Relevance of Endocrine Pancreas Nesidioblastosis to Hyperinsulinemic Hypoglycemia

Whereas surgery often concludes the saga of hypoglycemia, the pathologist has the final word. In children and occasionally in adults, that word usually is *nesidioblastosis,* a somewhat ill-defined and nebulous diagnosis (1–6). Exactly what is nesidioblastosis? Does it represent any sort of pathology at all?

More than 30 years after the initial description of infantile hypoglycemia by McQuarric (7), the pathogenesis of hyperinsulinism remains unclear in most cases. Few resected glands from these hypoglycemic infants show focal lesions: they either consist of a true adenoma exhibiting a compact ribbonlike pattern reminiscent of that observed in islet cell tumors of adults or of focal adenomatous hyperplasia. Surgical resection limited to the lesion is usually followed by disappearance of the hypoglycemia, which indicates that the focal abnormality was the cause of the hyperinsulinism.

In most cases, however, no focal lesion is detectable. Instead, a diffuse and disseminated proliferation of islet cells budding off from pancreatic ducts is usually observed and has been proposed repeatedly as the underlying pathological lesion (8–12,14–17). The term *nesidioblastosis,* currently used to describe this condition, was originally coined by Laidlaw (18) because pancreatic endocrine tumors originate from nesidioblasts, the stem cells that differentiate from the duct. Subsequently, Yakovac (9) defined nesidioblastosis as a continuous differentiation of β-cells from the ductular system of the exocrine pancreas.

Several recent studies that used quantitative immunohistochemical techniques have demonstrated that endocrine cells in close contact with ducts (nesidioblastosis) can also be observed in normoglycemic infants and young children and thus are not pathognomonic for the disease (15–21). Unfortunately, nesidioblastosis is a morphologic parameter difficult to quantitate, particularly in the neonatal and infantile pancreas in which scattered endocrine cells or small clusters are numerous. Even when careful morphometric studies have been performed, it cannot be certain that these morphologic findings are more prominent in hypoglycemic than in normoglycemic infants. On the other hand, precise quantitative studies have established that the total pancreatic mass of endocrine cells is not increased in hyperinsulinemic infants (30). Furthermore, more numerous small endocrine clusters in hypoglycemic than normoglycemic infants might reflect an abnormality in the formation of true islets (nesidiodysplasia) rather than a continuous proliferation and differentiation of endocrine cells (19–21).

Note that normoglycemia can occur in various individuals having a wide disparity in endocrine cell mass (20). Therefore, it is difficult to reconcile how a small increase in β-cell mass could cause hyperinsulinemic hypoglycemia, assuming the β-cells are functionally normal. The frequent recurrence of hypoglycemia after 60–80% pancreatic resection also suggests that a factor other than increased β-cell mass is involved.

Because somatostatin has been shown to inhibit insulin secretion, a quantitative deficiency of δ-cells (or a loss of cellular contacts between β- and δ-cells) has been incriminated as the etiology of the disease (22–25). Several studies have demonstrated a reduced density of δ-cells in hypoglycemic infants. However, this reduction is not present in all infants and must be interpreted with caution, because degranulation of δ-cells may impair immunohistochemical detection. An apparently normal topographic relationship between insulin and somatostatin cells in these cases has been reported, but abnormalities in the intercellular communications have not been excluded (6).

Several groups have observed abnormally large β-cell nuclei in these infants (8,19,26–31). This observation also suggests the existence of functional abnormalities, because the size of the nucleus may reflect the functional activity of endocrine cells (32). In a series of 16 infants with hyperinsulinism and hypoglycemia, such an increase of β-cell nuclear volume was demonstrated by morphometry in all cases without focal lesions. Indeed, increased β-cell nuclear volume may constitute a morphologic criterion useful in differentiating focal from diffuse lesions; although similarly large nuclei have been observed in adenomas, they appear in such cases to be restricted to the focal lesion (30). Hypertrophic β-nuclei are also present in the pancreas glands of infants born to diabetic mothers. Whether these nuclear features observed in hyperinsulinemic infants reflect a primary abnormality of the β-cells or whether they are secondary to a loss or an impairment of the mechanisms controlling β-cell function remains to be established.

In this issue, Fong et al. (p. 108) remind us that hyperinsulinemic hypoglycemia without endocrine tumor also occurs occasionally in adults (1–6). In adults and children, nesidioblastosis repeatedly has been proposed as the morphologic abnormality responsible for the hyperinsulinism. However, nesidioblastosis has been observed in normoglycemic adults in whom the frequency of ductuloinsular complexes has been quantified (33). Similarly, nesidioblastosis has been reported in association with several clinical conditions without hyperinsulinemic hypoglycemia (e.g., cystic fibrosis, chronic pancreatitis, overweight, endogenous hypergastrinemia, congenital heart malformation, deficiency of α_1-proteinase inhibitor, and androgen therapy; (34–40). Therefore, it appears that the presence of endocrine cells budding off from ducts or of small clusters of β-cells scattered throughout the exocrine pancreas is not suffi-

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cient to explain excessive insulin release. In certain conditions, nesidioblastosis could reflect β-cell replication compensating for β-cell destruction (chronic pancreatitis) or functional insufficiency. In such cases, it might represent a compensatory mechanism for normalizing the functional β-cell mass. Note that nesidioblastosis has also been reported in a patient with hyperinsulinemic hypoglycemia caused by ingestion of chlorpropamide, although whether nesidioblastosis represented an associated or secondary phenomenon in this case is unknown (41).

Finally, nesidioblastosis with hyperinsulinism might reflect a secondary response to some unrecognized stimulating factor or, conversely, a peculiar responsiveness of the endocrine pancreas to normal stimuli.

The coexistence of hyperinsulinemic hypoglycemia and nesidioblastosis does not prove that they are causally related. Because human pancreatic kinetic studies are still lacking, whether nesidioblastosis reflects accelerated endocrine cell replication is even uncertain.

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