

- Viscera, Together with Some Other Considerations. Bull. Johns Hopkins Hosp., 35:370-378, Nov., 1924.
41. Matthes, K.: Action of Blood on Acetylcholine. *J. Physiol.*, 70:338-348, Dec., 1930.
  42. Melville, K. I. and Stehle, R. L.: The Actions of Pituitary Preparations (Posterior Lobe) Upon the Intestine of the Dog. *J. Pharmacol. and Exper. Therap.*, 50:165-173, Feb., 1934.
  43. Mordwinkin, N.: Über den Einfluss einiger endokrinen Flüssigkeiten auf die motorische Funktion des Dickdarms. *Endokrinologie*, 2:117-121, Aug., 1928.
  44. Mulinos, M. G.: Studies on Cholin as a Motor Hormone for the Alimentary Tract. *Am. J. Physiol.*, 77:158-165, June, 1926.
  45. Mulinos, M. G.: The Gastric Hunger Mechanism. IV. The Influence of Experimental Alterations in Blood Sugar Concentration on the Gastric Hunger Contractions. *Am. J. Physiol.*, 104:371-378, May, 1933.
  46. Ochsner, Alton, Gage, I. M. and Cutting, R. A.: The Value of Drugs in the Relief of Ileus. An Experimental Study. *Arch. Surg.*, 21:924-958, Dec., 1930.
  47. Ochsner, Alton, Gage, I. M. and Cutting, R. A.: Influence of Hypertonic Salt Solutions on the Motility of Normal and of Obstructed Intestine: An Experimental Study. *Arch. Surg.*, 27:742-770, Oct., 1933.
  48. Orr, T. G.: The Action of Sodium Chloride Upon the Small Intestine. *Ann. Surg.*, 94:732-737, Oct., 1931.
  49. Quigley, J. P. and Barnes, B. O.: Action of Insulin on the Motility of the Gastro-Intestinal Tract. VI. Antagonistic Action of Posterior Pituitary Lobe Preparations. *Am. J. Physiol.*, 95:7-12, Oct., 1930.
  50. Quigley, J. P. and Hallaran, W. R.: The Independence of Spontaneous Gastro-Intestinal Motility and Blood Sugar Levels. *Am. J. Physiol.*, 100:102-110, March, 1932.
  51. Rose, W. B., Stucky, C. J. and Cowgill, G. R.: Studies in the Physiology of Vitamins. XII. The Effect of Parathormone on Gastric Motility in Vitamin B-deficient and Normal Dogs. *Am. J. Physiol.*, 91:554-562, Jan., 1930.
  52. Ross, J. W.: Hypertonic Saline in Adynamic Ileus. *Canad. M. A. J.*, 16:241-244, March, 1926.
  53. Salant, William and Washeim, Henry, Jr.: Effect of Calcium on the Action of Pilocarpine and Atropine. *Proc. Soc. Exper. Biol. and Med.*, 26:512-515, March, 1929.
  54. Sharnoff, V. N.: Concerning the Action of Various Pituitary Extracts Upon the Isolated Intestinal Loop. *Am. J. Physiol.*, 39:268-278, Jan. 1, 1916.
  55. Sheldon, Luther, Kern, R. A. and Hakansson, E. G.: The Treatment of Megacolon by Parathormone: with a report of three cases. *Am. J. M. Sc.*, 184:94-104, July, 1932.
  56. Steggerda, F. R., Gianturco, Cesare and Essex, H. E.: The Action of Pituitary Extracts on the Colon of the Cat. *Am. J. Physiol.*, 123:400-403, Aug., 1938.
  57. Tidmarsh, C. J.: The Action of Histamine on the Motility of the Large Intestine. *Quart. J. Exper. Physiol.*, 22:33-43, May, 1932.
  58. Trachtenberg, F.: Ephedrinwirkung auf die Magen-Darmtätigkeit. (Klinischexperimentelle Untersuchungen). *Arch. f. Verdauungsgr.*, 48:69-95, 1930.
  59. Weiland, Walther: Zur Kenntnis der Entstehung der Darmbewegung. *Arch. f. d. ges. Physiol.*, 147:171-196, Aug. 6, 1912.

## The Concentration of Pancreatic Enzymes in the Duodenum of Normal Persons and Persons With Disease of the Upper Part of the Abdomen

By

MANDRED W. COMFORT, M.D., ROBERT L. PARKER, M.D.\*

and

ARNOLD E. OSTERBERG, Ph.D.†

ROCHESTER, MINNESOTA

ORDINARILY when duodenal contents are removed with a tube from the duodenum and the enzymatic activity is studied the stimulants of external pancreatic secretion are: (1) the mechanical irritation caused by the entrance of the tube into the duodenum, and (2) physiologic stimulation by the acid gastric secretion entering the duodenum. The strength of such stimulants is uncontrollable and variable, and the concentration of enzymes in the duodenal fluid obtained under these circumstances consequently will vary greatly from time to time. While the importance of data obtained in this manner has frequently been minimized, and with much reason, we frequently have felt that we obtained information which was of value in the differential diagnosis of various diseases. We therefore have not been willing to condemn the method entirely. Analyses of our data presented in the following pages show that while there are definite limitations to the information obtained in this manner, the method is of sufficient value to warrant its continued use until there is available a stimulant which will produce a maximal quantity of external pancreatic secretion at all times.

### MATERIAL AND METHODS

The concentration of pancreatic enzymes was determined in samples of duodenal fluid taken from 111 persons, seventeen of whom were normal. Duodenal drainage was performed once on eighty-nine, or 80.2 per cent, twice on thirteen, or 11.7 per cent, three times on seven, or 6.3 per cent, four times on one, or

0.9 per cent, and six times on one, or 0.9 per cent of the 111 persons. Only one sample of duodenal contents was obtained from sixty-three, or 56.8 per cent of the 111 persons, two samples were obtained from thirty-two, or 28.8 per cent, three samples were obtained from ten, or 9 per cent, four samples were obtained from three, or 2.7 per cent, five samples were obtained from two, 1.8 per cent, and nine samples were obtained from one or 0.9 per cent. In short, in more than 85 per cent of the instances only one or two samples were obtained.

It has been the usual custom in studies of the concentration of pancreatic enzymes in the duodenal contents to choose samples unmixed with gastric contents and we followed this practice. When we were unable to secure such specimens, however, one as free of gastric contents as possible was taken. We soon found that most samples of bile contained enzymes but that this was not always true. We also found that samples of duodenal fluid which were free of bile often contained pancreatic enzymes in normal concentration.

The concentration of amylase and trypsin was determined by the method of McClure, Wetmore and Reynolds. The concentration of amylase is expressed in terms of grams of d-glucose liberated for each 100 cc. of duodenal contents. The concentration of trypsin is expressed in terms of grams of nonprotein nitrogen liberated for each 100 cc. of duodenal contents. The concentration of lipase was determined by the method of Crandall and Cherry and is expressed in terms of the number of cubic centimeters of twentieth-normal solution of sodium hydroxide necessary to neutralize the fatty acids liberated by 1 cc. of duodenal contents.

\*Division of Medicine.

†Section on Clinical Biochemistry, The Mayo Clinic, Rochester, Minn. Submitted February 6, 1939.

THE VALUE OF THE CONCENTRATION OF ENZYMES IN ONE SAMPLE OF DUODENAL CONTENTS AS AN INDEX OF THE FUNCTIONAL CAPACITY OF THE PANCREAS

Wide variations occurred in the concentrations of enzymes in different samples of duodenal contents obtained from the same person. Thus, in the duodenal contents of one person who did not have any abdominal disease the concentration of amylase varied from 6.1 to 11.5 gm. of d-glucose per 100 cc. In another case the concentration of amylase was 0 in the first sample and 6.5 gm. of d-glucose per 100 cc. of duodenal contents in the second sample. In the same case the concentration of trypsin varied from 1.4 to 5.0 gm. of nonprotein nitrogen per 100 cc. of duodenal contents, and the concentration of lipase varied from 15 to 179 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents. Many similar examples may be cited in cases of organic disease of the liver or biliary tract. Further proof of the variability of the concentration of enzymes in the different samples may be found in the fact that in ten instances the concentration of amylase was 0 in the first sample and well within normal limits in the second sample examined while in six instances it was well within the range of normal in the first sample and 0 in the second sample. Similar behavior was noted in the concentration of trypsin and lipase.

A single determination merely indicates the enzymatic activity of the particular sample and does not

give reliable information regarding the secretory activity of the pancreas nor does the concentration in two or four samples necessarily give reliable information. When the concentration in the first, or the first few, samples is high, the ability of the pancreas to secrete normal amounts of enzymes is obviously normal, but if the concentration is low or absent, no statement should be made regarding the degree of pancreatic function until the concentration of enzymes in many samples has been determined.

THE RELATIVE AMOUNTS OF THE THREE ENZYMES IN THE DUODENAL CONTENTS

In most instances comparable amounts of the three enzymes are present. In some instances it was obvious that this was not the case. In a sample taken from a normal person the concentration of amylase was high (14 gm. of d-glucose per 100 cc. of duodenal contents) and the concentration of lipase was low (3 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents) while in another instance the amylolytic activity was low (1.3 gm. of d-glucose per 100 cc.) and the activity of lipase was high (148 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents). Such lack of parallelism in the concentration of pancreatic enzymes in duodenal fluid deserves further investigation.

THE INCIDENCE OF DIFFERENT CONCENTRATIONS OF PANCREATIC ENZYMES IN THE DUODENAL FLUID

The incidence of different concentrations of the

TABLE I

Concentration of amylase\* in the duodenal contents of normal persons and patients with various diseases of the biliary tract and pancreas

Physical Condition	Number	Grams of d-glucose liberated for each 100 cc. of duodenal contents												High Concentration*	Low Concentration*		
		0	0.1-2	2.1-4	4.1-6	6.1-8	8.1-10	10.1-12	12.1-14	14.1-16	16.1-18	18.1-20	20.1-22				
Normal subjects	17	0	2	2	1	5	1	2	3	1						15	1.3
Intrahepatic jaundice resulting from cirrhosis of the liver or hepatitis	31	4	3	9	7	3	4	1								12.5	0
Obstructive jaundice resulting from a stone in, or a stricture of, the common bile duct	25	4	9	4	1	4	2								1	20.5	0
Obstructive jaundice resulting from carcinoma (15 cases)																	
Complete biliary obstruction; carcinoma of the head of the pancreas or ampulla of Vater	6	4	1		1											4.6	0
Complete biliary obstruction; carcinoma of the common bile duct	3	1		1	1											4.3	0
Incomplete biliary obstruction; carcinoma of the head of the pancreas or the ampulla of Vater	6	1	3	1	1											4.6	0
Biliary disease and subacute interstitial pancreatitis	10	2	1	2	2	2	1									8.5	0
Chronic pancreatitis with steatorrhea	7	7														0	0
Nontropical sprue	6	0	2	1	2				1							14	1.3

\*Expressed as grams of d-glucose liberated for each 100 cc. of duodenal contents.

three enzymes observed in the duodenal contents of the 111 persons are given in Tables I, II and III. When the concentrations were determined in more than one sample obtained from one person, only the highest concentrations encountered have been included in the tables.

*Normal persons.* Among the seventeen normal persons, the concentration of amylase varied from 1.3 to 15 gm. of d-glucose per 100 cc. of duodenal contents (Table I), the concentration of trypsin varied from 1.3 to 11.5 gm. of nitrogen per 100 cc. of duodenal contents (Table II) and the concentration of lipase varied from 3 to 179 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents (Table III).

The variability of the concentration of enzymes is thus seen to be extremely wide in samples of duodenal fluid taken from normal persons under the conditions described. Our attention has previously been called to this wide variability in the range of concentration of pancreatic enzymes in the duodenal fluid obtained from normal persons, by the report of the Special Committee on Enzymes of the American Gastro-Enterological Association for 1935. When material is collected under the conditions described the complete absence of enzymes in the duodenal fluid alone points to a pathologic alteration in the capacity of the pancreas to secrete enzymes, but only when a complete absence of the enzymes is found at repeated examinations.

*Patients with intrahepatic jaundice caused by cirrhosis or hepatitis.* Since we had no reason for believing that the pathologic process involved the pancreas as well as the liver in the thirty-one cases in which intrahepatic jaundice was due to cirrhosis or hepatitis, we expected to find pancreatic enzymes present in the same amounts found in the duodenal contents of persons who did not have any disease of the pancreas or liver. This proved to be the case, for

the values varied through about the same range found in the duodenal contents of normal persons. Thus, the concentrations of amylase varied from 0 to 12.5 gm. of d-glucose per 100 cc. (Table I), the concentration of trypsin varied from 0 to 6.7 gm. of nitrogen per 100 cc. of duodenal contents (Table II) and the concentration of lipase varied from 2 to 115 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of the duodenal contents (Table III). Amylase and trypsin were absent in single samples taken from five of the thirty-one patients in this group but other specimens showed that amylase or trypsin, or both were present in two of the five cases. If additional samples of duodenal contents had been examined, it is probable that the enzymes also would have been found in the remaining three cases. Again it is to be emphasized that many samples must be examined before deciding that pancreatic function is low or absent.

*Patients with surgically verified obstructive jaundice caused by a stone in, or a stricture of, the common bile duct.* In twenty-five cases in which obstructive jaundice was due to a stone in, or a stricture of, the common bile duct, and in which the surgeon found no evidence of pancreatitis, we found that the range of concentration of pancreatic enzymes was as wide as it was among normal persons. The concentration of amylase varied from 0 to 20.5 gm. of d-glucose per 100 cc. of duodenal contents (Table I), the concentration of trypsin varied from 0 to 9 gm. of nitrogen per 100 cc. of duodenal contents (Table II) and the concentration of lipase varied from 1 to 172 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents (Table III). In two cases amylase and trypsin were both absent. In both of these cases only one specimen was examined and it should not be concluded that obstructive jaundice which is the result of stone or stricture and which is not associated with

TABLE II

*Concentration of trypsin\* in the duodenal contents of normal persons and patients with various diseases of the biliary tract and pancreas*

Physican Condition	Number	Grams of nonprotein nitrogen liberated for each 100 cc. of duodenal contents									High Concentration*	Low Concentration*
		0	0.1-2	2.1-4	4.1-6	6.1-8	8.1-10	10.1-12	12.1-14	14.1-16		
Normal subjects	17	0	2	5	5	4	1	1			11.5	1.3
Intrahepatic jaundice resulting from cirrhosis of the liver or hepatitis	31	5	3	9	11	3					6.7	0
Obstructive jaundice resulting from a stone in, or a stricture of, the common bile duct	25	3	3	11	7						9	0
Obstructive jaundice resulting from carcinoma (15 cases)												
Complete biliary obstruction; carcinoma of the head of the pancreas or ampulla of Vater	6	5	1								1.1	0
Complete biliary obstruction; carcinoma of the common bile duct	3	1		1		1					8.3	1
Incomplete biliary obstruction; carcinoma of the head of the pancreas or the ampulla of Vater	6	1	3	2							3.2	0
Biliary disease and subacute interstitial pancreatitis	10	2	3	3	1	1					6.3	0
Chronic pancreatitis with steatorrhea	7	6	1								1.5	0
Nontropical sprue	6	0	1	1	1	2	1				9.4	1.7

\*Expressed as grams of nonprotein nitrogen liberated for each 100 cc. of duodenal contents.

pancreatic disease leads to loss of pancreatic function.

*Surgically verified obstructive jaundice resulting from carcinoma of the head of the pancreas and the ampulla of Vater or common duct.* Carcinoma of the head of the pancreas or carcinoma of the ampulla of Vater produced incomplete obstruction of the common bile duct (bile in the duodenum) in six instances and complete obstruction (no bile in the duodenum) in six cases. Amylase, trypsin and lipase (Tables I, II and III) were usually absent, or when they were present the concentration was low in the cases in which obstruction was complete; on the other hand, the enzymes were present in low moderate concentration in the cases in which obstruction was incomplete. In other words, when the obstruction of the common bile duct that is caused by carcinoma of the head of the pancreas or of the ampulla of Vater is complete, the obstruction of the pancreatic duct, as a rule, is also complete, and vice versa. However, the common bile duct may be completely obstructed and the pancreatic duct patent, as occurred in one case.

In the three cases of carcinoma of the common bile duct, the lesion produced complete obstruction of the common bile duct above the juncture of the pancreatic duct and common bile duct. In each case the enzymes were present in normal amounts, as one would expect.

When bile and pancreatic enzymes are both repeatedly absent from the duodenal contents, it may be assumed that both the common bile duct and pancreatic duct are obstructed. The carcinoma in such cases must be situated at the head of the pancreas or at the ampulla of Vater in order to obstruct both the common bile duct and the pancreatic duct. When bile is repeatedly absent and pancreatic enzymes are present in

the duodenal contents, the lesion may be situated in the head of the pancreas, at the papilla of Vater or in the common bile duct. The demonstration of enzymes in the duodenal contents will aid in the localization of the malignant lesion obstructing the common bile duct only when both bile and pancreatic enzymes are absent. The repeated absence of bile from the duodenum of a jaundiced patient is usually proof that the jaundice is obstructive. The malignant nature of the obstruction must be determined from the clinical history, by the palpation of a distended gall bladder and by the behavior of the concentration of bilirubin. The demonstration of the absence of pancreatic ferments in the duodenum may be important confirmatory evidence of the malignant nature of the obstruction and may be important in cases in which the abdomen is difficult to palpate.

Both bile and enzymes are usually present sooner or later in the duodenal contents of patients who have both intrahepatic jaundice and jaundice that is due to incomplete obstruction of the common bile duct by carcinoma; therefore, the demonstration of enzymes in the duodenal fluid will not aid in the differentiation of intrahepatic jaundice and jaundice caused by incomplete malignant obstruction. Crohn (2, 3, 4) has pointed out the value of the determination of the duodenal enzymes in the differential diagnosis of the types of jaundice and in the diagnosis of the situation of the obstruction.

*Biliary disease associated with subacute interstitial (edematous) pancreatitis.* In each of the ten cases in which biliary disease was associated with pancreatitis the surgeon described the pancreas as being enlarged,

TABLE III

*Concentration of lipase\* in the duodenal contents of normal persons and patients with various diseases of the biliary tract and pancreas*

Physical Condition	Number	Cubic centimeters of twentieth-normal solution of sodium hydroxide necessary to neutralize the fatty acids liberated by 1 cc. of duodenal contents											High Concentration*	Low Concentration*
		0	1-20	21-40	41-60	61-80	81-100	101-120	120-140	141-160	161-180	181-200		
Normal subjects	9		2	0	2	1	1			1	1	1	179	3
Intrahepatic jaundice resulting from cirrhosis of the liver or hepatitis	11		4	3	1		1	2					115	2
Obstructive jaundice resulting from a stone in, or a stricture of, the common bile duct	14		3		3	2	3	1	1			1	172	1
Obstructive jaundice resulting from carcinoma														
Complete biliary obstruction; carcinoma of the head of the pancreas or ampulla of Vater	4	1	3										9	0
Complete biliary obstruction; carcinoma of the common bile duct	3		2									1	143	3
Incomplete biliary obstruction; carcinoma of the head of the pancreas or the ampulla of Vater	4		2		2								59	3.6
Biliary disease and subacute interstitial pancreatitis	4	2				1	1						109	0
Chronic pancreatitis with steatorrhea	5		5						1				19	1.5
Nontropical sprue	5		1	1		1	1					1	163	6

\*Expressed as cubic centimeters of twentieth-normal solution of sodium hydroxide necessary to neutralize the fatty acids liberated by 1 cc. of duodenal contents.

edematous or indurated. The degree of abnormality was grade 2, on the basis of 4, in two cases, grade 3 in six cases and grade 4 in two cases. In these cases the range of concentration of duodenal contents was almost as wide as it was among the normal persons (Tables I, II and III). Little can be said about low values for only one specimen was examined in all cases in which such values were obtained. On the contrary, the high values obtained in certain cases showed that the changes found by the surgeon do not necessarily mean that such changes are associated with disturbance of external pancreatic secretion.

In eight of the cases the value for the serum lipase was normal. In the remaining two cases the value was high; in one case 3.5 cc. and in another case 8.3 cc. of twentieth-normal solution sodium hydroxide was required to neutralize the fatty acids liberated by 1 cc. of serum. It may be assumed from these values that any disturbance of pancreatic function secondary to the changes found by the surgeon had disappeared in eight cases but had persisted in two cases. It is interesting that in one of the two cases in which a disturbance of pancreatic function persisted, the duodenal contents contained no pancreatic enzymes, while in the other case the enzymes were present in normal amounts. In the last case, an acute disturbance of the pancreatic function (acute edematous pancreatitis) did not prevent the secretion of enzymes.

*Chronic atrophic pancreatitis with steatorrhea.* The concentration of pancreatic enzymes in the duodenal contents was studied in seven cases of chronic atrophic pancreatitis with steatorrhea. Pancreatic stones or pancreatic calcification was demonstrated roentgenologically in five of the seven cases. A pancreatic cyst was present in one case while diabetes mellitus was a complicating factor in two of the seven cases. Amylase was not demonstrated in the duodenal contents in any of the seven cases, although fifteen specimens were examined (Table I). Trypsin was demonstrated in only one case of the seven cases, in which fifteen specimens were tested (Table II) and in this case the concentration of trypsin in terms of grams of nitrogen per 100 cc. of duodenal contents was only 1.5 and 1.4 gm. Lipase was present, but only in very small quantities in the four cases in which the concentration of this enzyme was determined. Certainly there is a marked tendency to complete absence of enzymes in the duodenal contents in cases of chronic atrophic pancreatitis with steatorrhea. On the other hand, enzymes may be present in an adequate amount in cases of chronic pancreatitis with pancreatic stone but without steatorrhea. In one case not included in the tables the value for amylase was 4 gm. of d-glucose and the value for trypsin was 3.6 gm. of nitrogen per 100 cc. of duodenal contents.

*Nontropical sprue.* In the six cases of nontropical sprue, the concentration of amylase varied from 1.3 to 14 gm. of d-glucose per 100 cc. of duodenal contents (Table I), the concentration of trypsin varied from 1.7 to 9.4 gm. of nitrogen per 100 cc. of duodenal contents (Table II) and the concentration of lipase varied from 6 to 163 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents (Table III). In every case of nontropical sprue in this series, the duodenal contents contained enzymes in apparently adequate amounts. The constant presence of enzymes in these six cases was in contrast with the impression that enzymes are often absent in non-

tropical sprue. The regularity of occurrence of apparently adequate amounts of enzymes in the duodenal contents of patients with nontropical sprue also was in contrast with the regularity of their absence from the duodenal contents in cases of chronic pancreatitis with steatorrhea. Contrary to the opinions of some investigators, the examination of duodenal contents for pancreatic enzymes may be an important step in the differentiation of steatorrhea due to chronic atrophic pancreatitis and the steatorrhea of sprue, the two most important causes of steatorrhea.

#### SUMMARY AND CONCLUSIONS

The determination of the concentration of pancreatic enzymes in one or two samples of duodenal contents obtained in the manner described does not always give a satisfactory idea of the secretory capacity of the pancreas. In order to secure a satisfactory idea of secretory capacity of the pancreas, it is often necessary to examine not one but many samples.

The sample of duodenal contents chosen for analysis should probably be one as free as possible of gastric contents, but it need not contain bile. The concentrations of amylase, trypsin, and lipase in the duodenal contents usually run parallel, but this is not always the case.

Methods described by McClure, Wetmore and Reynolds for determination of the concentration of amylase and trypsin and the method of Crandall and Cherry for the determination of the concentration of lipase appeared to give results constant enough for clinical purposes. Among normal persons, the concentration of amylase varied from 1.3 to 15 gm. of d-glucose per 100 cc. of duodenal contents, the concentration of trypsin varied from 1.3 to 11.5 gm. of nitrogen per 100 cc. of duodenal contents, and the concentration of lipase varied from 3 to 179 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents. The range of concentration of pancreatic enzymes in the duodenal contents of normal persons is so wide that total absence of pancreatic enzymes alone may be taken as evidence of abnormal pancreatic function if pancreatic enzymes are absent from more than one specimen. The repeated finding of low concentrations may in all probability likewise be taken as evidence of diminished pancreatic function.

The range of the concentration of amylase, trypsin and lipase was practically normal in the presence of the following conditions: intrahepatic jaundice caused by cirrhosis or hepatitis, obstructive jaundice caused by a stone in, or a stricture of, the common bile duct, biliary disease which is associated with or a residuum of acute edematous pancreatitis, and nontropical sprue.

A marked contraction of the range of concentrations of amylase, trypsin, and lipase in the duodenal contents was found only in samples of duodenal contents taken from patients with carcinoma of the head of the pancreas, carcinoma of the ampulla of Vater, and chronic atrophic pancreatitis with steatorrhea. In cases of chronic pancreatitis without steatorrhea there was no remarkable contraction of the range of concentration.

The determination of the concentration of enzymes in the duodenal contents will aid in the localization of carcinoma obstructing the common bile duct when bile is not present in the duodenal contents. Absence of

both bile and enzymes from the duodenal contents localizes the carcinoma in the head of the pancreas or in the ampulla of Vater.

The constant finding of pancreatic enzymes in normal amounts in the duodenal contents in cases of

nontropical sprue and their almost constant absence in cases of chronic atrophic pancreatitis with steatorrhea is of considerable importance because it can help in the differentiation of these two most common types of steatorrhea.

#### REFERENCES

1. Crandall, L. A., Jr. and Cherry, I. S.: Presence of an Olive Oil Splitting Lipase in the Blood of Patients with Multiple Sclerosis. *Proc. Soc. Exper. Biol. and Med.*, 28:572-574, March, 1931.
2. Crohn, B. B.: The Chemical Examination of Duodenal Contents as a Means of Diagnosis in Conditions of Jaundice. *J. A. M. A.*, 64:565-569, Feb. 13, 1915.
3. Crohn, B. B.: Studies in Pancreatic Disease. Part I. Duodenal Content Analyses as an Index of Disease, and Functional Activity of the Pancreas. *Arch. Int. Med.*, 15:581-607, April, 1915.
4. Crohn, B. B.: The Early Diagnosis of Carcinoma of the Bile and Pancreatic Ducts. *Am. J. Surg.*, 29:270-274, July, 1915.
5. McClure, C. W., Wetmore, A. S. and Reynolds, Lawrence: New Methods for Estimating Enzymatic Activities of the Duodenal Contents of Normal Man. *Arch. Int. Med.*, 27:706-715, May, 1921.

## Relation of Constipation to Cancer

By

JOHN L. KANTOR, M.D.

NEW YORK, NEW YORK

SOME time ago Dr. Frederick L. Hoffman, the noted medical statistician, pointed out to me the confused state of the literature regarding the possible part played by constipation in the causation of cancer. His far-reaching studies and his wide experience showed how difficult it was to reach a satisfying conclusion on the basis of the existing statistics. With his cooperation, a grant was secured through the generosity of Mr. Samuel S. Fels of Philadelphia, for the purpose of studying this question by a critical review of personally controlled clinical material. The present report is the result of this study. It is a great pleasure, therefore, to acknowledge my appreciation of Dr. Hoffman's stimulating encouragement which made possible the investigation here presented.

#### OBJECT

The purpose of this study is to determine the relation of cancer and constipation, and particularly whether constipation plays a demonstrable role in the etiology of cancer.

#### MATERIAL, METHODS, CRITERIA

The material used is an unselected list of 4,700 private patients complaining of digestive symptoms. These constitute a homogeneous group uniformly studied according to a standard routine procedure developed by the writer. The material is the same as that used for other clinical and statistical studies already published.

Constipation was diagnosed clinically according to the following criteria obtained from the history:

1. Complete failure of spontaneous bowel movements.
2. Laxation rate less than 6 stools per week.
3. Severe cathartic, enema, or irrigation habit.
4. Persistent difficulty in rectal emptying as evidenced by marked suppository or enema habit.

In many cases where opportunity offered, the history was supplemented by roentgen determination of the total colon emptying time. The technic and

criteria of this particular type of observation have been published elsewhere (2).

In the general (unselected) series of 4,700 patients, the incidence of constipation was estimated at 54.2%.\* It was considered important to separate from the total group of the constipation cases those recent cases which might have developed during the course of the malignant disease. Since it has been shown by Hoffman (3) that the "average" duration of carcinoma before the patient seeks medical advice may be set at 18 months, the line between long and short term constipation was drawn at this point. In other words, 3 groups of constipated patients were considered throughout this study, as follows:

Group 1. Constipation of all durations.

Group 2. Constipation of 1½ years duration or less.

Group 3. Constipation over 1½ years in duration (1 minus 2).

In order to determine the incidence of "recent constipation," i.e. constipation lasting 1½ years or less, 200 consecutive cases of constipation were analyzed. In this group there were found 13 "recent" cases, an incidence of 6.5%. It was next necessary to calculate the incidence of "recent constipation" in the general or unselected series. This was done by multiplying the general incidence of constipation (54.2) by the factor 6.5 which gives the incidence of "recent constipation" *in general* as 3.5%. Conversely, the general incidence of constipation lasting over 1½ years was found to be almost 51% (100 — 6.5, or 93.5,

\*Before beginning the present study the general incidence of constipation was actually determined in 4,443 histories. There were found to be 1,963 cases of constipation, an incidence of 44.2%. In the course of the study there were added as a result of intensive review of the case histories:

To 13 esophagus cases	1 case of constipation
To 20 rectal cases	4 cases of constipation
To 101 stomach cases	9 cases of constipation
To 45 colon cases	5 cases of constipation

179  
19  
Thus there were added 19 cases of constipation to the 179 cancer cases, an increase of about 10%. Maintaining this increase for the unselected list of 4,700 cases, the general incidence of constipation becomes 54.2%. This figure is, therefore, adopted as the *corrected* general incidence of constipation in the present study.