Enteral Nutrition by Tube

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Summary

When p.o. intake is unsatisfactory or contraindicated, maintenance of nutrition by tube feeding is an alternative to the i.v. route. A number of factors will enter into the decision as to which alternative is better. In general, it is desirable to utilize the alimentary tract if it is functioning adequately. The potential hazard of aspiration and problems in inserting the tube into the appropriate part of the tract may offset advantages of tube feeding. The composition of the formula to be administered will depend upon the functional state of the gastrointestinal tract and the metabolic needs of the patient. Defined-formula diets have become commercially available for p.o. and tube feeding. These are both a boon and a problem to patient, physician, and dietician. They simplify ordering, storage, preparation, and administration, but they have drawbacks related to their fixed composition. The large number of diverse formulations require expertise for their proper use.

Entry of food into the alimentary tract is a stimulus to maintenance of structure and function of that tract and to hyperplasia when resection of bowel has occurred. Special formulations and modifications in route and rate of feeding may be beneficial in meeting the needs of patients with pancreatic insufficiency, malabsorption of various etiology, fistulas, and organ failures that modify nutritional requirements. Consideration should be given to adjunctive chemotherapy during nutritional rehabilitation of patients with known or suspected tumor.

Introduction

While it is desirable to have patients voluntarily ingesting an adequate diet p.o., a significant number of cancer patients are not able to do so for a variety of reasons. In such circumstances, the two alternatives to p.o., tube and i.v. feeding, must be considered. Some of the factors that should enter into the final decision on the route to be used are listed in Table 1. Where the patient is well nourished and ingesting a significant proportion of his nutritional needs p.o., or where depressed appetite or alimentary tract difficulty is likely to be of a few days’ duration, then no serious effort to meet total body needs by tube or parenteral means is indicated. Alternatives must be considered, and appropriate action must be taken when a current situation causing depletion is likely to be extended without expectation of immediate significant improvement, or where plans for further treatment are likely to preclude adequate p.o. intake and absorption for a significant time. The decision as to which alternative is preferable will depend upon the variables in the list of factors. When either tube or i.v. routes are feasible, the factors of safety, potential complications, duration of treatment, and cost to the hospital and to the patient must be considered.

A list of contraindications, either partial or total, to p.o. intake is given in Table 2. These clinical conditions often occur in cancer patients. Complete bowel obstruction obviously leaves only 1 suitable alternative pending definitive treatment, namely, parenteral feeding. If the small intestine is patent, if there is no obstruction below it, and if no surgery is required to prepare an entry for a tube, then feeding into the alimentary tract is an attractive alternative if aspiration is not a significant potential danger. These many qualifications indicate that need for careful consideration of the factors listed in Table 1 in conjunction with experience and competence in the necessary techniques.

Other situations in which tube feeding should be considered as an alternative to p.o. feeding include: (a) severe and persistent anorexia requiring a form of force feeding; (b) the treatment of a fistula in the upper alimentary tract where the feeding is given through a tube bypassing the fistula; and (c) severe malabsorption requiring the administration of a formula that must be fed slowly and continuously to permit absorption or that is so unpalatable that the patient refuses to ingest adequate amounts on a prescribed schedule.

Entry Sites for Tubes and Precautions

Nasopharyngeal Tube. It is preferable to have the tip of the tube in the lower esophagus rather than in the stomach since the latter may be associated with increased reflux, especially when the patient is supine. In the great majority of patients, it is easily and safely placed and replaced. Where required for long periods, some patients can be taught to remove and reinsert the tubes after a feeding.

Many cancer patients have had prior experience with nasal tubes for feeding or aspiration following surgery and are often strongly opposed to further encounters with them when they remember their sore throats and difficulty in swallowing with the tube in place. We have found that silicone elastomer (Silastic) tubes are tolerated much better than the same caliber of polyethylene or rubber feeding tubes. Once induced to allow insertion of the Silastic tube,
the patient is often willing to keep it. However, small-caliber Silastic tubes are so flexible that they tend to be expelled upon regurgitation or coughing. This may be overcome by weighing them with a small mercury bag (4) or by inserting mercury into the lower segment and sealing it. Fine-caliber catheters of the type used for antecubital central venous cannulation can be used (37). The soft small-caliber Silastic tubes may be inserted more easily after chilling or with a stylet to impart some rigidity on alongside a larger firmer tube with the ends of both tubes fitted into the half of a gelatin capsule. With the latter technique, after the tubes are positioned, water is forced through the larger tube, dislodging the capsule, and that tube is withdrawn. Small-bore tubes require a finely dispersed formula to prevent plugging of the tube.

The potential for aspiration of formula must always be considered. This hazard is increased in debilitated patients having depressed cough reflexes, particularly when there is a preexisting pulmonary problem. It is our policy to restrict the use of nasopharyngeal feeding in such patients. To minimize aspiration, it is essential that strict procedures be adhered to by the staff. These include preliminary testing with water and then diluted formula at slow infusion rates and progressive increases while monitoring the ability of the patient to tolerate the formula and while keeping the patient in a semisitting or sitting position during the feeding and for a period afterwards. The potential for aspiration is decreased by slow-drop feeding from a bag or bottle. Feeding is not done when there is hiccupping, nor is it continued when the patient is sent off the floor for a test.

**Esophagostomy Tube.** A tube may be inserted into the pyriform sinus as recommended by Graham and Royster (23). Where there is no contraindication, it is an alternative route to nasopharyngeal or gastrostomy tubes for long-term feeding. It is simpler to perform than a gastrostomy and eliminates the psychological and social problems faced by a patient who has to walk around with a tube protruding from his nose. Presumably, the larger-caliber tubes have the same long-term potential disadvantages as do nasopharyngeal tubes of inducing esophagitis and stricture. It is possible that small-caliber tubes, especially those of Silastic, will reduce the esophagitis. Esophagostomy is an alternative to jejunostomy for unobstructed patients needing long-term tube feeding who have had a prior subtotal gastrectomy or esophagogastrectomy with the stomach up in the chest.

**Gastrostomy Tube.** When surgically feasible this is a highly desirable procedure for patients who are likely to need tube feedings for prolonged periods of time. When intestinal surgery is performed that is likely to result in significant malabsorption, construction of a feeding gastrostomy should be included at that time. The usual gastrostome closes spontaneously and fairly quickly where there is no longer need for it. Simple, adequate, and reinforced directions to nursing staff, patient, and family are necessary to prevent leakage and to ensure proper skin care at the entry site.

**Jejunostomy Tube.** Insertion of a feeding tube into the jejunum is indicated when there is obstruction at a higher level. The availability of soluble formulas that flow through fine-bore tubes has made feasible needle catheter jejunostomy (37).

Rapid entry into the jejunum of hyperosmolar solutions may lead to the "dumping syndrome." This potential problem can be prevented by infusing the formula initially at reduced concentration and rate and increasing them as tolerance is demonstrated. Use is recommended of liquid formulas of relatively low osmolality incorporating dextromaltose or glucose oligosaccharides (in preference to mono- or disaccharides) and some fat. Intrajejunal feeding presents the possibility of inadequate mixing of the formula with bile and pancreatic juice with resultant depressed digestion. While usually not a significant problem it can be overcome by various procedures such as the use of pancreatic extract; medium-chain triglyceride (which has less dependence on pancreatic lipase and bile salts for its digestion); and oligosaccharides, protein hydrolysate, or free amino acids which can be absorbed without pancreatic extract or bile.

**Formula Composition.** For patients without digestive or absorptive disorders, a wide variety of foods in blended form may be used in tube feeding for those patients in whom digestion and absorption are normal.

Knowledge of the widespread occurrence of lactase "deficiency" and lactose intolerance in various population groups and in those with bowel disease has resulted in marked modification of the usual hospital tube formula that was once based primarily on milk and milk products. Hospital tube formulas with lower milk concentrations have been developed that have the added advantage that various nutrients such as fat, sodium, and potassium can be easily modified (6, 40). Commercial formulas are available that are restricted in lactose content (40, 46). Formulas of a more "purified" composition and with very little or no residue are also available and can be used for routine tube feedings (40, 46, 56). Many of these formulas are cheaper than liquid formulas made with natural foods such as eggs and meat. When these formulas are nutritionally complete and ade-

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2 Mercury-weighted tubes of various calibers are available from Hedeco, 2411 Pulgas Avenue, Palo Alto, Calif. 94303.
quate for long-term feedings, there is no objection to their use. Some patients who are accustomed to regular bowel elimination are unhappy with low-residue formulas that cause them to be “constipated.” There is inadequate information on the frequency of fecal impaction with prolonged use of such low-residue formulas.

Physicians and dietitians should give consideration to the costs of tube feeding formulas for inpatients and for outpatients. For the latter, formulas made from regular family fare (with assistance from a dietitian to ensure overall nutritional adequacy) are appreciably cheaper than commercial formulas as are those for which supplies are purchased in bulk and mixed at home. For hospitalized patients without absorptive disorders, there is no need for expensive “chemically defined”-type diets.

**Defined-Formula Diets for Medical Purposes**

In recent years there has been an outpouring from the pharmaceutical industry of special liquid formulations. These have been designated as “chemically defined” diets or “elemental” diets. Because most of these formulations are neither chemically defined nor elemented in a chemical sense, I have recommended that a more general term “defined-formula diets” be used to designate such formulations (44). Their numbers and diversity in composition have created a field requiring special expertise on the part of the physician and dietitian who are faced with decisions on their use. Comparative analytical data on composition are now being published (40, 46, 56). These defined-formula diets claim to be complete in all essential nutrients. Some are composed of purified amino acids (both essential and nonessential) with only small amounts of fat as polyunsaturated fats and with carbohydrates as glucose oligosaccharides. Others have their amino acids predominantly in the form of hydrolyzed protein with amino acid supplements or as intact proteins in the form of isolates from natural foods. Fats are added as long-chain fats and in some preparations with medium-chain triglycerides. Carbohydrates vary in type and quantity. All have added minerals and vitamins.

Being nutritionally complete, defined-formula diets are both a boon and a problem to the physician and dietitian. They are easy to store, order, and administer. Serious problems, however, may arise due to the very fact that formula compositions are “fixed.” Patients having metabolic problems may be unable to tolerate the amounts of 1 or more nutrients in the formula given in the volumes necessary to meet overall nutritional requirements. Such a formulation may, in fact, be either potentially or actually hazardous for such patients because of the development of adverse effects. This is true, for example, of patients with renal disease who cannot tolerate the levels of protein, sodium, potassium, phosphate, or magnesium present in a given formulation, or patients on corticosteroids who are accumulating salt and water and cannot tolerate the amount of sodium present, or those with hypercalcemia who should not be ingesting the amount of calcium present. The physician must be aware of specific composition and possible contraindications. In these situations, the dietitian must modify the formula by either adding desired ingredients while diluting out those that are undesirable or, alternatively, prepare a completely different preparation from specific nutrients.

Individual ingredients are available and can be combined with the proper medical prescription and the services of a dietitian trained in this field (6, 46).

Manufacturers could overcome the limitation of fixed formulations by preparing formula diets in “modular” form with certain critical items such as fat or sodium and potassium salts being made available in separate containers to be added or modified in amounts as indicated by a patient’s need.

**Other Precautions in Feeding**

The total calories and nutritional composition of the formula supplied should be that needed by the individual at that particular time. There is a serious tendency on the part of many attendants, housestaff, and nurses to underfeed patients via a tube even though precise suggestion on the objectives have been made by the nutrition team. Continuing education and oversight are essential to ensure achievement of nutritional goals. When serious absorption problems exist, slow continuous feeding utilizing a pump is often essential. Inasmuch as large fluid, protein, carbohydrate, and other nutrient loads may be involved in the use of some defined-formula diets, patients should be followed initially as closely as those on i.v. feeding. Formulas should be instituted in decreased concentration at reduced volume per time period. Serial physical examinations, laboratory studies, urine fractions, and weighings should be standard practice with frequency dictated by the patient’s response. Hyperosmolar nonketotic coma can occur in diabetic patients on high-carbohydrate tube-fed formulas when adequate precautions are not taken. There may be exacerbation of metabolic problems related to protein intake in patients with renal and hepatic disorders. Serious losses of water and electrolytes may result with tube feedings in patients with serious malabsorption secondary to bowel fistulas or damaged or resected small intestine.

**Effects on Enteric Organisms**

The intriguing possibility of markedly reducing the concentration and types of microorganisms in the large bowel through the use of defined-formula diets was presented by the report of Winitz et al. (55) in studies on normal volunteers. Since enteric organisms can conceivably enter the blood stream through mucosa damaged by chemotherapeutic agents or radiation with increased infection in patients with depressed bone marrow, this report had important clinical implications. Unfortunately, subsequent reports have been unable to duplicate these results (3, 8, 9, 16, 17, 22). These investigators uniformly found that the concentration of bacteria in the feces was unaffected by the test diet; however, since the fecal volume was markedly decreased the total number of organisms delivered from the large bowel also declined during the feedings. Nevertheless, the numbers of organisms in the large bowel were still enormous. Individual investigators found changes in cer-
taining constituents of the flora, but this could happen with certain individuals and not in others on the same diet and in the same study. There is no specific information relating to possible beneficial effects of diet-induced reduction of total bacterial burden on enterically related infections in cancer patients. It may be that the combination of p.o. antibiotics designed to sterilize the gut in patients with bone marrow dysfunction as the result of disease or chemotherapy (7) may be augmented by feeding a defined-formula diet.

Preventing Intestinal Epithelial Damage

Bounous et al. (11) have reported that the feeding of a complete formula diet (containing casein hydrolysate and other nutrients), in comparison with a rat chow, reduced the intestinal mucosa damage when 5-FU* in a single dose of 150 to 200 mg was injected into male rats weighing 350 to 400 g. Substitution of whole casein for the hydrolysate was only slightly more protective than the chow diet. Hematological and weight changes were not significantly different in the various experimental groups. Patients with advanced metastatic carcinoma subsisting on either "normal hospital food ad libitum" or on a defined-formula diet with protein hydrolysate were given 5-FU at 12 mg/kg body weight i.v. for 6 to 9 consecutive days. Patients on the "elemental" diet ate more calories per kg and did not lose weight, whereas the control group had a modest weight loss. Epithelial cells obtained by rectal biopsy were better preserved in the group on the elemental diets. No small bowel biopsies were performed (10). A similar type of diet was reported to decrease the intestinal lesions produced by radiation of the mouse (25). In these studies the diet was taken p.o. by the animals and patients. Emphasis is given to the possibility that the beneficial effects are related to decreased pancreatic secretion.

A contrary position has been expressed by Stanford et al. (48) in a brief communication. Comparison was made of the incidence of mortality, diarrhea, serum albumin decline, and positive blood cultures in rats given 5-FU while being fed a chow diet or 1 of 4 defined-formula diets. The latter included types with intact protein, hydrolyzed protein, or free amino acids; composition varied also with respect to other nutrients. The 100 day-old male rats were given 5-FU, 25 mg/kg s.c. for 6 consecutive days and were then sacrificed. Mortality and diarrhea were higher in rats on the formula diets than those on chow diet; positive blood cultures were more frequent in those on diets containing hydrolyzed protein or free amino acids, and serum albumin fell significantly more in the rats receiving the amino acid-containing diets. The authors concluded that "elemental diets enhanced the toxicity of 5-FU in the Sprague-Dawley rat" and correlated this with "the degree of protein hydrolysis of the particular elemental diet." In this brief report no attempt was made to correlate these effects with other differences in formulation composition.

It will be of interest to ascertain whether differences in the route of delivery (enteral versus parenteral) of the test formula affects drug toxicity. This question is pertinent since enteral feeding stimulates the secretion of pancreatic and other alimentary secretions.

Pancreatic Secretion and Defined-Formula Diets

Some of the best experimental work on defined-formula diets concerns their effects on pancreatic secretion and possible usefulness in the treatment of pancreatitis or pancreatic fistula. The data are applicable to cancer patients with pancreatic fistulas and to those with massive bowel resection and large intestinal fluid losses where an attempt is made to minimize fluid losses. The studies of interest relative to pancreatic secretions are of 4 types: (a) comparison of the effects of regular food versus defined formulas fed by mouth in dogs. In these the elemental diets appear to cause appreciably less volume of secretion without a change in enzyme concentration with a diet containing hydrolysate (34), or a delayed decrease in enzyme output requiring more than 2 weeks on Vivonex to manifest itself (36). In this connection Rivivils et al. (41) showed that diet with casein hydrolysate caused a markedly decreased gastric acid secretion when compared to regular dog food; (b) comparison of defined-formula diet fed p.o. or intraduodenally. Administration of Vivonex intraduodenally prevented the response of water and bicarbonate secretion observed with its p.o. administration and decreased but did not prevent the protein response (30). Hyperalimentation i.v. induced minor increases in pancreatic secretions when compared with the defined diet; (c) intragastric versus jejunal loop administration. Vivonex instilled intragastrically into dogs markedly stimulated pancreatic secretion, whereas the formula infused into a Thiry-Vella jejunal loop did not stimulate secretion significantly (39); (d) intrajejunal effects of regular and formula diets. The pancreatic secretory response to a diet with hydrolyzed protein was compared to that of "blenderized ward diet"instilled into the proximal jejunum in dogs who had a stable 50% maximum pancreatic secretory response to secretin and pancreozymin (13). Both diets increased the volume and bicarbonate secretion, but there was a marked reduction in the protein (enzyme) concentration of the pancreatic juice with the "elemental" diet. The composition of the diets differed in terms of major nutrients as well as in the amino acid sources.

Diversion of pancreatic secretions has been reported to decrease the susceptibility of the intestinal mucosa to radiation damage (35). If these findings are applicable to man the use of intrajejunally fed defined diets may be useful if they do decrease significantly the pancreatic enzyme secretion while maintaining adequate nutrition during treatment with abdominal radiation.

Fistulas of the Alimentary Tract

Intrajejuninal administration of a defined-formula diet was recommended for the treatment of duodenal fistulas in 1956 by Smith and Lee (47). With the advent of commercially available formulas, there have been additional reports of their use to achieve spontaneous fistula closure. In the treatment of high bowel fistulas, such as those in the esophagus, duodenum, or upper jejunum, bypass of the fistula

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* The abbreviation used is: 5-FU, 5-fluorouracil.
with a tube is feasible with the feedings entering distally. All of Smith and Lee's 11 duodenal fistulas closed; 64.8% of 37 varied gastrointestinal-cutaneous fistulas of Rocchio et al. (42) and 75% of those of Voitk et al. (53) closed spontaneously using tube feedings. Eleven of the 37 patients of Rocchio et al. (42) had fistulas associated with cancer; 6 had spontaneous closure, 1 had an operative closure, and 4 died; no data are given on the site of the fistula in the cancer patients and on whether there had been radiation to the abdomen.

In the studies of Rocchio et al. (42) and of Kaminsky and Deitel (29), i.v. feeding often preceded the use of the tube feedings. Feeding by the i.v. method is also a useful adjunct while tolerance of the tube and the volume of fistula drainage is evaluated as the formula is progressively increased to optimum amounts. When fluid and electrolyte losses are not serious, skin excoriation and pain are minimal, and the tube is well tolerated, formula feedings may be continued without i.v. support. Otherwise parenteral feeding is indicated as the alternative.

Treatment of Malabsorption Syndromes

The requirement for and successful use of these formulations will depend upon the degree of malabsorption. At one end of the spectrum are adult patients who have such severe malabsorption (defined as a 5-hr xylose excretion in the adult of less than 0.8 g following a 25-g p.o. dose) that they cannot be successfully maintained even on an optimum amount of total parenteral nutrition or other supplementary fluids. At the other end of the spectrum are those with moderate malabsorption who do not require the highly purified formulations and who can be successfully maintained on total iv. feeding until, hopefully, significant compensatory bowel hyperplasia occurs to permit maintenance on tube and/or p.o. feedings. At the other end of the spectrum are those with moderate malabsorption who do not require the highly purified formulations and who can be successfully carried out by tube. The intermediate group can often be carried successfully with defined-formula diets of proper composition and rate of feeding. Tube feedings can be administered successfully in very young infants with malabsorption (15) as well as in children and adults.

The most difficult types of patients to maintain in good nutritional condition are those who have had severe radiation damage of the intestine combined with significant bowel resection. These patients often have significant malabsorption, since a significant portion of their remaining bowel is damaged by radiation and they tend to have intermittent obstruction with fistulization and the need for further surgery. Careful attention to their nutritional needs using i.v. and tube feeding can have very beneficial results as exemplified in the following case history.

Case History (E. C. No. 29-99-97)

This 37-year-old woman with Stage III B carcinoma of the cervix was treated with 4000 rads of external radiation and 2 treatments with intracavitary radium in late 1974. Following the radiation she lost appreciable amounts of weight and had increasing weakness. A ureterovaginal fistula associated with bilateral hydronephrosis developed, necessitating total pelvic exenteration, sigmoid colostomy, and the formation of an ileal-loop bladder which were performed on December 20, 1974 (Figure 1). Following discharge the patient continued to deteriorate nutritionally. In late January she developed increasing diarrhea, spontaneous drainage of a pelvic abscess, and an ileal-vaginal fistula. She was admitted with dehydration, marked respiratory alkalosis, and hypomagnesemia and improved markedly on total parenteral nutrition. On March 18, 1975, resection of the distal ileum with an ileal transverse colostomy were performed (S1). There was no evidence of recurrent cancer. Following discharge, she had persistent nausea and vomiting, diarrhea, intermittent epigastric pain, poor p.o. intake, and further weight loss. There were successive emergency admissions with severe dehydration, metabolic acidosis, and psychotic behavior responding to treatment. The large draining pelvic cavity persisted with an opening through the anterior abdominal wall. A xylose test on June 25, 1975, showed marked malabsorption with xylose excretion of 1.4 g in 5 hr (normal, more than 4.2 g). The patient was deemed not to be a candidate for home total parenteral nutrition because of personality problems and an inadequate home environment. A feeding gastrostomy was recommended, and this was performed on July 7, 1975 (S2). The patient was discharged by the surgical service, continued to lose weight, and was readmitted on August 11, 1975, with the same symptomatology previously noted. After an excellent response to total parenteral nutrition, a systematic study was made of a series of defined-formula diets prepared by research dietitians, who based the diets on casein hydrolysate and varying in carbohydrate and electrolyte composition and osmolality. Initially, the formula resulted in colostomy outputs varying between 4500 and 5600 ml despite very slow infusion over 18 hr. During this time she required total parenteral nutrition or other supplementary fluids. Losses of electrolytes in the colostomy drainage were high, e.g., magnesium losses of 28 to 35 mEq/day. With formula modification the output decreased, and by October 1, 1975, she was able to tolerate 3 liters of a formula infused through her gastrostomy over 16 hr/day without supplementary i.v.
fluids and electrolytes and no p.o. intake other than clear fluids. She maintained her weight in the hospital and was discharged home on the same regimen with progressive improvement at home until she achieved her ideal weight. Clinically, she has done extremely well with cessation of pelvic drainage, near closure of the abdominal opening, and no further gastrointestinal, electrolyte, acid/base, or psychiatric problems. She is active, cares for her family, and takes more food p.o.

Her improvement is attributable to slow infusion of the special formula diet, since the results of another xylose test on January 12, 1976, were essentially the same as those 6 months earlier.

The Route of Feeding and the Intestinal Epithelium

Short-term fasting leads to decreased weight, DNA, protein, glycolytic, and disaccharidase concentrations of the small bowel (45). Entry of food into the alimentary tract increases such parameters in the epithelium of intact (27) and postresection residual bowel (20) when compared with feeding solely i.v. Certain gastrointestinal hormones have trophic effects on individual organs of the alimentary tract, e.g., gastrin on gastric, duodenal, and intestinal epithelium and on pancreas (26); cholecystokinin on pancreas (26) and insulin on liver (49). Pancreatic and biliary secretions also appear to have a stimulatory effect (2). An important factor in maintaining organ mass and composition is the passage of food through the alimentary tract with its stimulus to endocrine and paracrine secretions and/or neural mechanisms and consequent trophic effects. Dworkin et al. (18) have presented further evidence indicating that intraluminal nutrition augments small intestinal mass both by direct contact with epithelial cells and by indirect effects of hormonal or neurovascular stimuli. Intragastric infusion into rats of a complete formula with free amino acids had a significantly greater effect than i.v. infusion of the same solution in terms of gut and mucosal weight, DNA and protein content, and sucrase activity. While these differences between the different routes of feeding were greater in bowel in continuity, there were consistent and significant differences in bypassed segments of small bowel that were not exposed to food. When rats are fed a carbohydrate-free diet for 3 days, the normal proximal-distal small bowel gradient of the specific activities of 3 glycolytic enzymes disappears. When glucose is infused directly into the ileum, the normal gradient of these enzymes is restored, suggesting a humoral and/or neural mechanism rather than a direct local luminal effect of the sugar itself (19).

Treatment of Organ Failure

Because of depressed appetite and frequent nausea and lethargy seen in patients with serious renal dysfunction, p.o. intake of diets with restricted protein and electrolytes is often poor. Administration of formulas by tube may therefore be highly desirable. While special diets with essential amino acids including histidine (Amin-Aids; McGaw) are now available for those with advanced renal failure, diets containing restricted amounts of intact protein diets may do just as well (31). Formulas for tube feeding of nitrogen-free analogs of essential amino acids may prove useful in such patients in light of the studies of Walser (54).

Special formulations for tube feeding will be devised for patients with present or impending hepatic encephalopathy. Cancer patients in this category would include those who have had liver transplants, lobectomy, hepatic artery ligation with chemotherapy, and those in liver failure in whom various chemotherapeutic agents are being tested. Such formulations will presumably follow 1 of 2 leads. One lead is that of Fischer et al. (21) of a formulation developed for i.v. use. This contains decreased amounts of aromatic amino acid and increased levels of branched-chain amino acids as compared to usual amino acid solutions. Such liquid tube formulas would be useful in those patients whose neurological, anorectic, or other clinical status would preclude adequate p.o. intakes but who would not require parenteral nutrition. The other lead is that of Maddrey et al. (33) who noted improvement in patients with portal-systemic encephalopathy who were given keto analogs of essential amino acids.

Altered Nutrient Formulations as Potential Adjunctive Cancer Therapy

There is a long series of studies in experimental animals indicating that various dietary deficiencies inhibit tumor growth (43). The only effective current clinical application of such studies has been with antifolates such as methotrexate. In many of the studies with diet restriction the inhibition of tumor growth is associated with significant loss of host weight. However, there are tantalizing exceptions. Theuer (51) reported that restriction of tryptophan, threonine, leucine, or methionine inhibited both the transplanted tumor and mouse growth, whereas decreased phenylalanine, valine, or leucine inhibited tumor growth without affecting the host weight. Additional support for this approach is the report of Jose and Good (28) in which similar types of amino acid deficiencies apparently altered the formation of blocking antibodies without inhibiting cell-mediated immunity. Use of amino acid-deficient diets have been tested on a small scale in cancer patients without striking success (43). Broader and more aggressive studies are indicated using diets deficient in amino acids in combination with chemotherapy or immunotherapy both in experimental animals and in patients with advanced cancer. Such deficient diets can be given either i.v. or as special formulas, preferably fed by tube to avoid problems in palatability and to offset the anorexia that often occurs rapidly with deficient diets. It will be of great interest to ascertain whether differences in tumor response are related to the route of delivery of the test formula (enteral versus i.v.). This question is raised since the protein and amino acid content of intestinal secretions may, initially at least, modify the deficiencies of the test formula. Presumably, such diets will be most effective when cellular uptake is stimulated by an adequate caloric intake.

Forced Feeding and Tumor Growth

With certain transplanted tumors in rats, improved nutri-
tion in the form of forced feeding or increased protein favored the host in terms of weight and nitrogen content although the experimental tumor also grew larger (1, 5). However, when the tumors reached a certain size, forced feeding was unable to prevent loss of normal host tissue and death. In human studies Pareira et al. (38) stressed the possibility of temporarily reversing the cancer cachexia of terminal patients by tube feeding. Terepka and Waterhouse (52) also observed gains in body weight and positive nitrogen balance during forced feeding of patients with active widespread cancers; however, they found that the increases were often associated with accumulation of fluid and that weight loss was rapid upon discontinuation of forced feeding. There was a suggestion that some of the patients appeared to have acceleration of cancer during and after the feeding program. Recent studies with rats bearing transplanted tumors and fed i.v. have a bearing on this matter, although the infusions lasted only 10 to 14 days. Hepatomas were larger in the rats fed i.v. than in the control rats fed p.o. ad libitum (12). Mammary-tumor-bearing rats receiving total parenteral nutrition grew, whereas those receiving either 5% glucose or 5% amino acids lost weight. Despite weight loss, those receiving amino acids had tumor size not significantly different from those on total parenteral nutrition (50).

Our experience, which I believe is shared by others in this field, shows quite definitely that the great majority of patients with active cancers can be rehabilitated nutritionally with i.v. or tube feedings. It is a rare patient who has obvious and rapid growth of tumor during repletion. However, this does not mean that the tumor is not growing faster in conjunction with improved nutrition. On the basis of animal studies, one would presume that this is happening. Physicians are much more aggressive than ever before in the treatment of cancer, and there is a good rationale for improving or maintaining good nutritional status in patients undergoing various modalities of antitumor therapy. There are a number of cancer patients in whom there are periods of aggressive nutritional therapy without antitumor therapy, e.g., patients who are malnourished, have bowel obstruction or a fistula with or without recent surgery, are being supported nutritionally in the hope of spontaneous improvement, and are known or suspected to have residual tumor. Some form of nutritional therapy may continue for weeks or months. It seems to me that more thought should be given to utilizing chemotherapy in such patients if we suppose that the tumor is growing during host rehabilitation.

Ensuring Safety of Defined-Formula Diets

The development of the diverse and relatively complex formulations is a tribute to the state of our present nutritional knowledge and food technology. As physicians we must not unquestioningly accept the premise that all formulations are nutritionally and toxicologically safe under all circumstances, despite the imposing ingredient data on the labels. This questioning attitude is particularly appropriate in the case of the newborn and other rapidly growing children, but it also pertains to adults, particularly when a formulation is the sole source of nutrition for months or longer. The potential danger, if any exists, is lessened by the fact that in current clinical practice the duration of use is relatively short for most individuals, and the formula is supplemented often by other foods.

The need for careful animal testing of proposed new formulations and for surveillance in human use is underscored by an example from the work of Levenson (32). In the development of liquid diets for studies with experimental animals (the prototype for later “chemically defined diets” for human use), Greenstein et al. (24) included ethyl esters of cysteine and tyrosine because the free amino acids were relatively insoluble. Levenson found that the presence of cysteine ethyl or methyl ester (as well as cystine ethyl or diethyl ester) in liquid formulas fed to rats resulted in a number of adverse reactions. The ester reacted with menadione (but not with vitamin K₃) to produce an inactive compound with resultant vitamin K deficiency. Cysteine ethyl ester under certain circumstances also induced a syndrome of hemolytic anemia (secondary to changes in the RBC), azotemia, rise in serum alanine, and atrophy and necrosis of pancreatic acinar cells. The syndrome did not occur when the diet was fed in solid form, a finding that emphasizes the factor of increased chemical reactivity of components in solution. It did not occur when certain purified proteins or casein hydrolysate were added to the diet; there was, however, no protection on supplementation with a mixture of free amino acid duplicating the composition of casein. Germ-free animals did not develop the syndrome in contrast to conventional or “contaminated” previously germ-free rats.

Similar esters of these amino acids were not and are not used in diets for human use, and similar adverse effects have not been reported in man.

The responsibility for regulatory supervision of defined-formula diets for medical use is vested in the Bureau of Foods of the Food and Drug Administration. From the regulatory standpoint this is still a developing area. The Bureau’s position is to ensure the safety of such formulations without unduly curtailing their development and availability (14). It is essential that physicians and dietitians maintain an active interest to help assure that high standards of safety are maintained with respect to composition and use of such formulations. This can be done by close supervision of their clinical use, the conduct of objective comparative studies, and the reporting of untoward reactions or deficiencies.

References

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