CHAPTER 55

Hereditary Diseases of the Pancreas

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Several childhood diseases of the pancreas have been described. By far the most common and well-understood is cystic fibrosis (CF), which has been discussed in the chapter by Lebenthal, et al. Generalized pancreatic insufficiency occurs in both primary and developmental varieties, which are described herein. An autosomal mode of inheritance has been postulated in these generalized pancreatic insufficiency syndromes.

Isolated pancreatic enzyme deficiency syndromes have been reported but are distinctly uncommon. Little is known regarding the precise nature of the defect in these syndromes. Because these syndromes are so rare their mode of inheritance is poorly understood.

In this chapter, generalized and isolated hereditary abnormalities of pancreatic function are discussed. The present chapter is an update of a recent one (56).

SHWACHMAN-DIAMOND SYNDROME

The Shwachman-Diamond syndrome (SDS), the second most common cause of pancreatic insufficiency, was first described in 1964 (6,89). It is characterized by exocrine pancreatic insufficiency, cyclic neutropenia, metaphyseal dysostosis, and growth retardation (Table 1) (91,94). Its estimated incidence is 1 in 20,000 live births, but only about 120 cases have been reported (91). Both sexes are equally affected. The suggested mode of inheritance is autosomal recessive.

Clinical and Pathological Features

Gastrointestinal

The disease most often presents in infancy. The stools are pale, greasy, foul smelling and the frequency is increased. Growth is retarded, there is failure to thrive, and the patient is usually short stunted (1,93). Stool fat excretion is elevated. A repeatedly negative sweat test, despite abnormal tests of pancreatic function, confirms the diagnosis. Following pancreateozymin and/or secretin stimulation, amylase, lipase, and trypsin activities are low or absent in the duodenal fluid. The volume and bicarbonate content of the stimulated pancreatic fluid are normal or low (9,33,36,88,91), but its viscosity, unlike that of fluid obtained from patients with cystic fibrosis, is normal. Small intestinal biopsy reveals normal morphology and disaccharidase activities and normal-to-elevated enterokinase activities, unless the patient is severely mal-

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TABLE 1. Clinical features of the Schwachman-Diamond Syndrome

<table>
<thead>
<tr>
<th>Major features</th>
<th>Associated features</th>
<th>Infrequent features</th>
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<tr>
<td>Pancreatic insufficiency</td>
<td>Subtle disturbances in lung function</td>
<td>Cardiac lesions</td>
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<td>Cyclic selective bone marrow depression</td>
<td>Hepatomegaly</td>
<td>Testicular fibrosis</td>
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<td>Metaphyseal dysostosis</td>
<td>Dental abnormalities</td>
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<td>Short stature</td>
<td>Renal dysfunction</td>
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<td>Normal sweat electrolytes</td>
<td>Delayed puberty</td>
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nourished (53). Serum amylase activity may be low or normal, but serum pancreatic isoamylase is often absent. Some patients with mild pancreatic insufficiency show spontaneous improvement with disappearance of steatorrhea (41). In others, pancreatic insufficiency persists into adulthood (108).

Macroscopically the pancreas is normal to small in size and shows evidence of fatty infiltration. This can also be appreciated on ultrasound and CT scan (78). The ductal system appears normal. Microscopically, the marked fatty infiltration and the paucity of fibrosis and inflammatory cells are striking. The islets of Langerhans appear normal, but there is little acinar tissue (6). Hepatic abnormalities of varying degree are well recognized (1,12).

Hematological

The hematological picture is variable and is dominated by neutropenia in 95%, thrombocytopenia in 70%, and anemia in 50% of the patients (1). The neutropenia may be constant or cyclic. Fluctuations in the neutrophil counts may occur as often as every 1 to 2 days. The total neutrophil count is generally less than 1,500/mm³, but the neutrophil response to a bacterial infection remains appropriate. Recently, (2,81) an inherited defect in neutrophil mobility was reported in patients with SDS and their unaffected parents. The anemia and thrombocytopenia are rarely severe enough to produce clinical symptoms. The documentation of an unusual surface distribution of concanavalin A receptors on the neutrophils of patients with SDS may reflect a cytoskeletal defect that can contribute to the abnormal chemotaxis of neutrophils and explain the susceptibility of patients with SDS to infection (79).

The thrombocytopenia may be associated with increased levels of plasma alkaline phosphatase. Elevated fetal hemoglobin levels were reported in 45% of all patients. This later finding led the authors to suggest that there was an increased risk of malignant disease in these patients (1).

Bone marrow cellularity may be normal or decreased. Cells of the granulocytic series may be normal, increased, or decreased (1,82,89), and even in neutropenic patients, bone marrow aspirates may be normal. Maturational arrest mainly of the myelocytic element of the bone marrow has been observed most often and occasionally fatty and fibrosis infiltration of marrow (12,31).

Skeletal

Bone lesions are rarely observed during infancy. The most common lesion, metaphyseal dysostosis, has been reported in 10 to 15% of the patients. The skeletal parts affected are the femur, tibia, and ribs (1,13,88,89,95). The femoral neck is most often affected, and the lesion is generally symmetric and progressive and may result in disturbance of the child’s gait and coxa vara deformity.

Other Clinical Manifestations

A variety of additional clinical features associated with SDS have been described. Aggett, et al. (1) in reviewing 21 patients described subtle disturbances in lung function, which included reduced tidal volume and chest wall compliance during infancy and reduced forced expiratory volume and forced vital capacity later in life. In addition, respiratory morbidity is less than in younger patients, and there is only minor impairment of lung function (108). Other manifestations included in Aggett’s review are impaired cognitive capacity and/or developmental retardation in 85% of the patients studied. Hepatomegaly was found in 13 patients, primarily the younger ones, but this resolved with age (1). Six patients had severe panlobular fatty metamorphosis with mixed inflammatory infiltration and perportal fibrosis. Neonatal problems (80% of patients), dental abnormalities, renal dysfunction, delayed puberty, and ichthyotic muculopapular rash were found in 65% of the patients. Cardiac lesions (1,30), testicular fibrosis (30), diabetes mellitus (1), Hirschsprung’s disease (1), renal tubular acidosis (63), and central pontine myelinolysis (96) have been reported in association with SDS but are distinctly uncommon. Although the vast majority of cases are diagnosed before the age of 2 years, the syndrome may manifest later, as was illustrated by a recent report of a 14-year-old girl (43). Improvement of steatorrhea with age is known to have occurred (41).
Pathophysiology

The etiology of this multiorgan disease is unknown. In the past an acquired etiology was suggested. A prenatal injury at or before the 5th month of gestation, when pancreatic and myeloid bone marrow development is taking place, has also been suggested. The mode of inheritance, the multiorgan involvement, and the existence of a neutrophil mobility defect in heterozygotes, however, favors an inherited etiology (2).

Aggett et al. (1) recently suggested an abnormality in the cellular microtubular or microfilamental function as the pathophysiologic basis for SDS. These structures and functions are fundamental to cellular secretion, cell division, and neutrophil mobility (61). The microtubules are essential for pancreatic amylase secretion (109), and the chondrocytes affected in SDS contain inclusions in their dilated endoplasmic reticulum, which suggests a defect in secretion from this organelle (93). The recently reported in vitro restoration of defective chemotaxis by lithium further supports the microtubule theory since lithium can modulate the granulocyte microtubular system (3). The microtubule theory can also explain the multiorgan involvement of the disease. The description of a 5-month-old infant with SDS where only ininspissated secretions were found in the pancreatic ducts at necropsy (13) also suggests that the lipomatous changes in the pancreas are secondary and late findings in the disease. The main clinical observation that the microtubular dysfunction theory fails to explain is the cyclic dynamics of the hematological abnormality and the improvement in steatorrhea and lung function (41,108).

An alternative explanation for the pathophysiologic abnormalities in SDS is a maturational arrest. The relationship between the pathology of the pancreas and bone marrow is manifested in several genetic diseases such as the Johanson-Blizzard syndrome (46), sideroblastic anemia associated with pancreatic insufficiency (74), and SDS. These associations may suggest a fundamental interaction between the exocrine pancreas and bone marrow. During development, the exocrine pancreas of infants continues to mature for the 1st year of life (54,113). A maturational arrest occurring in a critical period by a genetic mechanism may delay the appearance of the above physiologic pancreatic insufficiency. The spontaneous improvement of steatorrhea in SDS with age (41) furthermore demonstrates that transient functional damage may not be compatible with a permanent genetically mediated ultrastructural abnormality of the pancreatic cell.

In the bone marrow a maturational arrest of the granulocyte series has been observed often (91). A patchy distribution of the lesion in the bone marrow may explain the intermittent nature of the hematological abnormalities. The maturational arrest might have occurred in utero, in only several clones of the pluripotential stem cells. Thus, genetically mediated and closely linked on one of the chromosomes, the abnormality can be expressed as a maturational arrest in the pancreas and bone marrow and manifest later in life. The increased incidence of hematological malignancies associated with SDS (111) may also be a result of an early genetically mediated insult affecting the progenitor cell in the bone marrow. The association between chromosomal aberrations and leukemias is known: trisomy 21, Fanconi anemia, chronic myeloid leukemia, Bloom syndrome, etc. Our recent diagnosis of SDS in one of four children in a family revealed that one died with acute lymphoblastic leukemia, one died with trisomy 21, the third child had a classical form of SDS, and the fourth is apparently normal. This family further supports the chromosomal-hematological-pancreatic association. The parents were not first-degree relatives and chromosomal studies on the parents, the nonaffected girl, and the boy with SDS were normal. As more sophisticated chromosome banding studies become available and are done on the affected patients, subtle somatic defects may be found and the enigmatic hematopancreatic pathology in SDS may well be clarified.

Diagnosis

Any child with symptoms, signs, and laboratory data suggestive of pancreatic insufficiency should be suspected to suffer from SDS. A normal sweat test makes the diagnosis of SDS likely. Sometimes the hematological manifestations are obvious, especially the neutropenia, but its cyclical nature may necessitate frequent blood counts before its presence is recognized. The skeletal manifestations are late features of SDS and are not essential for diagnosis in childhood SDS.

The diagnosis may be more difficult in younger infants, when a wide overlap of symptoms and signs may exist with other entities. The neurological, respiratory, or infectious manifestations are not specific and may mask the pancreatic and the hematologic manifestations. Rarely, the presenting symptoms of SDS may be one of the complications of the disease.

Complications

If pancreatic insufficiency associated with SDS is severe or the diagnosis is delayed, malnutrition may result. Infections are a common cause of morbidity and mortality in SDS. In treating a child with SDS, one should be aware of the increased susceptibility of these children to infection. Neutropenia, the inherited defect of neutrophil mobility, and the associated deficiency in immunoglobulins (20) predispose these patients to infections. Orthopedic complications such as coxa vara and gait disturbances may complicate the skeletal lesion espe-
cially if metaphyseal dysostosis affects the hip. Cardio-
megaly and increased incidence of myocardial lesions
that can result in death are known complications (85). A
procaine-induced methemoglobinemia has been re-
ported (50). Recently, eight patients with SDS and leuko-
emia were reviewed by Woods, et al. (111). This compi-
cation of SDS contributes further to the morbidity and
mortality associated with this syndrome.

Treatment

Treatment is symptomatic. Pancreatic enzyme re-
placement is aimed at decreasing steatorrhea and im-
proving the child’s nutrition. Growth, however, is rarely
improved. Since spontaneous improvement in steator-
rhea can occur (41), the physician should carefully and
frequently assess the need for replacement therapy. In
our practice, we use enteric-coated microspheres almost
exclusively. Fat-soluble vitamins and a low-fat diet
enriched with medium-chain triglycerides rather than
long-chain triglycerides, and one in which long-chain
polymers of glucose are replaced with oligomers of glu-
cose to enhance starch digestion by glucoamylase (49)
should be encouraged.

Infections should be treated promptly. Orthopedic in-
tervention should be carefully timed, and the clinician
should be aware of the increased risk of hematological
malignancies in these patients. Twenty-five percent of
infants with SDS develop aplastic anemia. Recently suc-
cessful treatment of aplastic anemia with cyclosporin A
was reported (5). This suggests that an immunological
mechanism is responsible for the hematopoietic suppres-
sion observed in SDS. Bone marrow transplantation
may be an alternate form of treatment for the hemat-
ological abnormalities observed in SDS in selected
patients (106).

JOHANSON-BLIZZARD SYNDROME

The Johanson-Blizzard syndrome was first described
in 1971 (46). Its mode of inheritance is autosomal rece-
sive, and there is no sex predilection. The main features
of this rare syndrome are congenital aplasia of the alae
nasi, deafness, hypothyroidism, dwarfism, microceph-
aly, absence of permanent teeth, and malabsorption.
Pancreatic enzymes secretion, especially trypsinogen, is
low. The syndrome was recently reviewed (26,56). Table
2 summarizes the 35 cases reported in the literature, and
Table 3 gives the incidence of the clinical features found
in the Johanson-Blizzard syndrome. Pancreatic insuf-
ciency is the most consistent feature of this syndrome.
Lately, hypopituitarism and growth hormone insuf-
ciency have been described in association with this syn-
drome (52,83) and together with hypothyroidism may
play a role in the short stature so characteristic of this
disease. A 19-year-old female with diabetes mellitus has
also been recently described (105).

The clinical manifestations include a typical dysmor-
phism, signs of hypothyroidism, and a clinical picture of
pancreatic insufficiency. The signs of malabsorption are
generally present during infancy, and at autopsy the pan-
creas may be absent or replaced by fat. The syndrome
is not well defined. Whether the cases reported represent
a distinct entity or a variation of other syndromes is not
known. The syndrome may be associated with cystic fi-
brosis in the same family. Patient 34 in Table 2 has two
sibs with documented cystic fibrosis (Dr. J. Oren, per-
sonal communication). Temporal bone defects have
been described for the first time in this patient (10). The
pathophysiology and the genetic abnormality are
unknown.

SIDEROBLASTIC ANEMIA AND EXOCRINE
PANCREATIC INSUFFICIENCY

Another syndrome that suggests an interaction be-
tween the bone marrow and the exocrine pancreas was
described by Pearson et al. (74). Four patients with sider-
oblastic anemia and generalized pancreatic insufficiency
have been reported. Two of these patients had splenic
atrophy. Pancreatic function tests in one of the patients
revealed very low bicarbonate, lipase, and amylase secre-
tion. Another patient had low bicarbonate, but trypsin-
gen was not measured. Acinar atrophy with fibrosis but
no liposis was found in the pancreas. No skeletal abnor-
malities have been described. Meanwhile, additional
cases have been reported (18,84,97). Most recently, a
deletion of 4,977 bp in mitochondrial DNA was de-
scribed in one of the patients. The deletion spanned the
genes coding for four subunits of NADH dehydrogenase,
one subunit of cytochrome oxidase, and one subunit of
ATPase. It is postulated that this syndrome is due to a
mitochondrial respiratory enzyme defect (14,80).

PANCREATIC EXOCRINE
APLASIA/HYPOPLASIA

A patient with total absence of pancreatic acinar cells
has been reported (98). This patient may serve as an ex-
ample of overlap between the different pancreatic
syndromes described above since the child shared fea-
tures common to the Shwachman-Diamond syndrome,
Johanson-Blizzard syndrome, and leprechaunism.

An additional syndrome of pancreatic insufficiency
involving both exocrine and endocrine functions has
lately been described in two brothers who were small at
birth and developed early-onset insulin-dependent dia-
betes and pancreatic exocrine insufficiency (110). The
authors suggested a recessive mode of inheritance.
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<th>Nasal alar hypoplasia</th>
<th>Hypothyroidism</th>
<th>Pancreatic insufficiency</th>
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<th>Aplasia cutis</th>
<th>Teeth abnormalities</th>
<th>Short stature</th>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*a* Male.

*b* Female.

?, Unknown.
TABLE 3. Incidence of clinical features reported in Johanson-Blizzard Syndrome

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Incidence</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic insufficiency</td>
<td>33/34</td>
<td>97.0</td>
</tr>
<tr>
<td>Nasal alar hypoplasia</td>
<td>32/33</td>
<td>97.0</td>
</tr>
<tr>
<td>Teeth abnormalities</td>
<td>21/24</td>
<td>87.5</td>
</tr>
<tr>
<td>Short stature</td>
<td>26/30</td>
<td>86.5</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>23/30</td>
<td>76.7</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>22/28</td>
<td>78.6</td>
</tr>
<tr>
<td>Ectodermal scalp defects</td>
<td>24/33</td>
<td>72.7</td>
</tr>
<tr>
<td>Rectourethral malformations</td>
<td>13/35</td>
<td>37.1</td>
</tr>
<tr>
<td>Imperforate anus</td>
<td>12/34</td>
<td>35.3</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>9/27</td>
<td>33.3</td>
</tr>
</tbody>
</table>

DEVELOPMENTAL DEFICIENCIES OF PANCREATIC FUNCTION

It has been clear for many years that term newborns have a transient, physiologic pancreatic insufficiency that persists for a number of months. Historically, deficiencies in coefficients of absorption of fat were recognized 20 to 30 years ago. As pancreatic function (by balance and enzyme studies) in term and preterm infants were studied in greater detail and the systematic evaluation of human fetal material became more widespread, it became clear that the enzymes studied had a distinct course of maturation in terms of tissue content and concentration within the duodenum. Furthermore, it was shown that term and preterm infants do not respond to pharmacologic doses of secretagogues with an increase in intraduodenal enzyme content (Table 4).

Lipase activity is present in fetal pancreatic homogenates as early as 16 weeks of gestation, but even at term, only 10% of the adult concentration is attained (104). In duodenal fluid, its concentration in term or preterm infants is extremely low (17,51,54,70,113). Adult lipase concentrations are probably not attained until nearly 1 year of age. These data are supported by balance studies. Katz and Hamilton (48) found a coefficient of fat absorption of 58.3 to 88.7% in preterm infants. Similarly, Signer et al. (90) demonstrated that breast-fed infants had a higher coefficient of fat absorption than bottle-fed infants (76 and 60%, respectively). Adult coefficients of fat absorption are not attained until 4 to 6 months of age (24). Recently, Gaskin et al. studied lipase and colipase secretion during childhood and delineated patients with steatorrhea secondary to relative colipase deficiency (25).

Amylase is essentially absent in fetal pancreas and duodenal fluid of infants less than 6 months of age (17,51,104,113). Paradoxically, pancreatic amylase is present in amniotic fluid from about 16 weeks of gestation (71). Despite the pitfalls associated with carbohydrate balance studies, most infants seem to tolerate moderate starch loads, presumably through recruitment of alternate compensatory pathways of starch digestion (55).

Pancreatic proteases are first detectable in homogenates at 26 weeks of gestation and are at least 10 to 60% of the adult value at term (17,51,104). It is important to note that the appearance of proteases coincides with the detection of enterokinase. Clinical balance studies reveal less severe limitations of protein retention than those for fat (8,42).

Infants less than 1 month of age do not respond with an increase in protein, protease, lipase, or amylase concentrations within the duodenum following stimulation of the exocrine pancreas with cholecystokinin or secretin (54). Although the exact time course of the maturation of the response to secretagogues is not known, most infants have an attenuated response, manifest by an early rise followed by rapid dilution, within the first several months of postnatal life. A mature response is most probably not attained prior to approximately 1 year of life. The mechanism of the lack of responsiveness to stimulation seems to be related to a deficit in either receptor number or affinity. Werlin and Stefaniak (107) have shown that in the suckling rat pancreatic slice model, calcium ionophore mediates an adequate release of pancreatic enzymes. This implies that at least for the group of receptors for which cholecystokinin is the model, postreceptor events seem to be intact. It is unclear whether the secretin class of receptors is at a similar stage of maturity at this time in this model or whether these findings can be duplicated in other species, including humans.

In summary, in humans the newborn is endowed with a transient physiologic pancreatic insufficiency characterized by low or absent amylase concentrations, minimal lipase concentrations, and adequate protease concentrations in duodenal fluid. In addition to low basal concentrations, no further incremental increase is obtained after a meal or secretagogue administration. The timing of maturation is unclear but is most probably at about 1 year of age.

Isolated Enzyme Deficiency

Isolated deficiencies of exocrine pancreatic enzymes are listed in Table 5.

TABLE 4. Physiologic developmental pancreatic insufficiency

<table>
<thead>
<tr>
<th>Basal fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate pH</td>
</tr>
<tr>
<td>Absence of amylase</td>
</tr>
<tr>
<td>Low lipase</td>
</tr>
<tr>
<td>Proteolytic enzymes adequate</td>
</tr>
</tbody>
</table>

Response to meal or secretagogues

<table>
<thead>
<tr>
<th>Absent for first several months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probably normal prior to 1 year of age</td>
</tr>
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</table>
TABLE 5. Isolated exocrine pancreatic enzyme deficiency

<table>
<thead>
<tr>
<th>Lipase</th>
<th>Lipase-collipase</th>
<th>Colipase</th>
<th>Amylase</th>
<th>Trypsinogen</th>
<th>Enterokinase</th>
</tr>
</thead>
</table>

**Congenital Lipase Deficiency**

Congenital deficiency of pancreatic lipase is rare (21,22,69,77,87). The etiology of this isolated deficiency is not known. Both sexes are affected, and the suggested mode of inheritance is autosomal recessive (87).

**Clinical Picture**

Severe steatorrhea is the dominant symptom. Stools are offensive, foul-smelling, bulky, and contain oil droplets. Soiling may occur between defecation and is typically oily. The steatorrhea starts early in life, and despite the maldigestion and malabsorption of dietary fat, failure to thrive is not a major feature. No signs of anemia or abdominal distention are present.

**Pathophysiology**

When pancreatic lipase is absent or concentrations low, the hydrolysis of the 1 and 3 ester bonds of the triglyceride molecule is deficient. Despite the severe steatorrhea that occurs in isolated lipase deficiency, the patients thrive and are not malnourished. This is most probably due to activation of some alternative pathway of fat digestion (35). Support for this concept comes from the surgical literature where a coefficient of fat absorption of 40% even after pancreatectomy has been documented (47). Recently (41) minimal pancreatic lipase secretion was found to be compatible with normal fat digestion and absorption if lipase concentrations are greater than or equal to 2% of the mean for normal subjects. Lingular and gastric lipase, phospholipase A₂, bacterial lipolysis, and intracellular lipase from sloughed enterocytes may provide sufficient lipolytic activity to prevent fatty acid deficiency and growth failure owing to pancreatic lipase deficiency (22). In congenital lipase deficiency, pancreatic phospholipase A₂, colipase, and bicarbonate secretions are believed to be normal. The residual lipase activity found in the duodenal fluid is believed to be due to lingual lipase. Additionally, no pancreatic lipase has been detected by immunologic means (23), suggesting a major structural alteration resulting in either the loss of the antigenicity of the lipase molecule or complete absence of the enzyme.

**Diagnosis**

The pancreozymin-secretin test reveals low or absent lipase activity. The amylase and trypsin activity may be normal or minimally decreased. Quantitative determination of stool fat is not severely abnormal despite the suspicion of steatorrhea.

**Treatment**

The goals of therapy are to replace the deficient enzyme and to use a suitable diet to bypass the enzymatic deficiency. A wide array of pancreatic enzyme preparations are available for use. We prefer the enteric-coated microspheres and monitor the dosage requirements based on the stool volume and consistency. To bypass the specific activity of the pancreatic lipase, long-chain fats should be replaced with medium-chain triglycerides (45).

**Combined Lipase-Colipase Deficiency**

Ghislan et al. (28) reported a patient with combined lipase-colipase deficiency. This patient had <2% of normal control values for these enzymes; however, normal concentrations of trypsin and bile salts were found, and duodenal pH was alkaline. Despite these deficits, the coefficient of fat absorption was 50% prior to treatment (at 5 months of age) and improved to 82% with pancreatic enzyme replacement. More recently, the first congenital combined lipase and colipase deficiency was reported in two brothers of Arab origin (57).

**Isolated Colipase Deficiency**

Isolated colipase deficiency has been reported in two brothers who presented with steatorrhea at the age of 5 and 6 years and was not associated with either short stature or failure to thrive (40). Pancreatic function studies revealed normal amylase, chymotrypsin, lipase, and bile salt concentrations. Fat balance studies were 49 and 52% respectively, prior to supplementation and improved to 95 and 88%, respectively, with enzyme supplementation. Similarly, [1⁴C] triolein breath tests improved markedly with purified colipase administration. This condition must be differentiated from relative colipase deficiency as a cause of steatorrhea (25,7).

**Congenital Amylase Deficiency**

The existence of isolated pancreatic amylase deficiency is controversial. An abnormally low amylase activity prior to the age of 1 year may represent a physiologic phenomenon of exocrine pancreatic maturation. Selec-
tive deficiency not related to development has, however, been reported (59,64). In 1951 Lowe and May (59) reported a 13-year-old boy with absent amylase, diminished trypsin, and normal lipase. In this patient no starch tolerance test or pancreatic stimulation test was performed. The fact that two pancreatic enzymes were low, that a sweat test was not reported, and that no skeletal survey or repeated complete blood counts were performed puts the diagnosis of isolated amylase deficiency in this patient in doubt.

Several patients from one family were reported by Martin du Pan and Infante (64) in whom deficiency persisted beyond 1 year of age. Clinically, the children had diarrhea and failure to thrive. The result of a starch-loading test was consistent with the diagnosis. When reinvesterigated at 16 years of age, one of these patients had normal duodenal amylase levels (33).

Hodorn (33) mentions in a review article two additional children who at the age of 2 years had low duodenal amylase levels, which normalized at the age of 3 years. An additional case reported by Lilibridge and Townes (58) represents the classic maturation curve of pancreatic amylase. The infant, who had absent duodenal amylase levels at 4 months of age, had low basal levels at the age of 1 year but tolerated starches by that age.

The lack of a comprehensive evaluation of these patients and more accurate laboratory methods have raised doubts regarding the actual existence of an isolated amylase deficiency in these or other patients. This controversy has resulted in omission of this entity in many of the recent textbooks dealing with this subject (31,91). In view of the physiologic pancreatic deficiency described above, we suggest the criteria listed in Table 6 for the diagnosis of isolated amylase deficiency.

Further studies and long-term follow-up are needed to investigate the nature of the defect to determine whether the amylase deficiency represents an exaggerated variant of the physiologic pancreatic amylase maturation or a life-long phenomenon.

### Congenital Trypsinogen Deficiency

Isolated trypsinogen deficiency is very rare. It was first described in 1965 (100), and since then only a few case reports have appeared in the literature (67,102). Townes et al. (102) suggest an incidence of 1 in 10,000, but the mode of inheritance is not known.

### Clinical Picture

All three children reported had a severe malabsorption syndrome associated with hypoproteinemia, edema, and anemia. The symptoms in each case started in the neonatal period. In one patient the presenting symptom was failure to gain weight by 1 month of age, followed by vomiting at 5 weeks of age. Edema developed at 5 months of age. In the other two patients the picture was similar, except that the edema presented at 8 weeks of age. Associated anomalies included imperforate anus in one patient and depigmentation of the hair in the other.

### Pathophysiology

The proteolytic enzymes of the exocrine pancreas are secreted in the inactive form and are activated in the duodenal lumen. Intestinal enterokinase activates trypsinogen, which in turn has the potential to activate the other proenzymes. Hence, trypsinogen, chymotrypsinogen, procarboxypeptidase, and proelastase are activated to trypsin, chymotrypsin, carboxypeptidase, and elastase, respectively. In isolated trypsinogen deficiency the activation cascade described is disrupted because of a lack of substrate (trypsinogen) for enterokinase. Alternate pathways of protein digestion represented by gastric pepsin,intestinal peptidases, and bacterial digestion are intact and minimize the magnitude of creatororhea in these individuals.

Congenital trypsinogen deficiency must be distinguished from congenital enterokinase deficiency. Since direct methods of measurement of enterokinase activity were not available at the time when the patients reported were studied, the relation of isolated trypsinogen deficiency to enterokinase deficiency has not been fully clarified.
Treatment

Two forms of treatment are available. One involves the use of an elemental diet containing protein hydrolysate, thus bypassing the deficiency of the protease activation. The second, more practical route, is the utilization of pancreatic extracts, thereby supplying exogenous trypsin. In each of the patients studied, a dramatic clinical response was reported.

Congenital Enterokinase Deficiency

The first case of isolated congenital enterokinase deficiency was described by Hadorn et al. in 1969 (34). Since then, an additional eight children have been reported (27,37,38,53,75,99). Four of the nine children were two pairs of siblings (38,53), suggesting that congenital enterokinase deficiency is an inherited disease.

Clinical Picture

In nearly all of the patients, the age of onset of symptoms was at birth, and the diagnosis was established prior to 1 year of age. The only exception is the patient described by Haworth et al. (37) in whom the diagnosis was made at 8 years of age. Diarrhea and failure to gain weight were consistent findings. Vomiting and edema were reported in 50% of the patients. Laboratory evaluation revealed the presence of hypoproteinemia in eight of the nine patients, anemia in two of three, and creatorexia in more than 50% of the children at presentation.

Pathophysiology

Enterokinase is an intestinal mucosal enzyme secreted in the duodenal lumen to activate the zymogen trypsinogen. When it is absent or severely diminished there is a lack of activation of procarboxypeptidase, chymotrypsinogen, and proelastase. Thus, the symptom complex seen with enterokinase deficiency is similar to that of trypsinogen deficiency. In the most recent report (27), enterokinase concentrations were low in mucosal homogenates, and the alteration in electrophoretic motility suggests a change in the molecular properties of the enzyme in the deficient patient. Similarly, no inhibitors of enterokinase were detected. Enterokinase activity in all of the reported patients was less than 10% ofagematched control values, and trypsin activity was low or absent but returned to normal after the addition of enterokinase. Patients with enterokinase deficiency show a tendency toward spontaneous improvement with age. This may represent a biological adaptation, resulting in development of alternate pathways in an attempt to bypass the congenital deficiency. This form of congenital enterokinase deficiency must be distinguished from secondary enterokinase deficiency reported in patients with small bowel mucosal injury suffering from chronic intractable diarrhea (53). The initial steatorrhea seen in the affected patients is probably secondary to their state of malnutrition (37) or results from the lack of trypsin, which is known to be required for colipase and phospholipase activation (19).

Diagnosis and Treatment

The diagnosis of enterokinase deficiency should be suspected in neonates or infants with failure to thrive, diarrhea, hypoproteinemia, and edema. A normal sweat test and normal small bowel histology should be followed by the pancreozymin-secretin test, which will show that the trypsin activity is low or absent. In order to diagnose enterokinase deficiency, trypsinogen activity must be present in normal concentration and intestinal enterokinase is absent or present in very low concentrations. Addition of exogenous enterokinase to the duodenal fluid activates the trypsinogen and results in an increase in the trypsin level. In the case of trypsinogen deficiency, the increase in trypsin activity after adding exogenous enterokinase does not occur. The patients respond very favorably to pancreatic extracts. Trypsin replacement bypasses the deficiency as it also does in children with trypsinogen deficiency, and the children respond dramatically. An elemental diet containing protein hydrolysate is also a useful treatment modality.

REFERENCES


59. Lowe CV, May DC. Selective pancreatic deficiency: absent amy-


