Effects on Nutrition of Surgery of the Liver, Pancreas, and Genitourinary Tract

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Summary

Carcinoma of the pancreas is increasing in the United States and has a grave prognosis. Surgical treatment has moved from subtotal pancreatectomy to total pancreatectomy and now to en bloc resection and vascular replacement. Pancreatic exocrine and endocrine insufficiency following resection add to the nutritional problems presented by this major surgery and its high complication rate. Recognition of these problems and adequate treatment decrease morbidity and mortality. Major hepatic resection imposes metabolic problems in the immediate postoperative period that are minimized by improving preoperative nutritional status and by providing adequate postoperative support with albumin and carbohydrate. Urinary tract diversion for pelvic cancer involving the ureters and/or bladder has progressed from ureterosigmoidostomy with its high incidence of disturbances of electrolyte and acid-base balance to ureterileostomy with its appreciably lower rate of complications.

Carcinoma of the Pancreas

Carcinoma of the pancreas is increasing and now ranks 4th as the most common cause of death by cancer in males, exceeded only by lung, large bowel, and prostate cancer. The American Cancer Society estimated that in 1976 cancer of the pancreas would cause 20,000 deaths in the United States with an estimated 23,000 new cases that would be diagnosed (1). The incidence of carcinoma of the head of the pancreas exceeded only by lung, large bowel, and prostate cancer. Weight loss in patients with ductal carcinoma of the pancreas commonly occurred in 39%, anorexia and asthenia in 15 and 14%, respectively, and steatorrhea in 9% (5). Resectability in the latter group is only 19%, and 5-year survival after total pancreatectomy is very low (5, 56).

Pancreatoduodenectomy

This operative procedure was described by Whipple et al. (66) in 1935 for the surgical treatment of carcinoma of the ampulla of Vater. During the early years of its application, operative mortality was extremely high (10) but has appreciably decreased with experience and improved support techniques and antibiotics. Other carcinomas of the peripancreatic region that are amenable to treatment by this operation include those of the distal common bile duct and duodenum. Some surgeons utilize it for carcinoma of the head of the pancreas. In the usual operative procedure the distal portion of the stomach is removed; the pancreas is transected (usually at its neck but varying amounts may be removed or even the entire organ), and the duodenum and a few inches of jejunum distal to the ligament of Treitz are resected. The entire specimen is removed by division of the common bile duct. A cholecystectomy is usually performed, and some surgeons perform a vagotomy. Various methods of reconstruction are possible. The extent of resection is indicated in Chart 1A; 1 type of reconstitution (retrocolic method) is shown in Chart 1B.

Three options are available to the surgeon in dealing with the pancreatic stump: (a) inversion of the transected end of the pancreas into the jejunal lumen; (b) suturing the cut end of the duct of Wirsung to the jejunal mucosa; and (c) ligation of the pancreatic duct with oversewing of the transected pancreas (Chart 2). There appear to be major differences of opinion among surgeons on the value of perform-
Table 1

Frequency of Periampullary Cancers

<table>
<thead>
<tr>
<th>Site</th>
<th>Ref. 35</th>
<th>Ref. 37</th>
<th>Ref. 47</th>
<th>Ref. 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>83</td>
<td>50</td>
<td>50</td>
<td>38</td>
</tr>
<tr>
<td>Ampulla</td>
<td>10</td>
<td>27</td>
<td>32</td>
<td>37</td>
</tr>
<tr>
<td>Duodenum</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Bile duct</td>
<td>3</td>
<td>16</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

No. of patients: 159, 44, 239, 253

Pancreatic Insufficiency

The problem of exocrine enzyme insufficiency following pancreateoduodenectomy has been examined. Wollaeger et al. (69) studied 10 patients who had a number of variants in their surgical reanastomosis. In 8 patients with pancreatic duct reanastomosis observed 3 weeks to 1 year after surgery, fat and nitrogen losses varied from normal to high. Fish et al. (20) studied the absorption of 6 patients surviving 20 to 84 months postpancreateoduodenectomy in whom the pancreatic stump was invaginated into the end of the jejunum. When no pancreatic extract was ingested, 3 patients had marked fat malabsorption (17 to 30%); this improved completely in 2 patients with pancreatic extract and partially in 1. Fecal nitrogen was increased in 3 patients and im-

Table 2

Postoperative complications of pancreateoduodenectomy for malignant disease

<table>
<thead>
<tr>
<th>Complications</th>
<th>Ref. 47</th>
<th>Ref. 31</th>
<th>Ref. 56 (a)</th>
<th>Ref. 56 (b)</th>
<th>Ref. 28 (c)</th>
<th>Ref. 28 (d)</th>
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</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>8</td>
<td>23</td>
<td>28</td>
<td>15</td>
<td>9</td>
<td>9</td>
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<tr>
<td>Pancreatic fistula</td>
<td>9</td>
<td>14</td>
<td>12</td>
<td>22</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Biliary fistula</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritonitis and/or abscess</td>
<td>5</td>
<td>19</td>
<td>11</td>
<td>13</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>9</td>
<td>14</td>
<td>33</td>
<td>11</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Ileus or obstruction</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>7</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Intestinal fistula</td>
<td>0.4</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>239</td>
<td>68</td>
<td>36</td>
<td>27</td>
<td>45</td>
<td>34</td>
</tr>
<tr>
<td>No. of patients with total pancreatectomy</td>
<td>12</td>
<td>2</td>
<td>36</td>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(a\) From 1942 to 1968.
\(b\) From 1969 to 1972.
\(c\) Pancreatic duct ligated.
\(d\) Pancreatic duct anastomosed.
proved with enzyme therapy. Two of 4 patients with periampullary carcinoma had marked steatorrhea following pancreatoduodenectomy, with the pancreatic remnant anastomosed to the stomach (12). Even for those undergoing resection for cancer of the ampulla, pancreatic exocrine insufficiency occurred in 27.7% (47). Following implantation of a portion of distal pancreas into the duodenum of dogs, the pancreatic remnant at sacrifice was found to be atrophied with dilation of the pancreatic duct and obstruction of the orifice in the duodenum (20). Others have also found atrophy and fibrosis of exocrine tissue after autotransplantation of the canine pancreas to the neck with an external fistula (16). Warren2 has emphasized that anastomosis of the duct to jejunal mucosa had a much greater likelihood of maintaining a patent duct. Nevertheless, with this technique he has reported that 22% of his patients developed evidence of pancreatic exocrine insufficiency (65). Aston and Longmire (3) found that 7 of 28 patients had pancreatic insufficiency and 2 of these had had duct to mucosa anastomosis.

The probability of pancreatic enzyme deficiency should be considered and checked in any patient with pancreatoduodenectomy even with ductal reanastomosis. Pancreatic exocrine insufficiency leads to the loss of calories in the stool and to a deficiency of absorption of important nutrients such as amino acids, calcium, magnesium, and fat-soluble vitamins. Effective replacement necessitates the choice of an effective pancreatic extract and its use in adequate amounts. Although there are a number of products marketed for use as enzyme replacement therapy, there is relatively little quantitative information on their actual enzyme activities and comparisons of clinical effectiveness. There have been a number of clinical reports of increased fat absorption with commercial pancreatic extracts in patients following pancreactectomy (38, 53). Commercial extracts showed considerable differences in lipase activity when tested in vitro, with best results being obtained with Cotazym, Lipan, Panetric granules, and Viokase. It has been estimated that complete replacement of the pancreatic lipase secreted in 1 day by a normal man would require approximately 34 g of a high-potency preparation (27). Giulian et al. (26) and Pairent et al. (53) have tested various commercial pancreatic supplements for their effectiveness in improving fat absorption in dogs with the pancreatic duct ligated. Again, there was a considerable difference in effectiveness among such preparations with variations also depending on the method of measuring fat absorption. When fat absorption from regular test meals was measured, Progestive, Convertin, Viokase, Cotazym, and Panetric were among the better preparations. However, in the doses administered (6 tablets or capsules per day), none were capable of returning fat absorption to normal (53).

We have found some patients to be intolerant of certain preparations and tolerant of others. In a few instances it has been necessary to use enteric coated preparations to avoid nausea and abdominal distress.

The amounts of pancreatic extract recommended for treatment of such patients has varied from a minimum of 1.2 g² up to 2.5 to 5.0 g (20, 38) per meal. Others have recommended administration of 8 g divided into 12 hourly doses (36). Others have found no benefit of hourly dosage when the amounts given with meals were adequate (38). It has been suggested that, if a fully satisfactory result is not achieved with Viokase or Cotazym in doses of 2 to 3 g with each meal, the same daily dose should be given on an hourly basis. Where gastric secretion is normal, concomitant administration of sodium bicarbonate may improve digestion. Since the surgical procedures for pancreatic carcinoma usually involve major gastric resection, bicarbonate administration does not appear indicated.

Diabetes

Another aspect of this procedure concerns the endocrine function of the remnant of pancreas. Decreased glucose tolerance has been noted in 10 pancreatoduodenectomized patients (5 to 39 months, post operative) in whom fasting blood sugar levels were within normal limits (12, 20). Miyata et al. (45) have investigated this matter in more detail in pancreatoduodenectomized patients in whom at least the caudal half of the pancreas was preserved; the control group was composed of 12 gastrectomized patients with a Billroth II anastomosis. Fasting levels of glucose, nonesterified fatty acids, and immunoreactive insulin were within normal limits; however, following glucose ingestion the blood sugar levels were appreciably higher than those of gastrectomized and normal individuals. The immunoreactive insulin levels in the pancreatoduodenectomized patients were appreciably less than those of gastrectomized patients and only slightly higher than those of normal individuals at 30 and 60 min. Hence, insufficient insulin response from the remnant of the pancreas appears to be a major cause of glucose intolerance in these cancer patients. This problem is complicated by the fact that approximately 10 to 12% of patients presenting with carcinoma of the pancreas are overtly diabetic (5, 28, 31) and 10 to 35% (depending on the site of the tumor) have asymptomatic glycosuria or hyperglycemia (65).

The effect of pancreatic duct ligation in dogs on endocrine function was studied for approximately 7 months. One of the 16 dogs became continuously diabetic, although the others maintained normal blood sugars; but 9 had latent diabetes with intermittent hyperglycemic levels and abnormal glucose tolerance curves (34). Four of 5 dogs with ligation with subsequent acinar tissue atrophy were found by Pairent et al. (53) to have diabetic glucose tolerance curves. Others have found the ligated pancreas in dogs to retain adequate endocrine function for prolonged periods (40). canine pancreas autotransplanted to the neck and with free flow of secretion became atrophic and fibrotic (16).

The question has been raised as to the role of preexisting pancreatic pathology in the remnant of pancreas in contributing to pancreatic insufficiency (exocrine and endocrine) following pancreatoduodenectomy in patients with carcinoma or pancreatitis. This has been studied in patients in whom such surgery had been performed following acute trauma and in whom residual pancreas was normal. Eighteen to 24 months after the pancreatic remnant was sutured to the intestine, there was only mild elevation of fecal fat above normal, and jejunal lipase concentration following a
test meal was normal; there was no clinical diabetes or need for insulin (57). In the 1 patient tested, serum insulin with and without glucose load was within normal limits. It was suggested that pancreatic insufficiency in patients with carcinoma or pancreatitis following partial resection is related to pathology in the remnant.

**Total Pancreatectomy and Regional Pancreatectomy**

The low 5-year survival rate of patients with carcinoma of the head of the pancreas (approximately 15%) has resulted in increasing advocacy of total pancreatectomy. This has been recommended because it eliminates the danger of pancreatic fistula without significantly increasing the surgical risk and because it eliminates the possibility of failure to remove carcinoma existing more distally either because of spread or multifocal tumor (5, 9, 15, 56).

Total pancreatectomy poses a difficult metabolic situation with its resultant exocrine and endocrine insufficiency. Even with the optimum use of pancreatic extract, there tends to be increased loss of fat and nitrogen in stool. The usual diabetic-type diet with its increased protein and fat tends to exacerbate malabsorption and diarrhea. Replacing dietary fat with glucose to decrease steatorrhea increases the requirement for insulin. In a series of 48 totally pancreatectomized patients followed with respect to their control of diabetes, Pliam et al. (54) found that 50% were easily managed, 8% were managed with difficulty only when there was concomitant illness, 18% had occasional hypoglycemic reactions managed with carbohydrate p.o., 4% did poorly with persistent glycosuria, and 20% were found to be very difficult with ketoacidosis or hyperglycemic episodes requiring hospitalization.

Following pancreatectomy in dogs, plasma glucagon is present and may increase when insulin is not given (42). Following total pancreatectomy in a man, plasma (pancreatic) glucagon disappeared within 30 min after resection but was present again after 18 hr and disappeared after 9 days. After an initial decrease, plasma glucagon-like immunoreactive substance(s) (measured by an antiserum that cross-reacts with glucagon-like products from small bowel mucosa) rose abruptly on the 2nd postoperative day and remained elevated thereafter (46).

Because pancreatic tumors often extend beyond the pancreas at the time of exploration, resectability rate is low and survival is much lower despite total pancreatectomy. This is emphasized in the recent review of 101 cases of ducal carcinoma of the pancreas by Brooks and Culebras (5) who reported that 21.8% were deemed inoperable because of metastases or poor condition of the patient, 24.8% had only a biopsy of the tumor at laparotomy, and 34.6% had some sort of palliative bypass, leaving only 18.8% who had surgery performed with intention of cure. Survival of the latter group was poor. More radical surgery termed regional pancreatectomy has been developed by Fortner (21) in an effort to remove en bloc the pancreas, adjacent tissue, and nodes along the primary lymph drainage. In the type 1 procedure there is total removal of the pancreas, pancreatic segment of portal vein, transverse mesocolon with middle colic vessels, surrounding soft tissues, regional lymph nodes, distal stomach, duodenum, spleen, gallbladder, and common bile duct with skeletonizing of portal vein and hepatic artery. In type 2 there is the additional resection of the celiac axis and hepatic and/or superior mesenteric arteries. In individual patients gastrectomy may be total or subtotal, and varying amounts of colon and jejunum are removed as indicated (23, 24). Of 18 patients undergoing 1 of the procedures, 16 had been explored and deemed unresectable elsewhere. There were 3 postoperative deaths; 6 patients were alive at 1 year (24).

In this complex and radical surgery a number of postoperative complications with nutritional significance have occurred. There were 6 patients with either gastrojejunal or colonic fistulas; 8 patients had significant infections, and many had prolonged postoperative recovery. Adequate nutritional support has played a major role in permitting recovery of many of these individuals. Because of infection, fistulas, anorexia, diarrhea, and malabsorption, usually in combination, prolonged total parenteral nutrition was used in maintaining a number of these patients and proved to be lifesaving. Because Intralipid has not been readily available, we have relied upon high-glucose infusions as the major source of calories, with insulin added to the total parenteral nutrition solutions initially at 1 unit of regular insulin for every 100 carbohydrate calories. Fractional coverage with regular insulin is given for glycosuria. The i.v. insulin is then adjusted upward or downward as indicated.

A xylose tolerance test has been performed preoperatively and postoperatively in a number of patients, in some cases with serial follow-up. Almost all of these patients have had depressed xylose absorption postoperatively; absorption returned to normal after a period of 4 to 9 months. Weight loss associated with depressed appetite and malabsorption has been significant; surviving patients are approximately 30% below their preoperative weight. Watery diarrhea has been frequent and has been associated with magnesium depletion and acidosis in some patients. The reason for this diarrhea and malabsorption of xylose is not clear but may be related variably to a number of factors including gastrectomy and duodenectomy, derenervation and severance of lymphatics, small bowel resection in some instances, and bacterial overgrowth of small bowel. Five of 6 bowel fistulas closed spontaneously with total parenteral nutrition. Home total parenteral nutrition (58) permitted survival in 1 patient during a prolonged critical period of malabsorption. With cessation of parenteral support, anorexia, diabetes mellitus, pancreatic insufficiency, and other types of malabsorption continue to present serious nutritional problems to the radically pancreatectomized patient. There must be administration of adequate amounts of pancreatic extracts with all meals and snacks. Good control of the diabetes maximizes carbohydrate utilization and minimizes fluid and sodium losses secondary to osmotic diuresis caused by glycosuria. Medium-chain triglycerides are neutral fats the fatty acids of which are primarily of the C16 and C18 type; these are more efficiently absorbed in the absence of pancreatic enzymes than are the usual long-chain fats. They are also absorbed more efficiently when there is an insufficiency of conjugated bile salts or when there are impaired absorptive mechanisms (32). Glucose oligosaccharides may also be helpful in increasing the caloric intake.
and absorption in pancreateically insufficient patients, since these relatively short-chain glucose polymers can be hydrolyzed to glucose by the brush-border enzyme sucrase-\(\alpha\)-dextrinase (30). This white powdery material is not sweet and may be used in a variety of ways to supplement intake.

There may be reduction in vitamin B\(_{12}\) absorption in approximately 40 to 50% of patients with chronic pancreatic insufficiency (64). Malabsorption of this vitamin has been observed in patients with total pancreatectomy (48). In these subjects the B\(_{12}\) absorption is improved by administration of pancreatic extract.

Liver Resection

Until the early 1950's removal of liver tissue was usually limited to wedge or guillotine type of resection with relatively minor losses in terms of function. With a description of a controlled technique for resection of the right lobe of the liver (39), major hepatic resection became frequent. It is not surprising that some of the earliest efforts thereafter involved resection of cancer (49–52). Advances in anesthesia and operative techniques, blood replacement, antibiotics, and understanding of metabolic derangements caused by massive liver resection have appreciably decreased morbidity and mortality. The surgeon is now greatly aided by preoperative information for more precise localization of the tumor provided by computerized transaxial tomography and selective hepatic arteriography. Arteriography also provides valuable information on the pattern of hepatic artery branches to aid in their dissection.

Major resection for cancers has been performed for the most part in 5 situations: primary malignant liver tumors in adults; primary malignant liver tumors in infants and children; cancer metastatic to liver from other sites; to permit en bloc excision of cancer of adjacent organs in stomach and colon; and to palliate the malignant carcinoid syndrome. Up to 90% of the liver may be resected with survival of the patient. Total hepatectomy and orthotopic liver transplantation is possible in those patients who have extensive primary cancer of the liver, gallbladder, and bile ducts or metastatic colon cancer confined to the liver. In addition, resections are done for nonmalignant tumors such as benign hepatomas, cholangiomas, hamartomas, angiomas, teratomas, and cysts.

The natural history of primary malignant liver tumors in adults is such that almost all die with 3 to 7 months following onset of symptoms. It is rare that a patient survives more than 1 year. Foster's review (25) indicates that following resection there is a survival rate of 36% in non-Asian adults with hepatoma; this excludes operative death in 22%. Presumably, this survival rate should increase with more effective chemotherapy. Hepatoma in infants and children is less likely to metastasize early than is the adult variety (25). Operative death rate in this age group is 23% with a survival of other patients for more than 5 years of 33.3%; a significant number of other patients were alive and free of disease at less than 5 years. Resection of metastases remains a controversial subject, but the data reviewed by Foster give encouragement for removal of localized and solitary metastatic disease of the liver.

Recurrence of cancer after transplantation has been high. Starzl (62) recommended that patients with primary hepatoma should not be treated by transplantation. Williams et al. (68) reported 1 patient of 6 with primary hepatomas living 3 years; 2 patients who had transplantation for metastatic disease and 4 of 5 patients having transplantation for carcinoma of the hepatic duct were found to have tumor at autopsy.

Preoperative Nutritional Care

Many patients with primary or secondary liver involvement are undernourished; there may also be a history of alcoholism and the combination may result in extensive fatty infiltration. This state imposes increased surgical risk in terms of normal metabolic response to surgical stress and increases mortality. McDermott and Ackroyd (43) have stressed the importance of delaying surgery if possible until some degree of nutritional repletion can be accomplished in malnourished patients. The mode of nutritional rehabilitation may involve p.o., tube, or parenteral feedings, with the route and the nutrient composition depending upon the clinical situation.

Postoperative Care

Normal liver tissue is endowed with a tremendous capacity for regeneration. Nevertheless, after major hepatic resection the early biochemical and metabolic changes that can occur can be serious and life-threatening. Appropriate steps are necessary to manage these changes to permit recovery and rapid regeneration. McDermott et al. (44) have reported a significant drop in blood sugar following resections of 70% or more, and severe hypoglycemia has been noted in patients following total hepatectomy and liver transplantation. Other groups have not observed such marked blood sugar changes following resection, perhaps because of routine use of glucose postoperatively (2, 52). In any case, it seems wise to obviate this danger by monitoring blood sugar and infusing 10% glucose solution i.v. continuously for at least the 1st several days or until adequate p.o. intake of carbohydrates is assured. Often following p.o. carbohydrate, blood sugar may be elevated for several weeks. Since the liver is the site of albumin synthesis, it is not surprising that hypoalbuminemia will occur to a significant degree unless replaced by parenteral administration. Failure to do so can lead to progressive fall in osmotic pressure in the vascular compartment and accumulation of marked interstitial fluid with increased vascular load and the danger of pulmonary edema. The need for supplementary albumin persists for approximately 1 week. The amounts of albumin given have usually averaged 25 g/day for the 1st 5 days or so (22, 44, 52). By the end of the 3rd postoperative week, near-normal albumin levels are usually found.

Preoperatively, some patients [20% in the series of Pack and Molander (52)] may have elevated serum prothrombin time, which is corrected by preoperative administration of vitamin K, oxide i.m. Fibrinogen, prothrombin, and other
coagulation factors (V, VII, IX, X) that are synthesized by the liver will fall following major resection (22, 44, 52). Despite the postoperative administration of vitamin K, prothrombin levels remained depressed in the postoperative phase; such depression is not reflected in any clinical disorder. These factors gradually return to normal as hepatic regeneration progresses.

After subtotal hepatectomy there is a rapid fall in serum triglycerides. This is expected since the liver is the major source of serum triglycerides and since peripheral tissues are continuously removing circulating fat. As serum triglycerides fall there is a rapid rise in levels of nonesterified fatty acids, that reflects an increased mobilization of fatty acids from adipose tissue (44). As hepatic regeneration proceeds there is progressive rise of the triglycerides and a fall in nonesterified fatty acids over the first several weeks. Decreased total serum calcium reflects a fall in serum albumin. Transient low serum sodium and potassium have been reported in some patients after liver resection (2), while others have reported low levels of serum inorganic phosphates following clinical hepatic resection and hepatic transplantation (22, 23). Hypophosphatemia in dogs following partial hepatectomy is associated with increased hepatic uptake and diminished urinary excretion of phosphate (22).

Evidence of liver decompensation has been observed in cases of extended right hepatic lobectomy (52). In such instances reduction of protein intake and initiation of a medical regimen for hepatic precama are indicated. These disturbances disappear in a short period. At this time it is important to provide sufficient intake of protein and other nutrients to permit optimum liver regeneration. When hepatic dysfunction persists following resection or liver transplantation, and especially when this is associated with portal vein shunting, the i.v. amino acid regimen developed by Fischer et al. (19) may be useful. The rationale for this therapy has been reviewed by Soeters and Fischer (60). They postulate that, in catabolic states such as liver failure and associated conditions such as sepsis, catecholamine discharge is associated with marked increases in glucagon secretion and a decreased insulin:glucagon ratio. The result is a release of large amounts of amino acids from protein sources; the aromatic amino acids cannot be catabolized by the failing liver and accumulate in the circulation. Decreased plasma branch-chain amino acids together with the increased aromatic amino acids allow toxic aromatic amino acids to penetrate the blood-brain barrier in increased amounts and encephalopathy develops. The nutrient formulation is designed to reverse the catabolic state by providing sufficient calories and other nutrients and to reverse encephalopathy by increasing branch-chain amino acid concentration while decreasing aromatic amino acid concentration in order to restore the normal plasma molar ratio of branch-chain amino acids to aromatic amino acids and to reverse the amino acid losses from muscle and liver. The administration of the keto analogs of 5 essential amino acids (valine, leucine, isoleucine, methionine, and phenylalanine) and 5 amino acids (histidine, threonine, tryptophan, lysine, and arginine) i.v. or p.o. has been reported to improve portal-systemic encephalopathy in 8 of 11 patients (41).

Hepatic Regeneration

Massive hepatic resection in man brings into focus the question of rate of regeneration and the factors affecting that rate. The remarkable ability of the liver in experimental animals to replace lost tissues rapidly and completely by compensatory cellular hypertrophy and hyperplasia has long been recognized and also occurs in man. The morphological and biochemical sequence of events during regeneration in laboratory animals (primarily the rat) have been reviewed together with consideration of regulatory mechanisms (7, 33). Almost immediately after extirpation of approximately two-thirds of the liver, a series of morphological changes appear; by as early as 6 hr postoperatively, there is increased capacity to synthesize protein. These changes culminate in an outburst of mitotic division in parenchymal cells at 24 to 30 hr. The rat liver returns roughly on an exponential course to approximately normal size in 10 to 20 days. In his review Harkness (33) has pointed out that considerable variations in diet have little effect on the initial process of regeneration that may take place even on a protein-free diet in the rat. The increase in number of parenchymal cell nuclei is practically the same in starved as in fed animals, although the increase in weight of the liver is markedly less.

Observations in man are relatively limited. Pack et al. (50, 51) had opportunities for direct visualization of liver of patients after major hepatic resection. In 1 patient there was an estimated 50% increase in liver size in 1 week following resection; another patient had complete regeneration in 5 months. McDermott et al. (44) have followed liver regeneration by 131-Iabeled rose bengal following major hepatic resection, and their data also indicate that there is restoration of normal liver mass within 6 months.

The question of the specificity and nature of "regenerative stimulus" or the hepatotropic substance or substances has been of continuing interest and appears to be gaining momentum. One stimulus to this subject has been the observation that Eck-fistula dogs develop not only hepatic encephalopathy but also liver atrophy. Recent interest has centered on the probability that such a factor or factors derive from pancreas or other viscera and enter the liver via the portal blood and on the role of pancreatic hormones. Rats made alloxan diabetic had a marked proliferative response of their livers to insulin administration, although there was some regeneration after hepatic resection even if insulin treatment was withheld, suggesting that more than insulin was involved (70). Bucher and Swaffield (8) reported that insulin and glucagon together stimulated hepatic regeneration in rats. Further support for the concept that glucagon and insulin are needed to produce maximal response to partial hepatectomy in rats has been advanced (67). Starzl et al. (63) found that infusion of insulin, but not of glucagon or of insulin and glucagon mixtures infused into the left portal vein of dogs following portal cava shunt, reduced atrophy, preserved hepatocyte structure, and increased cell renewal. Since the insulin protection in this study was not quite complete, there may be missing ancillary substances. Contradictory data have been advanced in suggesting that insulin is not a critical factor in regeneration in.
rabbits (11) or dogs (17). Regardless of the origin or nature of the hepatotropic factor(s), it would appear that optimal regeneration rates of the liver require adequate nutritional support during the hypertrophic stage.

**Urinary Diversion for Pelvic Cancer**

Urinary diversion is required for pelvic malignant tumors that necessitate cystectomy. The simplest methods of urinary diversion are nephrostomy, which involves simply inserting a tube through the skin into the pelvis of the kidney, or a cutaneous ureterostomy, in which 1 or both ureters are brought to the skin. Serious problems of infection and patient comfort led Coffey in 1911 (14) to publish a description of an implantation of ureters into the sigmoid colon (ureterosigmoidostomy). A high incidence of obstruction of the ureters following implantation with resultant hydronephrosis led to a variety of modifications for ureteral implantation. In addition, there was frequent pyelonephritis caused by ascending infection from continual fecal contamination. Metabolic problems also occurred. In a large series Ferris and Odel (18) found that 79% of their patients had some degree of hyperchloremia and 80% were acidic at varying intervals following ureterosigmoidostomy. A clinical syndrome was associated with the acidosis consisting of thirst, anorexia, vomiting, fatigue, and malaise, and in children a failure to grow and vitamin-resistant rickets were noted. In addition to the hyperchloremic acidosis, hypophosphatemia and hypokalemia developed. Prior to discovery of the relation of this syndrome to potassium homeostasis, the accepted treatment for this syndrome was a low-salt diet with added sodium bicarbonate (18). A number of urologists felt initially that the primary problem related to the development of pyelonephritis with renal dysfunction. However, it became increasingly apparent that the metabolic basis for the syndrome was the result of absorption in the colon of significant amounts of sodium and chloride from the urine with resultant osmotic diuresis and potassium loss (61). Local secretion of potassium by the colon was another source of ionic loss. Metabolic acidosis markedly increases aldosterone secretion, and this plays a role in potassium wastage. Potassium depletion intensifies acidosis because of decreased urinary bicarbonate reabsorption. Because of the inherent metabolic problems of ureterosigmoidostomy, this procedure has essentially been abandoned. However, there are still patients who had this procedure done some years ago who continue to have the metabolic problems.

Ureterosigmoidostomy was replaced by a cutaneous ureteroileostomy (ileal conduit) (4). In this surgical procedure a segment of ileum approximately 20 cm long is resected with its blood supply; the continuity of the ileum is restored, the segment is closed, and the distal end is brought to the abdominal opening. When the resection has healed, the ureters are sutured to the ileal mucosa, the proximal end of its blood supply; the continuity of the ileum is restored, the segment is closed, and the distal end is brought to the abdominal opening. When the resection has healed, the urine is collected in the bag. There is some reabsorption of urea and other urine constituents by the ileum. However, the relatively short segment of ileum with runoff into the bag minimizes metabolic problems as compared to the ureterosigmoidostomy. In addition, this procedure has the advantage of separating the urine contents from intestinal contents with resultant decreased retrograde kidney infection. It has been found that in approximately 2 years the villi of the mucosa of the segment are lost (29).

Approximately 10 years ago there was a short-lived interest in using a jejunal segment instead of an ileal segment for bladder formation. However, clinical experience soon demonstrated that metabolic problems occurred with this approach. These changes were the opposite of those occurring with ureterosigmoidostomy. Hyponatremia, hypochloremia, and hyperkalemia occurred because of loss of sodium and chloride in excess of water into the jejunal bladder and reabsorption of potassium; azotemia developed secondarily to hypovolemia and impaired glomerular filtration (13). Clinically, the patients developed anorexia, nausea, vomiting, abdominal cramping, personality and neurological changes, and weakness. As a result of these findings the use of jejunal loop was abandoned and is used only for patients in whom no other bowel loop is available.

Since treatment of bladder cancer with resultant total cystectomy also includes pelvic radiation therapy, some patients may have significant bowel damage and delayed postoperative recovery. Weight loss is not uncommon. As a result of these complications and poor food intake, nutritional support in the presence of these complications is often beneficial in maintaining the patient during a critical period.

**References**

Effects on Nutrition of Surgery of the Liver, Pancreas, and Genitourinary Tract

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