The Exocrine Pancreas in the Malnourished Child

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The exocrine pancreas, the main source of digestive enzymes, fluid, and bicarbonate required for food digestion, is known to secrete more protein per gram of tissue than any other gland in the human body other than the lactating mammary gland (1). In a 70-kg man, the pancreas synthesizes and secretes roughly 10 g of protein daily. The pancreas represents only 0.1% of body weight but has 13 times the synthesizing capacity of the liver and reticuloendothelial system combined, which between them weigh 4% of body weight. The functional unit of the pancreas consists of pyramidal-shaped cells clustered around a narrow lumen (2). This cluster of cells constitutes an acinus. Its central lumen communicates with intercalated ducts lined by centro-acinar cells. A group of these functional units constitutes a lobule. The intercalated ducts communicate with intra- and interlobular ducts, which in turn lead to the main pancreatic duct. Acinar cells, which comprise 90% of the total cell population, synthesize, store, and secrete digestive enzymes as well as fluid rich in electrolytes. Ductal cells secrete fluid rich in sodium and bicarbonate.

Approximately 30 different digestive enzymes are synthesized and stored in zymogen granules within the acinar cells. These are characterized into three groups according to their enzymatic action, namely, proteases, lipases, and amylases (2). Proteolytic enzymes are stored and secreted as inactive proenzymes, but following secretion into the duodenal lumen, they are activated by a cascade phenomenon. First, trypsinogen is activated to trypsin by enteropeptidase, a brush-border enzyme that cleaves the N-terminal end of trypsinogen (3). Trypsin, in turn, induces an autocatalytic reaction and activates many of the other proteases (4). The lipase group includes lipases 1 and 2, phospholipase, and the carboxylesterases (2). For lipolysis to occur, lipase requires a cofactor, pancreatic colipase, a small glycoprotein that also exists as a proenzyme (procolipase) and requires activation by trypsin (5). Colipase stabilizes the binding of pancreatic lipase to substrate in the presence of physiologic concentrations of bile salts. α-Amylase is secreted in the active form. Its biochemical properties are similar to those of salivary amylase—both hydrolyze the α-1,4 linkages of natural polymers of glucose (6).
In humans, basal low-grade pancreatic secretion is enhanced 100-fold by ingestion of a meal (7). Fluid, electrolyte, and enzyme secretions are regulated by a complex system of neurologic, neurohumoral, and hormonal stimulations and blockades. The mechanisms regulating pancreatic secretion can be categorized into cephalic, gastric, and intestinal phases (7). Cephalic-phase mechanisms involve conscious or conditioned responses to psychic, visual, olfactory, and gustatory stimuli, acting directly via the brain stem and vagal stimulation. Gastric distension also stimulates pancreatic secretion through vagal stimulation. Probably the most important phase of pancreatic secretion, the intestinal phase, requires hormonal release (predominantly secretin and cholecystokinin) by cells located in the upper intestinal mucosa. Secretin is mainly released by acidic pH in the duodenum and stimulates ductal fluid and bicarbonate secretion (8). Cholecystokinin is released by the presence of amino acids, peptides, fatty acids, monoglycerides, and other foodstuffs in the duodenum and causes the discharge of zymogen granules from the pancreatic acinar cells (9).

It must be remembered that the exocrine pancreas is functionally immature at birth. Embryologic studies show that the pancreas arises at 5 weeks of intrauterine life from ventral and dorsal entodermal pouches of the abdominal foregut (10). Rotation then fusion of the two buds occurs at 7 weeks of life, and by 8 weeks, the pancreas produces diffusely branched epithelial tubules. Lobar, intralobular, and intercalated ducts are present at 10 weeks, while formed acini become apparent at 15 weeks of intrauterine life. Relatively mature zymogen granules are detectable by the 22nd week of gestation. The appearance and rate of maturation of individual enzymes vary considerably. Lieberman (11) detected proteolytic activity in the fetal pancreas at about 20 weeks' gestation. Trypsin activity increases rapidly with advancing gestational age (11) and at birth is only slightly lower than that seen in healthy infants at 1 year of age (12,13). Pancreatic lipase activity, on the other hand, is not consistently apparent until the 32nd week of gestation (14), and lipase secretion is extremely low at birth, approximating 1/10 of adult values. Postnatally, there is a twofold increase by 1 month, but lipase secretion remains low even at 1 year of age (13). Although amylase activity has been detected as early as 22 weeks of gestation (14), the pancreatic content of this enzyme is extremely low at birth, and amylase secretion remains low until after the first year of life (13).

It is not surprising, therefore, that the exocrine pancreas, with its high rate of protein synthesis, is adversely affected in states of protein deprivation. This appears to be particularly true in infancy and early childhood, when the exocrine pancreas is still undergoing maturation and when malnutrition is often encountered in its severest form. Despite considerable advances in our knowledge of the effects of malnutrition on the pancreas, the exact pathophysiologic mechanisms are not well-understood. The frequency with which severe pancreatic dysfunction occurs, or the degree and duration of malnutrition required to produce temporary or permanent pancreatic effects, is largely unknown. There remains much controversy regarding the reversibility of the pancreatic lesion once malnutrition has been treated.
THE PANCREAS IN MALNUTRITION

Structural Changes

Fairly extensive information has been gathered that shows that malnutrition has profound structural effects on the exocrine pancreas. In 1926, Normet (15) first provided evidence of pancreatic atrophy in children dying of severe malnutrition. Since then, many other structural changes within this vital digestive organ have been described (16). In fact, Davies (17), in his classic paper on the essential morphology of children dying of kwashiorkor, even suggested that malnutrition was primarily a pancreatic disorder, which in turn produced other organ defects such as hepatic cirrhosis and nephritis.

The early histologic alterations of malnutrition appear to be acinar cell atrophy with disorganization of the typical "rosette" pattern of acinar cells (15,18). There is marked reduction in the number of zymogen granules, cell vacuolization, metaplasia, and cystic dilatation of the ducts (19). In advanced malnutrition, variable degrees of focal pancreatic fibrosis have been described, which may progress in patients with long-standing malnutrition to total replacement of the organ with fibrous tissue (18). It is significant that Veghelyi et al. (20), who evaluated children suffering from starvation during the siege of Budapest, noted severe pancreatic fibrosis in children who died of other causes several months later, at a time when they had been renourished. Electron microscopic observations of Blackburn and Vinijchaikul (21) revealed major disturbances of intracellular organelles. These include altered organization of the rough endoplasmic reticulum, widely dilated cystic vesicles containing cytoplasmic material, degeneration of reticular and cytoplasmic elements, and an increased frequency of intracytoplasmic bodies resembling lysosomes. The number of mitochondria was decreased and those remaining were greatly enlarged and distorted in appearance.

Similar cellular changes within the pancreas have been noted in animals following experimentally induced malnutrition (22,23). Adult rats maintained on a protein-free diet showed morphologic changes within 10 to 12 days (23). There was a gradual disappearance of zymogen granules, together with diminution in the size of the acinar cells. More pronounced changes were noted with prolonged malnutrition, and after several weeks, there was marked atrophy of the acini. By 10 weeks, the normal pancreatic architecture was lost, and there was mild proliferation of connective tissue and dilatation of some of the smaller ducts and ductules. Pancreatic damage has been noted to be more severe in pure protein malnutrition than in total inanition. The reason for this is thought to be that, following ingestion of a meal devoid of protein, the stimulus to secrete endogenous pancreatic proteins into the lumen results in considerably more depletion of protein than would occur with fasting alone.
Functional Changes

In view of the widely reported histopathologic changes occurring within the exocrine pancreas in malnutrition, it is not surprising that it is also functionally impaired. Decreased activities of all enzymes have been found in fasting duodenal juice (24,25). Analysis of individual enzymes revealed that they were affected sequentially, lipase disappearing first, followed by trypsin, chymotrypsin, and amylase (25). However, no distinction was made in this study between salivary and pancreatic amylase, and duodenal amylolytic activity may well have been salivary in origin.

These earlier studies provided no data regarding enzyme secretion under conditions of stimulation. More detailed evaluation of stimulated secretions has since been carried out in children and adults (Table 1). Barbezat and Hansen (26) evaluated pancreatic function in malnourished South African children by intestinal intubation and aspiration of duodenal contents while stimulating the pancreas with intravenous secretin and pancreozymin. The volume of secretions and alkali production did not appear to be altered, but severely malnourished infants had deficient enzyme output. There was an overall correlation between total enzyme output and serum albumin concentration, suggesting that protein deficiency had a direct effect on the ability of the pancreas to synthesize enzymes. Secretion of the individual enzymes was affected differently. Amylase and chymotrypsin secretion were the most sensitive to malnutrition, decreasing by over 90% of control values. Lipase secretion was also severely depressed in patients with kwashiorkor. Trypsin output was the least affected, decreasing by only 60 to 70% of control values. Some of these children were reevaluated several years later after nutritional recovery. There did appear to be recovery of enzyme output, particularly in those with malnutrition of relatively brief duration, but it is important to note that the chronically malnourished patients had persistently poor function. Danus et al. (27), who studied chronically malnourished South American infants, also showed depression of pancreatic en-

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zyme activity (amylase and lipase) when using a similar intubation technique. There was no obvious effect on fluid or bicarbonate secretion, suggesting that pancreatic ductal function was preserved. Unlike the South African study, however, little or no recovery of pancreatic function occurred, particularly with respect to lipase activity, after 30 days of successful nutritional management. The findings in children differ somewhat from the observations in adults with severe malnutrition (Table 1). Tandon et al. (28), Kumar et al. (29), and Descos et al. (30) showed that protein-energy malnutrition (PEM) induced moderately deficient enzyme output but also reduced bicarbonate secretion. Pancreatic fluid secretion was normal. After a normal diet, there was rapid and full recovery of all functions.

Critical evaluation of the methodology used in some of these studies of children (26,27) reveals a number of technical difficulties, which could greatly affect data interpretation. Pancreatic juice was aspirated without the use of intestinal perfusion with a nonabsorbable marker (31). As a result, distal losses of pancreatic fluid may have been considerable, and quantitative recovery of pancreatic secretions (enzyme, fluid, and electrolyte secretion) could not be accurately determined (31,32). In Barbezat's study (26), bicarbonate was determined by simple duodenal pH measurements rather than by actual measurement of bicarbonate secretion. Submaximal infusions of pancreozymin and secretin were infused during the stimulation test (32). Also, neither study accounted for the dramatic maturational changes in pancreatic development in normal infants (12,13). As a result, a number of important questions remain unanswered and await more critical evaluation. In this regard, the factors determining the reversibility of the pancreatic lesion following childhood malnutrition deserve closer attention. Future studies should account for a variety of other variables including the nature, severity, and duration of malnutrition required to produce temporary or permanent effects, together with the impact of malnutrition on various stages of postnatal pancreatic development. Finally, the precise effects of pancreatic dysfunction on digestive function have not been evaluated. In other primary disorders of the exocrine pancreas in childhood [cystic fibrosis (CF) and Schwachman syndrome], in excess of 98% of pancreatic acinar function must be lost before fat maldigestion becomes manifest (32). The large reserve capacity of the exocrine pancreas may in fact protect the patient from developing significant maldigestion, even in severe childhood malnutrition.

EVIDENCE OF PANCREATIC DAMAGE IN ACUTELY MALNOURISHED CHILDREN

We have had the opportunity to evaluate infants and young children with varying degrees of acute malnutrition due to a number of different causes using a sensitive indirect probe of pancreatic dysfunction, serum immunoreactive cationic trypsinogen (33). In a variety of pancreatic disorders of childhood, this test is of proven diagnostic value. Except in CF, serum levels of cationic trypsinogen are greatly re-
duced in infants and children with primary exocrine pancreatic failure (34). In contrast, in CF infants, serum trypsinogen levels are greatly raised as a result of pancreatic ductal obstruction and regurgitation of enzymes into the circulation (35). With advancing age, serum trypsinogen levels decline to low or undetectable values in CF patients with pancreatic insufficiency but remain normal or elevated in those with preserved pancreatic function. Similarly, in children with acute pancreatitis, serum trypsinogen levels are greatly elevated (36).

In our study, malnourished patients were classified into groups according to the severity of malnutrition using the height/weight/age standards of McLaren and Read (37). The patients were monitored longitudinally during a period of renourishment. Serum trypsinogen concentrations (mean ± SD) were significantly elevated in 25 patients with "severe" malnutrition (77.4 ± 42.0 ng/ml, p<0.001) and in 23 with "moderate" malnutrition (54.2 ± 16.1 ng/ml, p<0.02) when compared with values for well-nourished controls (32.5 ± 10.4 ng/ml) (Fig. 1) (33). The concentration of serum trypsinogen appeared to rise in proportion to the severity of malnutrition. There was no obvious relationship between serum trypsinogen and other variables such as age, sex, specific diagnosis, or mode of feeding. Elevated serum trypsinogen levels could not be attributed to renal disease, and CF had been excluded. Size fractionation of serum samples demonstrated a single peak of immunoreactive mater-

![FIG. 1. Serum cationic trypsinogen (ng/ml) plotted against the severity of malnutrition. Shaded area shows the normal range (mean ± SD). Serum trypsinogen was significantly above normal in the severely (p<0.0001) and moderately (p<0.02) malnourished patients. (Reproduced from ref. 33, with permission of CV Mosby Co.)](image-url)
rial in the form of free trypsinogen, with no measurable trypsin complexed to the major plasma protease inhibitors, α₂-macroglobulin and α₁-antitrypsin. In 22 of these patients, there was a significant improvement in nutritional status during the monitoring period. Coincident with this improvement, serum trypsinogen concentrations tended to revert toward the normal range. The severely malnourished patient group showed a highly significant drop in serum cationic trypsinogen \((p<0.01)\) to values no different from normally nourished controls. Individuals whose nutritional status remained unchanged during the monitoring period had persistently raised serum trypsinogen values. Thus, raised serum levels of trypsinogen appear to be a direct consequence of acute malnutrition, and following nutritional intervention, these changes are readily reversible.

These findings differ strikingly from the results reported by Fedail et al. (38), who found low levels of serum trypsinogen in African children with severe malnutrition. It should be emphasized that the patients included in our study were acutely malnourished, with wasting and relative preservation of height growth, whereas the infants in Fedail’s study appear to have been chronically malnourished, with stunting. The two studies seem to have been carried out at different stages in the development of the pancreatic lesion following malnutrition. During acute malnutrition, therefore, increased concentrations of circulating trypsinogen may result from a pancreatic disturbance, either acinar cell damage or ductal obstruction. In contrast, low serum trypsinogen levels in children with severe, prolonged malnutrition may reflect severe pancreatic acinar atrophy, with or without fibrosis, which is well-described in histopathologic studies.

There is other evidence to support the concept that pancreatic damage occurs in childhood following acute malnutrition. Children with malnutrition from anorexia nervosa and other causes develop clinical and biochemical evidence of acute pancreatitis (39–43), particularly as a result of forced feeding (40,43). Similarly, prolonged lack of stimulation to the pancreas can produce acinar atrophy and irreversible pancreatic failure. This is best exemplified by the observation of irreversible pancreatic insufficiency in patients with celiac sprue who were not diagnosed until late adulthood (44). We have now reported this phenomenon in a 17-year-old patient with celiac disease who, prior to diagnosis, was suffering from severe growth failure and delayed puberty (45). In these cases, irreversible pancreatic atrophy is thought to occur as a result of chronic understimulation of the pancreas by a deficiency of pancreatic agonists (cholecystokinin and secretin), but, in addition, the direct contribution of chronic malnutrition must be considered.

TROPICAL PANCREATITIS

There may well be a link between the pancreatic effects of malnutrition in early childhood and an interesting form of chronic calcifying pancreatitis, which has been described in older children and young adults in a number of developing countries (16,46–51). A vast array of terms have been used to define this condition (16,46–
including nutritional pancreatitis, tropical chronic calcifying pancreatitis, tropical pancreatitis, and, perhaps the most appropriate term, coined by Nwokolo and Oli (51), juvenile tropical pancreatitis syndrome. It is a condition affecting young people of both sexes and is characterized by abdominal pain, pancreatic calcification, and diabetes, occurring among the young in impoverished areas of developing nations (Table 2). It is accompanied by malnutrition and the notable absence of other causes of acute pancreatitis, especially alcohol abuse. Typically, the disease first presents in adolescence with severe abdominal pain and then diabetes mellitus. Recurrent attacks of abdominal pain last from hours to days and are aggravated by food consumption. The pain is severe in the early stages but becomes less intense and frequent with disease progression. Diabetes mellitus becomes clinically manifest 2 to 5 years after the onset of symptoms of pancreatitis. Clinical symptoms of steatorrhea are not usually apparent, but most patients normally consume low quantities of fat in their diet. Pancreatic function studies using duodenal aspirates have shown a marked decrease in volume and enzyme output to levels consistent with pancreatic failure; in addition, 50% of the patients also have reduced bicarbonate secretion (46).

In this condition, the pancreas is firm and gritty in appearance, with focal areas of fatty replacement (46). Microscopically there are dilatation of the ducts, pancreatic lithiasis, chronic inflammatory cell infiltration, fibrosis, and atrophy of the parenchyma (46). The greatly dilated main pancreatic duct and collecting ducts usually contain pancreatic calculi of varying size, with or without inspissated periodic acid–Schiff (PAS)-positive mucoproteinaceous material. Larger stones, usually extremely irregular in appearance, are often seen in the head of the pancreas and at the ampulla of Vater. The inflammatory infiltrate comprises mainly plasma cells and lymphocytes, and on occasion, there is eosinophilic infiltration. Focal, segmental, interlobar fibrosis is characteristic early in the disease, and this progresses to diffuse fibrosis between acini.

When all the associated factors are considered, there remains compelling evidence to support a connecting link between the pancreatic disorder of early childhood malnutrition and the late onset of tropical pancreatitis. However, there is a confusing distribution of this condition in specific geographic regions of certain developing countries, notably in parts of Indonesia, India, Central Africa, West Africa, South America, and most recently, in Mexico (52,53). It is likely that "pure"

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<th>Table 2. Clinical features of tropical pancreatitis</th>
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<td>Extreme emaciation</td>
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<td>Abdominal distension</td>
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<tr>
<td>Parotid gland enlargement</td>
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<td>Severe, recurrent abdominal pain</td>
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<td>Few symptoms of maldigestion (low-fat diet)</td>
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<td>Diabetes mellitus</td>
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protein malnutrition alone is not the sole associated cause. Nwokolo and Oli (51), who described a number of cases in Nigeria, proposed that it occurs as a result of blockage of pancreatic ducts, which later calcify. Sluggish pancreatic flow could result from low-protein diets, perhaps worsened by gastroenteritis and dehydration. Sarles (52,53), in an epidemiologic survey of pancreatic disease in various countries, noted that the distribution of chronic calcifying pancreatitis could be linked with alcoholism only in industrial countries, where high-protein, high-fat diets were commonly eaten, whereas in a number of developing countries, it was clearly associated with malnutrition (Table 3). The tropical form of chronic pancreatitis occurs at a much earlier age and is distributed more equally between the sexes than that seen in industrial nations. Most reports agree that nutritional pancreatitis is only seen in individuals from an extremely poor background who were most likely to experience severe malnutrition in childhood.

Various arguments have been put forward against protein malnutrition as the primary or initiating cause of tropical pancreatitis. It has been suggested, for example, that malnutrition in early childhood rarely leads to permanent pancreatic damage and there is striking lack of ductular stones, inflammation, or necrosis. Furthermore, in some countries where protein malnutrition is endemic, tropical pancreatitis is not seen. To add to the confusion, the prevalence of the disease shows tremendous regional variability even within each country. In Nigeria, the incidence of the disease is higher in the south than in the north (46). As a result, other factors such as toxic agents, viral infections, or specific micronutrient deficiencies have been implicated. The role of a genetic predisposition to this condition has also been considered.

There has been some interest in the effects of selenium or copper deficiency in the pathogenesis of various types of pancreatitis (46). Newborn rats fed a copper-free diet experienced acinar cell atrophy, failure of zymogen granule synthesis, and disarray of intracellular organelles. The effects of trace metal deficiencies on the human pancreas are unknown.

Another hypothesis put forward by Pitchumoni and Thomas (54) for the pathogenesis of the disease in India is the role of natural toxins in food products, for example, cyanide, which is present in large quantities in cassava. At present, there is

### TABLE 3. Epidemiologic characteristics of alcoholic and tropical pancreatitis

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<th>Alcoholic</th>
<th>Tropical</th>
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<td>Age of onset</td>
<td>Adulthood (35–44 yr)</td>
<td>Adolescent/Adult (10–25 yr)</td>
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<td>Sex distribution</td>
<td>Male predominance</td>
<td>Equal</td>
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<td>Geographic distribution</td>
<td>Developed nations</td>
<td>Developing nations</td>
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<td>Diet</td>
<td>High protein and fat</td>
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<tr>
<td>Etiologic association</td>
<td>Excessive alcohol</td>
<td>?Malnutrition</td>
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<tr>
<td>Development of pancreatic failure</td>
<td>After 15–20 yr</td>
<td>After 5–10 yr</td>
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no experimental evidence to suggest that dietary cyanide causes pancreatitis, and in other parts of the world where cassava is a staple diet, tropical pancreatitis is not seen.

A deficiency of specific vitamins or essential amino acids has been implicated. There is little information on the effects of vitamin deficiencies on the human pancreas, although Blackfan and Wolbach (55) did report epithelial metaplasia and pancreatic fibrosis in vitamin A–deficient subjects. Ethionine deficiency is known to produce acute pancreatitis in experimental animals, an effect that may be counteracted by the simultaneous administration of methionine.

In conclusion, although pure protein malnutrition appears to be closely associated with tropical pancreatitis, by itself it does not fully explain the pathogenetic mechanisms of this disorder. The role of other agents such as nutritional toxins or specific nutrient deficiencies deserves closer attention. Until we obtain more specific epidemiologic and experimental data on these matters, the etiology of tropical pancreatitis remains uncertain.

ACKNOWLEDGMENTS

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DISCUSSION

Dr. Suroto: In one study, we found that parotid gland impairment in malnourished children was correlated with the albumin concentration. We recognized that when there is derangement of the acinar cells of the pancreas, there may be similar changes in the parotid. With parental permission, we assessed impairment by determining the parotid uptake of intravenous technetium. Analysis showed a correlation between impairment in the uptake test with albumin concentration, regardless of the type of malnutrition.

Dr. Durie: Although I did not distinguish in my presentation between marasmus and kwashiorkor because I was not sure the distinction was relevant, both published studies on the pancreas refer to marasmus and kwashiorkor as distinct entities. The parotid gland has many physiologic similarities to the pancreas. It would be interesting to be able to measure both organs simultaneously in order to be able to determine whether assessment of the parotid alone might provide indirect information about the pancreas. Until one did, I do not think one can assume that the same process is happening simultaneously in both organs.

Dr. Okeahialam: The syndrome of chronic pancreatitis, pancreatic calcification, as seen on X-ray, and juvenile diabetes mellitus is well-known in Nigeria (1). Clinical features include chronic malnutrition with stunting and bilateral painless enlargement of the parotid glands. The syndrome is seen mainly in malnourished poor children between 9 and 15 years of age. Infection, viral or bacterial, is present, affecting the exocrine glands, such as the parotids, as well as the islets of Langerhans in the pancreas.

Dr. Durie: Nwokolo and Oli (1) suggested that the pancreatic lesion, which develops in the malnourished child, may be aggravated by recurrent gastroenteritis and dehydration, causing reduction in pancreatic secretions and pancreatic duct obstruction. I have observed a similar pathologic state in cystic fibrosis, where there is duct obstruction, caused as a result of impairment of pancreatic fluid secretion.

Dr. Brunser: The mechanisms used by the acinar cells of the salivary glands and the pancreas to secrete their products into the ductal system are the same. It would be interesting to see if these morphologic mechanisms are damaged in comparable ways in malnutrition. Then we might be able to point to a specific type of damage associated with alteration of a specific mechanism.

Dr. Aggett: I should like to comment on the possible contribution of copper and selenium to the observed pancreatic abnormalities. The histopathology of pancreatic damage in these deficiencies predominantly affects the acinar cells. With copper deficiency, there is disorga-
nization of the acinar cells, with loss of cytochrome oxidase staining in the exocrine rather than the endocrine cells. There are marked mitochondrial changes that include dilatation, altered shape, abnormal cristae, and other degenerative appearances.

Dr. Pudjiadi: We have never seen diabetes mellitus in a child who had survived kwashiorkor (2). Zuidema (3) speculated that its occurrence was due to permanent changes in the pancreas.

Dr. Brasel: The diabetic state in the malnourished child is very difficult to manage as a result of the additional loss of the alpha cells that results in glucagon deficiency. When these patients receive more insulin than they need, they can have wide fluctuations in blood sugar levels and serious hypoglycemia.

Dr. Durie: From an epidemiologic point of view, tropical pancreatitis seems to occur only in specific, isolated parts of the world, predominantly in developing countries. Even within one country, it may occur only in isolated geographic pockets that have similar states of nutrition. For example, I believe it is much more common in northern than southern Nigeria, indicating that malnutrition is not the sole factor.

Dr. Okeahialam: It is actually more prevalent in the south and was seen mostly during and after the civil war, at which time there was also a high incidence of hepatitis. Some studies have indicated a strong correlation between the two clinical states.

Dr. Brunser: Do people who have moved from areas where tropical pancreatitis occurs to developed countries continue to develop this type of disease?

Dr. Durie: There is no evidence that they do.

Dr. Soriano: One of the rare situations in which acute pancreatitis is observed is chronic renal failure. The French Society of Pediatric Nephrology was able to find only six cases for a collaborative study.

Dr. Durie: Is it seen in association with peritoneal dialysis?

Dr. Soriano: It occurs in children surviving on long-term hemodialysis or peritoneal dialysis.

Dr. Aggett: Can you comment on what effect changes in the intestinal mucosa or microfloral colonization of the bowel may have on the enteropancreatic circulation of pancreatic enzymes, nitrogen, and on the colonic salvage of protein?

Dr. Durie: I think there are some animal data that would suggest that pancreatic deficiency might reduce epithelial cell turnover, but I do not think there are any human data.

Dr. Jackson: You say there are 10 g of protein produced per day, and that only 1 g reaches the stool, yet you do not believe that the nitrogen is reclaimed in any form?

Dr. Durie: I am suggesting that there is no evidence that the enzymes are recirculated intact to the pancreas. I am not questioning that there are degradation of pancreatic enzymes and reabsorption of degraded protein.

Dr. Suskind: Is there any evidence that there is an effect of protein-energy malnutrition (PEM) on those gut hormones that normally stimulate the pancreas? Is that an area that needs to be investigated?

Dr. Durie: The data I showed were based on exogenous stimulation of the pancreas, using artificial means. An accurate quantifiable method of evaluating all the facets of the pancreatic response during ingestion of a meal in normal conditions as well as in the malnourished state does not exist.

Dr. Suskind: Does the exocrine pancreas put out trace elements, such as zinc?

Dr. Aggett: Overall, there is a large enteroenteric or enteropancreatic circulation of zinc which, in adults, can be as much as 14 mg/day, that is, one and a half to two times the normal dietary intake. Zinc enters the gut lumen in the proximal small bowel from the pancreas and
intestinal secretions. It is reabsorbed in the distal small intestine and possibly the colon. We do not know how this cycle is affected in protein-energy malnutrition or in zinc deficiency, but, certainly with zinc depletion, the amount of endogenous zinc that is lost in the feces is reduced. This could be achieved by either a reduction in the amount of zinc being secreted into the small intestine, by improved distal reabsorption of the element, or by a combination of both mechanisms, even though one can show decreases in some of these enzyme activities occurring in fairly marked zinc deficiency.

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