, 1963.

Thyrotoxicosis

Causes diarrhea in 20%. In masked hyperthyroidism, severe diarrhea and weight loss may dominate the picture. Mechanism not known and no well studied cases from the GI standpoint were found.

Welbourn, R.B. Proc. Soy. Soc. Med. 56:1080, 1963.

Hypoparathyroidism

Diarrhea is an occasional symptom. It may be a direct effect of hypocalcemia on the bowel. Cramps, steatorrhea and tetany may be present, and there may be a history of previous thyroidectomy (a common cause of hypoparathyroidism). Sometimes the differentiation between hypocalcemia secondary to malabsorption and vice versa is difficult. The serum inorganic phosphorus is raised in hypoparathyroidism, and normal or low in most malabsorption syndromes.

Jackson, W.P.U., et al. Steatorrhea and pseudohypoparathyroidism. J. Clin. Endocrinol. 16:1045, 1956.
Snodgrass, R.W., and Mellinkoff, S.M. Idiopathic hypoparathyroidism with small bowel features of sprue without steatorrhea. Am. J. Dig. Dis. 7:273, 1962.
Welbourn, R.B. Proc. Roy. Soc. Med. 56:1080, 1963.
Russell, R.I. Hypoparathyroidism and malabsorption. Brit. Med. J. 3:781, 1967.