Nutritional Problems Arising From the Treatment of Cancer

Maurice E. Shils, M.D., Sc.D. While cancer may cause malnutrition of various etiologies in the patient, nutritional problems may also arise as the result of the specific treatment given to control the neoplastic disease. This paper outlines and discusses briefly some of the more common problems in this area (See Table.)

RADIATION

A moving account by a physician relating her subjective reactions to the effects of destruction of the sense of taste following radiotherapy for cancer of the pharynx serves to emphasize the need on the part of the attending physician to understand the profound psychological, physiological, and nutritional after-effects which may occur with the varied treatments for cancer. In the case of "mouth blindness" resulting from loss of taste sensation and in other situations reducing food acceptance and leading to anorexia, improper food preparation and serving creates a serious situation since "the patients are not hungry anyway, and it is easier to starve." When all food becomes tasteless, appearance and aroma become much more important, as do supplementary liquid feedings.

Radiation damage to small and large bowel occurs in a small but significant number of patients receiving external or internal radiation therapy for cancer. The epithelium of the small bowel is

---

Dr. Shils is Associate Professor of Medicine, Cornell University Medical College, and Associate Member, Sloan-Kettering Institute for Cancer Research, New York, New York.

Portions of this article appeared in "Nutrition in Neoplastic Diseases" in Wohl and Goodhart's MODERN NUTRITION AND DISEASE. Fourth edition. Philadelphia, Lea & Febiger, 1968.
second only to bone marrow in its sensitivity to radiation. Altered intestinal function may occur during therapy and usually disappears. In those where significant “late” radiation changes are developing, symptoms recur usually within a year, but sometimes not for ten or more years. Flattening and ulceration of the mucosa, telangiectasis, fibrosis, endarteritis of small vessels and stenosis of the bowel develop and these changes are often progressive. Obstruction and fistula formation may occur and require bowel resection which complicates preexisting diarrhea and malabsorption. While the damaged tissue may make surgery difficult, the obstructive symptoms may be caused by a local stenosis; consequently, exploratory laparotomy is recommended before malnutrition increases the risk. In our experience, these patients with severe radiation damage and previous resection are more difficult to manage than patients with massive small bowel resection alone. Intermittent obstruction, diarrhea, malabsorption, and chronic intestinal and bladder blood loss create a multitude of problems in nutrition and electrolyte balance. However, with close follow-up and attention to nutritional requirements these patients often do very well.

SURGERY

The effects of ablative surgery may be varied and many. Most of these procedures and their sequelae are, of course, not peculiar to surgery for cancer. However, certain resections are much more common or limited almost entirely to patients with cancer (e.g., extensive resection of the head and neck, total esophagectomy in the adult, total gastrectomy, or ureterosigmoidostomy).

Radical Surgery of the Head and Neck Region

Radical surgery of the head and neck region, including partial or total glossectomy and/or mandiblectomy, often interferes with mastication and swallowing. With some training or with laryngectomy, oral food intake is possible (in the laryngectomy, aspiration of saliva must be prevented). In others, tube feeding may be required. Liquid diets are prepared by blending the types of foods ordinarily consumed by the family, having made certain that the pattern is nutritious. Where the personal situation does not permit this, simple and inexpensive tube formulas may be used. In our experience, many elderly individuals do not tolerate the large amount of milk or milk powder often recommended for liquid formulas; nor do they tolerate large amounts of fluids. The composition of the formula should be modified as concomitant cardiovascular, renal, or endocrine disease indicates. Attention should be paid to psychologic aspects of food with
tube feedings; e.g., the aroma of a separate cup of coffee may be important.

Surgery of the Digestive Tract

Esophagectomy often induces significant malabsorption of fat. The etiology of this peculiar dysfunction appears to be the bilateral vagotomy inherent in the procedure; however, the precise intestinal mechanism causing the steatorrhea is unknown. The previously recognized sequelae of vagotomy—gastric stasis (necessitating a drainage procedure) and diarrhea—also occur in esophagectomized patients. Carbohydrate absorption is normal. Where previous mediastinal radiation has been given to such patients, malabsorption of vitamin B₁₂ is not uncommon, but this seems to be related to radiation rather than to esophagectomy. The use of medium-chain length triglycerides (MCT) as a major portion of fat intake diminishes the steatorrhea and frequently associated diarrhea.

With gastrectomy, the dumping syndrome, hypoglycemia, and malabsorption often occur. The dumping syndrome consists of the onset within approximately 15 minutes of ingestion of a meal of one or more of the following symptoms: sensation of epigastric fullness, nausea, abdominal cramping, warmth, sweating, and weakness; tachycardia, tachypnea, and pallor may be noted and the patient obtains relief in lying down. The intensity of symptoms varies from mild to severe and tends to improve with time; however, severe symptoms have been reported to persist in two to eleven percent of patients with partial gastrectomy. The nutritional significance of this condition lies in the fact that its symptomatology becomes associated with an aversion to food and consequent malnutrition. A possible relationship of the vasomotor and gastrointestinal disturbances to release of bradykinin-like peptides and serotonin has been postulated.

Symptoms of hypoglycemia may occur if the meals are high in carbohydrate and widely spaced. This may be prevented by frequent feedings of the type recommended below.

A more general finding in gastrectomized patients is malabsorption—especially for fat. Again, patients vary greatly in the degree of malabsorption but the majority may have some steatorrhea. Lawrence et al. have found an average fat absorption of 82 percent in 25 totally gastrectomized patients with a range of 41 to 97 percent; only 3 patients had normal fat absorption above 92 percent. Nitrogen losses in stool also vary widely in these patients, but, with a few exceptions, do not appear to average more than one or two gm. per day more than normal individuals on the same intake. A discussion of the possible mechanisms of the malabsorption is not possible here, but the interested reader is referred to recent summaries. From the clinical viewpoint these fecal losses are not usually important in overall nutrition if the patient is willing and able to eat well, since efficiency of absorption does not vary appreciably with increased fat and nitrogen intake. However, in the patient who is not eating adequately because of the dumping syndrome, bile regurgitation or other reasons, the impaired efficiency of absorption imposes a further impediment to good nutrition. Where dumping syndrome is a problem, it has been recommended that serious attention be paid to diet planning and guidance with frequent small feedings and with a diet composition high in protein, moderate in fat, and relatively restricted in carbohydrate; benefit may be obtained by omitting liquids at meals.

Small bowel obstruction in gastrectomized patients secondary to phytobezoar is known to occur, presumably as the result of a large undigested food bolus passing directly into the small intestine. Such patients should be cautioned to chew food well and to avoid the ingestion of a large amount of bulky fiber-containing foods. Systemic antibiotics may be helpful in certain patients with symptomatic malabsorption and steatorrhea.
presumably secondary to bacterial overgrowth in the afferent loop.\textsuperscript{39} The development of a number of nutritional deficiencies has been described in patients with partial gastrectomy, including those of protein, various fat-soluble vitamins, iron, calcium, and folic acid.

It is now well recognized that near-total or total gastrectomy with its removal of intrinsic factor-secreting cells will lead to failure to absorb vitamin B\textsubscript{12}, and eventually to the symptoms and signs of pernicious anemia. The interval before symptoms occur is variable, but macrocytosis will occur in six months to seven years after gastrectomy.\textsuperscript{40}

Institution of nutritional measures to insure early and continued adequate intake and absorption of these and other nutrients is important since the development of deficiency of many of these factors is slow and insidious and, hence, escapes attention until late.

Clinical studies in normal subjects and in those with ablation of varying portions of small intestine indicate that all nutrients studied, with the exception of vitamin B\textsubscript{12}, are most efficiently and (in the usual dietary amounts) rather completely absorbed in the proximal small bowel.\textsuperscript{41-43} However, with jejunal resection, the ileum with its reserve absorptive capacity can absorb these nutrients in good degree.

Massive small bowel resection, with a residual of three feet or less, presents very serious and long-term problems in maintaining adequate nutrition including water and electrolytes. If there is additional loss of the ileocecal valve and portions of the colon, the problems are intensified. However, the application of present knowledge with respect to care of these patients will permit a successful outcome.

These principles include the following:

1. The postoperative period is often a stormy one, complicated by infection, ileus, and weight loss. During this period, it is essential that all factors tending to weight loss and malnutrition be combated vigorously. This includes preparation at surgery for long-term parenteral nutrition with sterile insertion of an indwelling catheter or A-V shunt, and the formation of a feeding gastrostomy.\textsuperscript{44-46}

2. Absorptive capacity of many of these patients improves with time so that patience plus a carefully developed nutritional program, designed to meet the changing needs, often achieve a successful outcome. Our armamentarium of intravenous nutrients is now sufficient to permit good nutrition by this route alone for periods of months, provided the vascular route can be kept open. As gastrointestinal function returns, special gastrostomy feedings can be initiated, utilizing round-the-clock feedings, if indicated, with hydrolyzed protein or amino acids and other nutrients capable of rapid absorption. This route is increasingly utilized as conditions improve, to the point where i.v. feedings are discontinued and eventually oral intake commences, supplemented by the gastrostomy feedings when necessary.

3. A marked reduction in the intake of long-chain fats reduces diarrhea and decreases fecal calcium, magnesium and other electrolyte losses.\textsuperscript{47} The use of medium-chain triglycerides (MCT) in increasing amounts (as tolerated by the patient and consistent with an acceptable level of diarrhea) is often of value in increasing calories.\textsuperscript{48} This product in significant amounts will cause some ketosis and acidosis which may require additional sodium bicarbonate.\textsuperscript{49}

4. The acidosis associated with malabsorption and diarrhea will tend to increase calcium and potassium losses in urine and should be watched for and treated on a continuing basis.

5. Persistent gastric hypersecretion may occur in occasional patients, and this possibility should be investigated. When it does occur, vagotomy (preferably selective) and pyloroplasty may be helpful.
in decreasing fistula or fecal losses.29

6. Where resection of the distal ileum has occurred, physiologic doses of vitamin B₁₂ cannot be absorbed and periodic injections of this vitamin are necessary.

7. The terminal ileum is also the site of absorption of conjugated bile salts. Hence, the usual entero-hepatic circulation of these emulsifying agents is disrupted and their concentration in the intestine is decreased since the liver is incapable of making up the massive loss. Administration of conjugated bile salts to such patients may make the diarrhea worse.29 Attempting to chelate the bile salts with cholestyramine (to minimize possible deleterious effects on the large bowel) is apparently without effect in those with really severe malabsorption, and the treatment may result in complications.30

8. The surgeon should retain the ileocecal valve whenever possible since it appears to slow the exit of small bowel contents and, hence, improve absorption and perhaps act to hinder retrograde movement of colonic bacteria. The use of an antiperistaltic segment of bowel as a replacement for the valve has been recommended with more or less enthusiasm.31-32

The inherent danger posed by the possibility of sacrificing further absorptive surface in a patient with massive bowel resection must be carefully considered before such a procedure is done.

**Ileostomy** is usually followed by large sodium and water losses but within seven to ten days these usually decrease to the range which will characterize the otherwise healthy individual on a stable diet. Generally, these stabilized individuals lose 300 to 600 ml. of water daily with 40 to 100 mEq. of sodium and 2.5 to 10 mEq. of potassium, emphasizing the physiologic role of the colon in absorbing water and sodium and in exchanging potassium for sodium.30-34

**Gastroenteritis**, partial intestinal obstruction and prolonged excessive sweating impose additional losses which must be taken into consideration. Studies in man and in dogs during sodium depletion have demonstrated a reduction in sodium concentration of ileostomy material as depletion progressed, accompanied by increased potassium concentration.30-36

**Blind loop syndrome:** For more than 70 years, it has been recognized that certain mechanical intestinal abnormalities could cause a hematologic syndrome which resembles pernicious anemia. Location and type of lesion may vary but the common denominator in association with absorptive defects appears to be stasis and retarded drainage from some part of the small intestine. This condition has been termed the blind loop syndrome.

It may occur in patients with multiple jejunal diverticuli, improperly draining afferent loop in Billroth II gastrectomies and gastroenterostomies, entero-enteroanastomoses (usually side to side) with dilated blind pouches, and strictures with proximal dilatation.37-38

Deficiencies of absorption of vitamin B₁₂ occur most commonly, but defects in absorption of fat, fat-soluble vitamins, proteins, and minerals may also occur. When the jejunum is markedly involved, defective carbohydrate absorption may be noted. In this syndrome there may be no significant loss of absorbing surface of the small intestine but the presence of the anatomic lesion appears to encourage the overgrowth of intestinal flora.

Conjugated bile salts are split by bacteria in the small bowel with resultant impairment of micelle formation necessary for fat absorption and with increased free bile acids which may be toxic to small bowel mucosa.39-40

A diagnostic test as well as temporary treatment pending corrective surgical procedure involves the use of systemic antibiotics such as the tetracyclines. Presumably, improvement occurs as a result of the reduction in bacteria in the affected area.

**Pancreatectomy** with consequent loss of digestive enzymes leads to loss.
### TABLE—CONSEQUENCES OF CANCER TREATMENT PREDISPOSING TO NUTRITION PROBLEMS

1. **Radiation Treatment.**
   a. Radiation of oropharyngeal area.
      (1) Destruction of sense of taste and impaired intake.
   b. Radiation of abdomen and pelvis.
      (1) Bowel damage, acute and chronic, with diarrhea, malabsorption and anatomic complications.

2. **Surgical Treatment**
   a. Radical resection of oropharyngeal area.
      (1) Dependency on tube feeding.
   b. Esophagectomy and esophageal reconstruction.
      (1) Gastric stasis.
      (2) Malabsorption.
      (3) Fistula development or stenosis with long-term dependency on tube feeding.
   c. Gastrectomy.
      (1) Dumping syndrome.
      (2) Malabsorption.
      (3) Hypoglycemia.
   d. Intestinal resection.
      (1) Jejunum.
         (a) Decreased efficiency of absorption of many nutrients.
      (2) Ileum.
         (a) Vitamin B₁₂ deficiency.
         (b) Bile salt losses.
      (3) Massive bowel resection.
         (a) Malabsorption.
         (b) Malnutrition.
      (4) Ileostomy and colostomy.
         (a) Complications of salt and water balance.
   e. Blind loop syndrome.
   f. Pancreatectomy.
      (1) Malabsorption.
      (2) Diabetes mellitus.
   g. Ureterosigmoidostomy.
      (1) Hyperchloremic acidosis.

3. **Chemotherapy Treatment**
   a. Corticosteroids and other hormones.
      (1) Fluid and electrolyte problems.
   b. Antimetabolites.
      (1) Gastrointestinal damage.
      (2) Anemias.
into the stool not only of fats and of protein, but also of significant amounts of various vitamins and minerals. Since pancreatectomy necessitates partial gastrectomy, this is a complicating factor, as noted above.

Pancreatic enzyme insufficiency may be effectively replaced by potent pancreatic extracts given with meals or at two-hour intervals; occasionally, sodium bicarbonate supplements are helpful. The diabetes mellitus following the resection is usually of the "brittle" type, requiring relatively small amounts of insulin and rather difficult to control with precision. Hence, tolerance of some glycosuria is safer than the hypoglycemic episodes which may occur with achievement of glucose-free urine.

Ureterosigmoidostomy performed in certain patients where the bladder must be removed with implantation of the ureters into the sigmoid colon often leads to significant disturbances in acid-base balance with development of a hyperchloremic acidosis. Potassium depletion may occur in association with the acidosis. These abnormalities occur significantly less in patients with ileal bladder construction.

CHEMOTHERAPY

Hormones

Hormones and other chemotherapeutic agents may also lead to disturbances in nutrition. The effects of adrenocortical steroids are well known and include losses of protein, calcium, and potassium; these may be significant, depending on the type of steroid, dosage, and duration of treatment.

Most of the present chemotherapeutic agents aside from hormones inhibit one or more key steps in the intermediary metabolism of cells—normal as well as neoplastic. Since the epithelial cells of the small intestine have a relatively rapid turnover, it is to be expected that many of these drugs will adversely affect intestinal functions to a degree depending on drug, dosage, duration of treatment, altered rates of excretion and metabolism, and individual susceptibility.

Antimetabolites

A major effect of folic acid antagonists is exerted on the gastrointestinal mucosa and the bone marrow. The morphologic changes induced in the intestines of experimental animals are similar to those seen in sprue. These morphologic changes are accompanied by alterations in metabolism and decreased absorptive ability for xylose and presumably other nutrients. In man, a single intravenous injection of Methotrexate (2 to 5 mg. per kg. body weight) is followed by the inhibition of mitotic activity in the jejunal mucosa as well as by marked fine structural changes in the cells observable with the electron microscope. These pathologic changes may be prevented or reversed by leucovorin.

The fluorinated pyrimidines have a marked action on gastrointestinal mucosa. In patients receiving an adequate course of 5-fluorouracil the bone marrow may become megaloblastic with associated changes in various epithelial and cancer cells; these morphologic changes are similar to those found in pernicious and other megaloblastic anemias resulting from nutritional deficiencies. Actinomycin D also induces marked gastrointestinal changes. Malabsorption of fat and other nutrients has been observed in rats following its administration.

Intestinal mucosal changes with associated changes in intestinal function have been noted in experimental animals and/or in man with other agents, including glutamine antagonists, hydroxyurea, daunomycin, Vinca alkaloids, and polyfunctional alkylating agents.

References

1. Shils, M. E.: Nutrition in neoplastic diseases. In: Wahl, M. G., and Godhardt, R. S. (eds.), Modern Nutrition in Health and Disease, 4th Ed., Philadelphia, Lea & Febiger, 1968, Pp. 1012-1024.
2. MacCarthy-Leventhal, E. M.: Post-radiation mouth blindness. Lancet 2:1128-1139, 1959.
3. Shils, M. E., and Gilat, T.: The effect of esophagectomy on absorption in man: clinical and metabolic observations. Gastroenterology 50: 347-357, 1966.
4. Shils, M. E.: Unpublished observations.
21.40: digestion

20. Harvey, J. C.: The vitamin B12 deficiency state engendered by total gastrectomy. Surg. Gynec. Obstet. 1: 485-492, 1955.

19. Deller, D. J., and Witts, L. J.: Changes in the blood after partial gastrectomy with special reference to vitamin B12. Quart. J. Med. 17: 71-81, 1952.

18c. Deller, D. J.; Richards, W. C., and Witts, L. J.: Changes in the blood after partial gastrectomy with special reference to vitamin B12. II. Quart J. Med. 31: 81-92, 1962.

17. Zeitlin, I., and Smith, A. N.: S-Hydroxyindoles and kynins in the carcinoid and dumping syndromes. Lancet 2: 926-931, 1966.

16. Holdsworth, C. D.; Turner, D., and McIntyre, N.: Pathophysiology of postgastrectomy hypoglycaemia. Brit. Med. J. 4: 257-259, 1969.

15. Lawrence, W., Jr., et al.: Alterations in fat and nitrogen metabolism after total and subtotal gastrectomy. Surg. Gynec. Obstet. 110: 403-416, 1960.

14. Lundk, G.: The mechanism of postgastrectomy malabsorption, (Editorial) Gastroenterology 42: 637-640, 1962.

13. McCabe, R., and Knox, W. G.: Phytobezoar in gastrectomised patients. Arch. Surg. (Chicago) 85: 264-266, 1963.

12. Neale, G., et al.: Protein malnutrition after partial gastrectomy. Quart. J. Med. 36: 469-494, 1967.

11. Adams, J. F.; Johnstone, J. M., and Hutter, J. D.: Vitamin-A deficiency following total gastrectomy. Lancet 1: 415-417, 1960.

10. Bordier, Ph., et al.: Subclinical vitamin-D deficiency following gastric surgery. Lancet 1: 437-440, 1962.

9. Leonard, P. J.; Losowsky, M. S., and Pulvertaft, C. N.: Vitamin-E levels after gastric surgery. Gut 7: 578-580, 1966.

8. Grokax, M. C., and McKenna, R. D.: Iron-deficiency anemia after partial gastrectomy. Canad. Med. Ass. J. 94: 411-417, 1967.

7a. Pyrah, L. N., and Smith, I. B.: Osteomalacia following gastrectomy. Lancet 1: 528-531, 1956.

7b. Harvall B.; Krogsgaard, A. R. and Lous, P.: Calcium deficiency following partial gastrectomy. Acta Med. Scand. 172: 407-409, 1962.

6c. Deller, D. J., et al.: Metabolic effects of partial gastrectomy with special reference to calcium and folic acid. I. Gut 5: 218-225, 1964.

6d. Clark, C. G., et al.: Dismembered calcium metabolism after polyga partial gastrectomy Lancet 1: 714-715, 1965.

Markkanen, T.: Absorption tests with natural folate material in controls and gastrectomized patients. Amer. J. Clin. Nutr. 21: 473-481, 1966.

20. Harvey, J. C.: The vitamin B12 deficiency state engendered by total gastrectomy. Surg. Gynec. Obstet. 40: 577-589, 1955.

19. Borstström, B., et al.: Studies of intestinal digestion and absorption in the human. J. Clin. Invest. 36: 1321-1325, 1957.

18. Booth, C. C.: The metabolic effects of intestinal resection in man. Postgrad. Med. J. 37: 725-739, 1961.

17. Wilmore, D. W., and Dudrick, S. J.: Safe long-term venous catheterization. Arch. Surg. (Chicago) 84: 254-258, 1966.

16. Shils, M. E., et al.: Submitted for publication.

15. Booth, C. C.; Macintyre, I., and Molin, D. L.: Nutritional problems associated with extensive lesions of the distal small intestine in man. Quart. J. Med. 33: 401-420, 1964.

14. Boedehsek, W.; Rogers, J. B., Jr., and Bolint, J. A.: Effect of changes in dietary lipids on intestinal fluid loss in the short-bowel syndrome. Ann. Intern. Med. 70: 205-213, 1970.

13. Bergen, S. S., Jr.; Hashim, S. A., and Van Itallie, T. B.: Hyperketonemia induced in man by medium-chain triglyceride. Diabetes 15: 723-725, 1966.

12. Frederic, P. L.; Sieer, J. S., and Osborn, M. P.: Relation of massive bowel resection to gastric secretion. New Eng. J. Med. 272: 509-514, 1965.

11. Hardison, W. G., M., and Rosen, R. H.: Ileal transit time in normal and altered states of the small intestine. J. Clin. Invest. 23: 747-754, 1962.

10. Wilmore, D. W., and Johnson, C. J.: Metabolic effects of small bowel resection in patients with short-bowel syndrome. Ann. Surg. (Chicago) 94: 782-785, 1966.

9. Simiczy, P., and et al.: Gastric acid and electrolyte disturbances in patients with short-bowel syndrome. J. Clin. Invest. 23: 219-223, 1962.

8. Field, W., Jr., and et al.: Effect of reduction in dietary sodium on electrolyte composition of the contents of the terminal ileum. Amer. J. Physiol. (Editorial) 179: 477-480, 1954.

7. Donalson, R. M., Jr.: Intestinal bacteria and malabsorption. (Editorial) Ann. Intern. Med. 64: 544-552, 1966.

6. Tabachuck, S., and Booth, C. C.: Relationship of the intestinal bacterial flora to absorption. Brit. Med. Bull. 22: 285-290, 1966.

5. Kim, Y. K., et al.: The role of altered bile acid metabolism in the steatorrhea of experimental blind loop syndrome. J. Clin. Invest. 45: 556-562, 1966.

4. Heaton, R. W.: The importance of keeping bile salts in their place. Gut 10: 487-493, 1969.

3. Littman, A., and Hanscom, D. H.: Pancreatic extracts. New Eng. J. Med. 281: 201-204, 1969.

2. Ferris, D. O., and Odel, H. M.: Electrolyte pattern of the blood after bilateral ureterostomy.
moidostomy. J.A.M.A. 142: 634-641, 1950.

43. Dowling, M. D., Jr.; Krakoff, I. H., and Karnofsky, D. A.: Mechanism of action of anti-cancer drugs. In: Cole, W. H., (Ed.) Chemotherapy of Cancer. Philadelphia, Lea & Febiger, 1970, Pp. 1-74.

44a. Thiersch, J. B., and Philips, F. S.: Effects of 6-amino-pteroyl-glutamic acid in dogs with special reference to megaloblastosis. Proc. Soc. Exper. Biol. Med. 71: 484-490, 1949.

44b. Wall, E., and Oleson, J. J.: Effects of folic acid antagonist (aminopterin) on albino rats. Brit. J. Exper. Path. 32: 458-461, 1951.

44c. Rybak, E. J.: Electron microscopic studies of intestinal lesions. I. Aminopterin-induced lesions in mice. Gastroenterology 42: 206-218, 1962.

45. Vitale, J. J., et al.: Effects of aminopterin administration on the respiration and morphology of the gastrointestinal mucosa of rats. J. Lab. Clin. Med. 43: 581-594, 1954.

46. Small, M. D., et al.: The effect of aminopterin on the absorption of xylose from the rat small intestine. Amer. J. Dig. Dis. 4: 700-705, 1959.

47. Trier, J. S.: Morphologic alterations induced by methotrexate in the mucosa of human proximal intestine. Gastroenterology 43: 407-424, 1962.

48. Heidelberger, C., et al.: Studies on fluorinated pyrimidines. II. Cancer Res. 18: 305-317, 1958.

49. Muggia, A. L., et al.: Response of the gastrointestinal tract of the mouse to 5-fluorouracil. Amer. J. Path. 42: 407-414, 1963.

50. Brennan, M. J.; Vaitkevicius, V. K., and Rebuck, J. W.: Megaloblastic anemia associated with inhibition of thymine synthesis. (Observations during 5-fluorouracil treatment.) Blood 16: 1535-1545, 1960.

51. Philips, F. S., et al.: The toxicity of actinomycin D. Ann. N.Y. Acad. Sci. 89: 348-370, 1960.

52. Yeh, S. D. J., and Shils, M. E.: Effect of actinomycin D and colchicine on intestinal absorption in rats. Fed. Proc. 25 (Abstracts): 322, 1966.