Hyperinsulinemic Hypoglycemia of the Neonate Associated with Persistent Fetal Histology and Function of the Pancreas

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Early in development, the fetal pancreas is characterized by the presence of two distinct generations of endocrine cells and a B-Cell mass that is unresponsive to acute changes in circulating glucose levels. Near the end of intrauterine development, the normal pancreas has "matured" and contains a single generation of endocrine cells and B-Cells that are responsive to changes in glucose concentrations. Recent microscopic examination of resected pancreatic tissue from an infant with hyperinsulinemic hypoglycermia revealed a combination of all three of the currently accepted findings in this neonatal condition: hyperplasia, adenomatosis, and nesidioblastosis. These observations prompted the following hypothesis: When compared to the usual histology of the developing pancreas, nesidioblastosis may be interpreted as an abnormal continuation of normal proliferation of endocrine cells; hyperplasia may be a specific overproduction of the Secondary Islands of Langerhans; and adenomatosis may be an abnormal continuation or overgrowth of the Primary Island of Langerhans. Such extrapolation suggests that infants with hyperinsulinemic hypoglycemia may represent a failure in the normal histological and functional maturation of the endocrine portion of the fetal pancreas.

THE ENDOCRINE CELLS of the human pancreas arise by differentiation from pancreatic ductal epithelium. Recognition of the endocrine function of these cells is based upon the histochemical localization of the specific hormone within the cell. In the human fetus this differentiation is recognized between the eighth and ninth week of gestation.

Morphology

Potter[12] has shown two distinct generations of islet cells evolving between the first and third trimester of human fetal development. The two generations have unique characteristics which allow their morphologic differentiation. The differences relate to; a) time for appearance, b) location, c) composition and, d) overall size.

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The first endocrine cells to appear in the eight- to nine-week-old fetus coalesce to form the Primary Islands of Langerhans. They are located within the connective tissue of the interlobular septum and contain an equal number of A and B Cells. They eventually exceed 85 microns in diameter, and by the fifth month of gestation are predominantly A-Cell in composition. During the fifth to seventh month of gestation, the Primary Islands of Langerhans degenerate, a process characterized by an intense lymphocytic infiltration.

The Secondary, and eventually permanent, Islands of Langerhans appear at the 16th week of gestation. These islet groups are situated within the pancreatic lobules in close association with the centroacinar ductule cells from which they arise. They are initially composed of equal numbers of A and B Cells, but the A-Cells appear to undergo a widespread degeneration during the seventh month, leaving the typical adult composition of a central preponderance of B-Cells ringed by a thin mantle of A and D Cells (Fig. 1).

Function

Normal fetal growth and development requires a continuous supply of glucose. This supply is provided by the mother and is under the control of the placenta. No cross-over of the pancreatic hormones between mother and fetus occurs.[7] The fetal pancreas exhibits little, it any, response to acute changes in fetal glucose levels. This is in spite of the early presence of fetal hormones at concentrations in excess of adult levels. The lack of responsiveness of fetal B-Cells to changes in glucose concentration is currently ascribed to an immaturity of glucose receptor sites on the fetal B-Cells. Why the glucose receptors fail to recognize glucose as a signifi-

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cant stimulus throughtout fetal development is unknown. Under normal circumstances, as term approaches, the B-Cell responsiveness "matures."[4,1,2]

With this brief review of the development morphology and function of the endocrine portion of the fetal pancreas, let us examine the clinical presentation of the infant with hyperinsulinemic hypoglycemia, as well as the current list of pathologic conditions associated with this clinical picture. The majority of infants with hyperinsulinemic hypoglycemia will display seizure activity during the first three months of life. Documentation of serum glucose levels below 40 mg/dl with simultaneous serum insulin levels of $\geq 12\mu$U/ml is the biochemical basis for exact diagnosis. Subsequent lack of successful medical control of the hypoglycemia is accepted as the indication for surgical exploration of the pancreas and subtotal pancreatectomy in this setting.[9,10,6]

The rationale behind subtotal pancreatectomy is simply to decrease the total mass of B-Cells in the hope of allowing maintenance of serum glucose levels sufficient to prevent further central nervous system injury. Since Graham's[8] initial report, experience has shown this resection must be in excess of 80% of the total pancreatic mass.

Upon proper pathologic examination of submitted specimens of pancreas, the three diagnoses associated with hyperinsulinemic hypoglycemia are: 1) Islet cell hyperplasia, 2) Islet cell adenoma or adenomatosis, and 3) Nesidioblastosis. The histologic requirement for the diagnosis of hyperplasia is the presence of increased endocrine cells within the normal intralobular distribution, mixed with pancreatic acinar cells. The diagnosis of an adenoma or adenomatosis requires identification of an isolated nodule or clumps of endocrine cells outside the lobule of pancreatic exocrine cells. Nesidio-

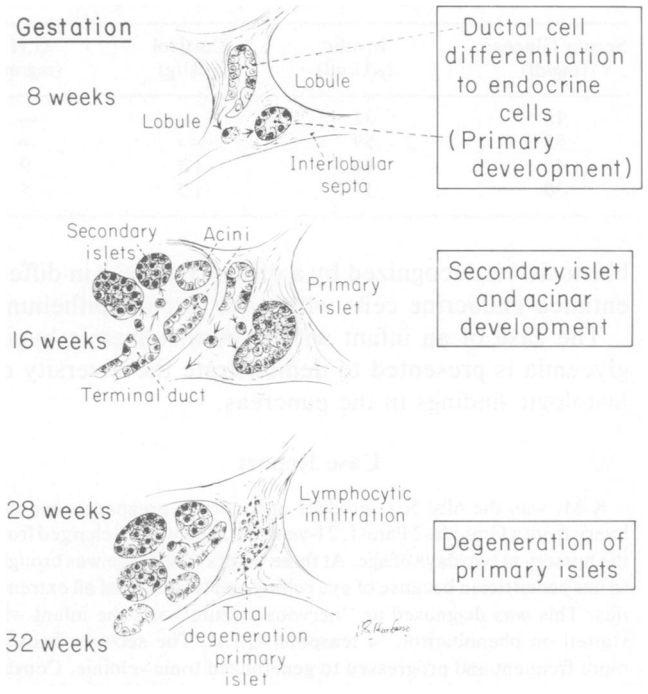

FIG. 1. Embryological development of pancreas. Differentiated endocrine cells arising from ductal epithelium form either intralobular secondary islet groups or interlobular primary islet groups. Normal development of pancreas results in degeneration of primary islets.

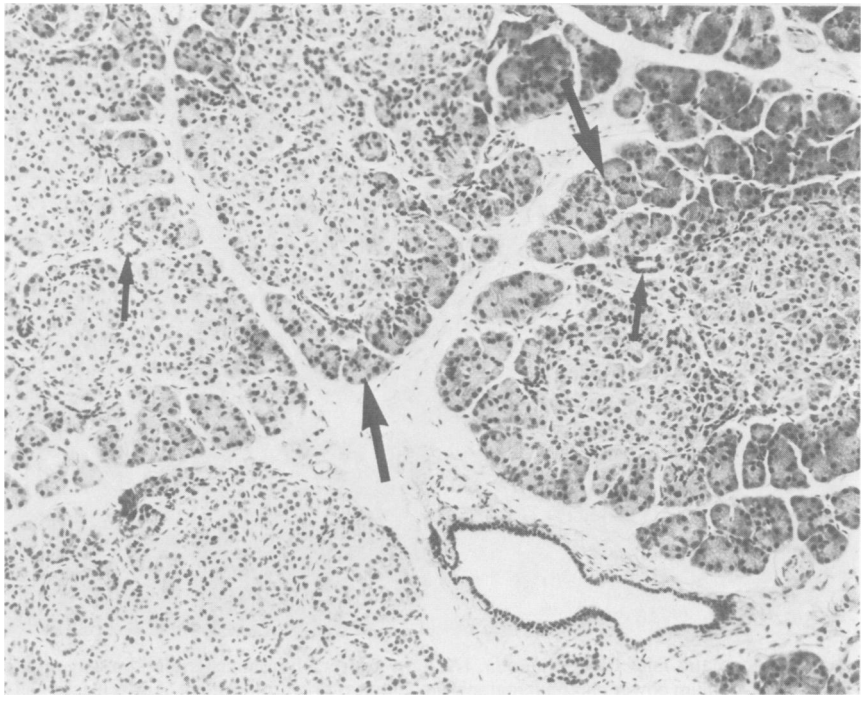

FIG. 2. Nesidioblastosis and islet cell hyperplasia. Note large nests of islet cells partially surrounded by residual pancreatic acinar tissue (large arrows). Small ductules (small arrows) can be seen within the nests of islet cells (Hematoxylin and eosin. ×140).

TABLE 1. *Laboratory Results of Blood Samples*

Serum Glucose (mg/dl)	Insulin (μU/ml)	Cortisol (μU/g)	G.H. (mg/ml)
15	32	—	—
33	59	—	—
10	61.5	1.1	9
30	17.7	1.5	5

blastosis[11] is recognized by a diffuse increase in differentiated endocrine cells within the ductal epithelium.

The case of an infant with hyperinsulinemic hypoglycemia is presented to demonstrate the diversity of histologic findings in the pancreas.

Case Report

K.M. was the 6lb. 5oz. product of a normal pregnancy and delivery from a Gravida-2 Para-1, 21-year-old. She was discharged from the nursery at two days of age. At three weeks of age, she was brought to her pediatrician because of eye rolling and twitching of all extremities. This was diagnosed as "nervous seizure" and the infant was started on phenobaritol, ¼ teaspoon Q.I.D. The seizures became more frequent and progressed to generalized tonic-cloinic. Consultation with a neurosurgeon resulted in concurrence with the diagnosis of a seizure disorder and continuation of the medication program. The infant was admitted to a local hospital at 11 weeks of age because of refractory seizure activity during which a CAT scan of the head and an EEG were normal. During this admission, hypoglycemia was first documented with serum glucose levels as low as 8 mg/dl. She was begun on a continuous intravenous solution of 10% dextrose and water. In spite of increasing concentrations of glycose, hypoglycemia continued to be documented both clinically with seizures and by serum glycose determination. She was then transferred to The Johns Hopkins Childrens Center. Her physical examination on admission was entirely normal. She was active, alert and able to focus on and follow objects. She was fed formula every two hours, without iv supplement with Dextrostix in the range of 45–90. After 18 hours of this program, her serum glucose was found to be 10mg. Laboratory results of blood drawn for growth hormone, cortisol and insulin over the following 24 hour period are shown in Table 1.

A glucagon stimulation test was carried out with elevation of serum glucose to 87 mg/dl at 10 minutes and 116mg/dl at 20 minutes. Oral diazoxide 5mg/kg/dose was started as well as intravenous infusion of 10% dextrose and water and q2° oral formula. Hypoglycemia continued on the above program and hydrocortisone 15mg/kg/day was added as well as an increase in diazoxide to 25mg/kg/day.

Failure to maintain serum glucose levels above 40 mg/dl prompted a decision to carry out an exploratory laparotomy and 80% pancreatectomy. The pancreas was normal in gross appearance except for a 0.5cm nodule on the superior anterior surface of the body. The nodule had a pink color initially but as the pancreatic resection progress from the tail towards the nodule it became progressively darker in appearance. The pancreas was transected at the level of the confluence of the splenic and mesenteric veins. The pancreatic duct was suture ligated wth 5-0, dexon and the spleen left intact.

Postoperatively, the infants' serum glucose reached a maximum of 400mg/dl eight hours after surgery and the intravenous glucose in-

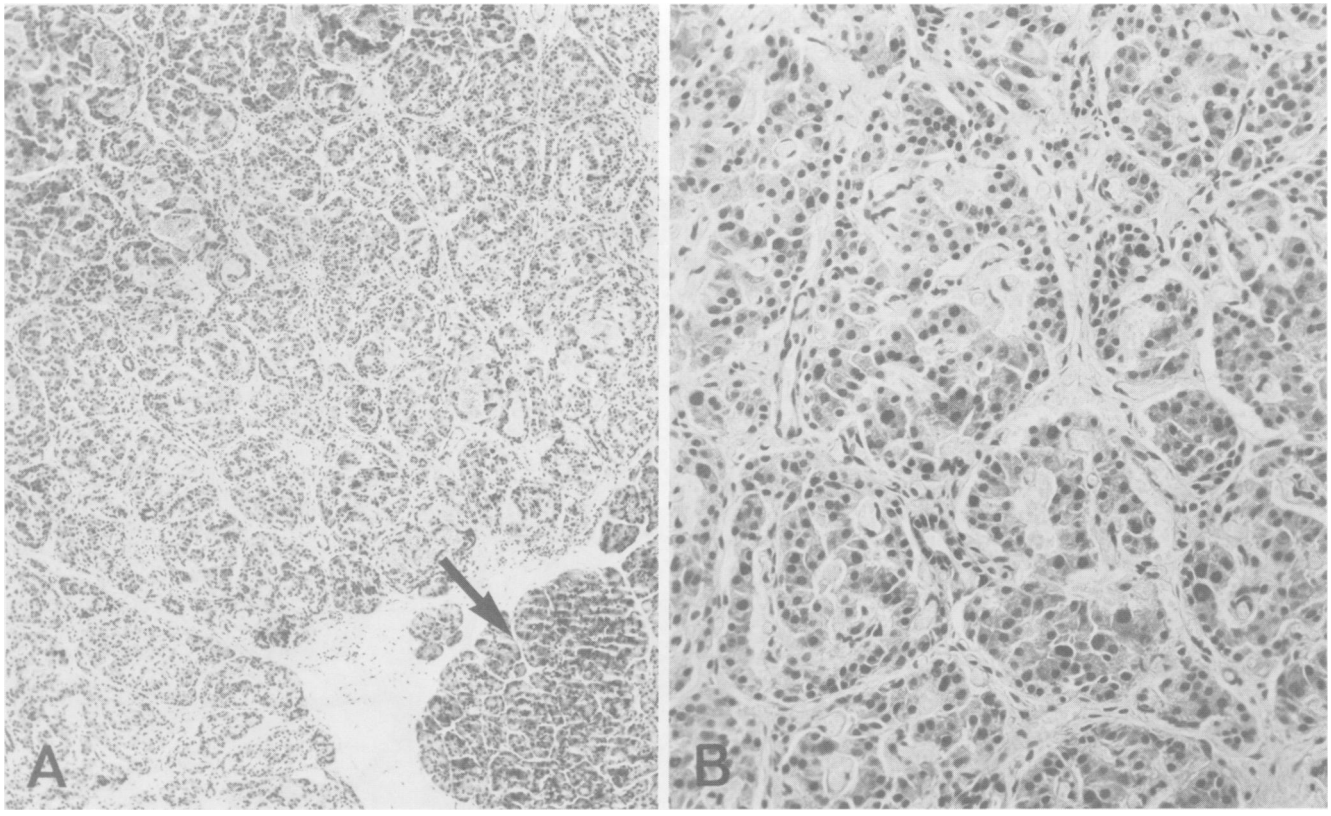

FIG. 3. Pancreatic Islet Cell Adenoma. (A) Low power photomicrograph showing islet cell adenoma and adjacent pancreatic acinar tissue arrow). (B) Medium power photomicrograph showing gyriform arrangement of cells in islet cell adenoma (Hematoxylin and eosin. A, ×100; B, ×280).

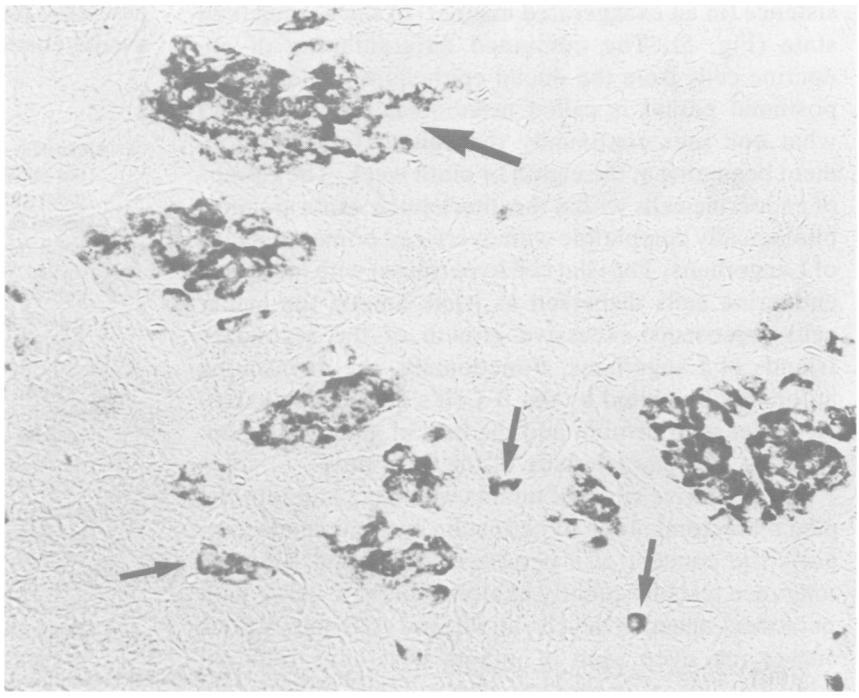

FIG. 4. Immunoperoxidase demonstration of diffuse increase in insulin-producing (dark-staining) cells within the pancreatic parenchyma. In addition to the slightly irregular islets (large arrow), numerous single positive cells and small clusters of positive cells (small arrows) can be seen (light green counterstain ×140).

fusion was decreased to 5% dextrose/water at 20cc hour. She was started on central venous hyperalimentation of 10% glucose, 2% Freeamine[R] and 10% Intralipid[R] 24 hours after surgery which was calculated to deliver 150cal/kg/24°. This was continued for a period of two weeks during which time her serum glucose remained between 90 and 130mg/dl. Serum insulin values were between 2 and 7μU/ml. Her transition to enteral alimentation between the second and third week was uneventful and she was discharged on a diet of 6oz. of Similac[R] and iron.

Follow-up endocrine evaluation demonstrated a mildly diabetic glucose tolerance curve with insulin response to the glucose delayed to 120 minutes with a maximum of 8μU/ml. Human growth hormone continued to be below normal for her age at 6mg and 3mg/ml. The child remains in the sixtieth percentile for height and weight but she has demonstrated appropriate developmental milestones in the ensuing six month period.

Comment

Employing hormone specific immunoreactive staining techniques for analysis of the pancreas removed from this patient, the following results were obtained: 1) Extensive areas of increased endocrine cells within the pancreatic lobule mixed with normal appearing acinar cells, typical of islet cell hyperplasia (Fig. 2), 2) A large, grossly identifiable islet adenoma located within the interlobular connective tissue (Figs. 3a and b), and 3) Larger numbers of insulin containing cells within the ductal epithelium (Fig. 4).

By definition, this infant suffered from all three pathological conditions in the pancreas. However, viewing this case from the known embryologic development of the pancreas, one can interpret these findings as a per-

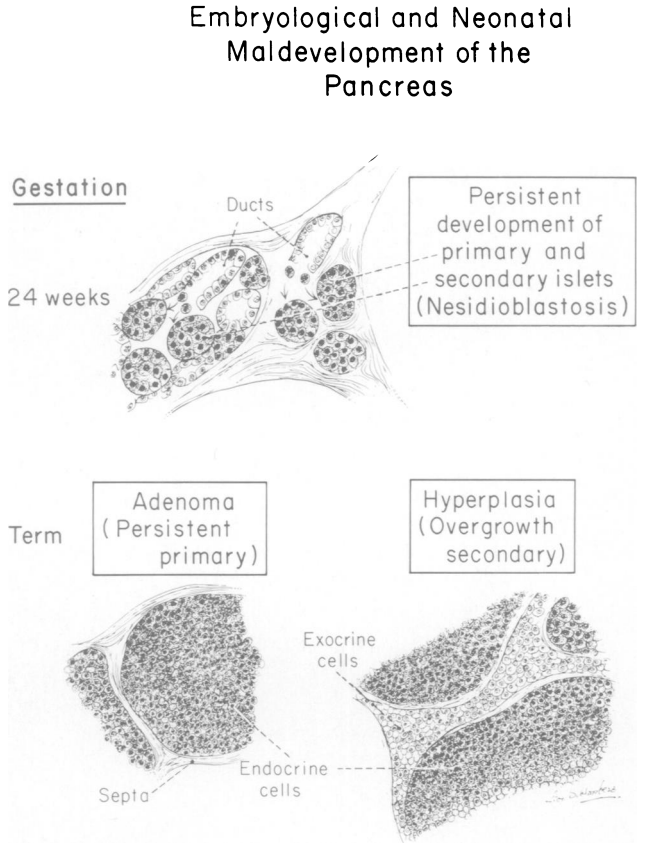

FIG. 5. Continued or accelerated differentiation of endocrine cells from dectal epithelium and failure of degeneration of primary islet groups may result in the increased pancreatic endocrine cell mass associated with neonatal hyperinsulinemic hypoglycemia.

sistence (in an exaggerated manner) of the normal fetal state (Fig. 5). The continued differentiation of endocrine cells from the ductal epithelium (which in the postnatal period is called nesidioblastosis) is in fact what one sees continually throughout fetal development beginning at the eighth or ninth week. The clumps of endocrine cells within the interlobular septa are morphologically compatible with oversized primary Islands of Langerhans. The islet cell hyperplasia with increased endocrine cells dispersed as islets among the acinar cells represents excessive growth of the secondary Islands of Langerhans. Functionally, the devastating autonomy exhibited by the B-Cell's continuous excessive release of insulin, and the lack of glucose responsiveness are characteristic of the fetal state.

Postoperative study of infants who have had subtotal pancreatectomies for hyperinsulin hypoglycemia supports the concept of a persistent fetal state. Glucose tolerance tests frequently exhibit a diabetic curve with persistent glucose levels at 90 and 120 min.[3] Such curves are even seen in infants who have required adjuvant diazoxide therapy after surgery to lower insulin levels. The apparent lack of glucose receptor responsiveness reflects the continued primitive autonomy of the remaining B-Cell mass.

Therapy for this challenging problem continues to be dependent upon arbitrary surgical reduction of the total pancreatic mass. Future therapy may well involve induction of maturation of the endocrine portion of the newborn pancreas, but obviously this forward step awaits elucidation of a maturation factor or factors.

References

1. Alexander DP, Britton HG, Nixon DA. Further observation on the administration of anti-insulin serum to lambs in the perinatal period. Biol. Neonate 1971; 19:451.
2. Aspluna K. Dynamics of insulin release from the fetal and neonatal rat pancreas. Eur J Clin. Invest. 1973; 3:338.
3. Crowder WL, MacLaren NK, Gutberlet RH, et al. Neonatal pancreatic b-cell hyperplasia report of a case with failure of diasoxide and benefit of early subtotal pancreatectomy. Pediatrics 1976; 57:897.
4. De Los Monteros A, Driscoll SG, Steinke J. Insulin release from isolated human fetal pancreatic islets. Science 1970; 168:111.
5. Ferner J, Stoechenius W, Jr. The a and b cells of the pancreatic islets as sources of antagonistic hormones glucagon and insulin: the shift of a-b relation in diabetes mellitus. Am J Dig Dis 1953; 20:301.
6. Fonkalsrud EW, Trout HH, Lippe B, et al. Idiopathic hypoglycemia in infancy. Surgical management Arch Surg 1974; 108:801.
7. Gabbe SC, Quilligan EJ. Fetal carbohydrate metabolism: it's clinical importance. Am J Obstet Gynecol 1977; 127:92.
8. Graham EA, Hartman AF. Subtotal resection of the pancreas for hypoglycemia. Surg Gynecol Obstet 1934; 59:474.
9. Hamilton JP, Baker L, Kaye R, Koop CE. Subtotal pancreatectomy in the management of severe persistent idiopathic hypoglycemia in children. Pediatrics 1967; 39:49.
10. Harken AH, Filler RM, Avruskin TW, Crigler JR, Jr. The role of "total" pancreatectomy in the treatment of unremitting hypoglycemia of infancy. J Pediatrics Surg 1971; 6:287.
11. Heitz PU, Kloppel G, Hacki WH, et al. Nesidioblastosis: the pathologic basis for persistent hyperinsulinemic hypoglycemia in infants. Diabetes 1977; 26:632.
12. Liu HM, Potter EL. Development of the human pancreas. Arch Pathol 1962; 74:439.