Hyperinsulinemic Hypoglycemia with Nesidioblastosis after Gastric-Bypass Surgery

TO THE EDITOR: The causal links between bariatric surgery and pancreatic nesidioblastosis are unclear. Service et al. (July 21 issue) suggest a link between nesidioblastosis and glucagon-like peptide 1 (GLP-1), since GLP-1 causes beta-cell expansion in animal models of diabetes. GLP-1 and the incretin mimetic exenatide enhance insulin secretion in a glucose-dependent manner. Similarly, incretin-induced beta-cell expansion appears to be glucose-dependent. It is relevant that studies of two years’ duration in normal mice and rats of exenatide at doses of more than 100 times those given to humans showed no pathological changes in the islets (data on file, Amylin Pharmaceuticals); a study of nine months’ duration in healthy cynomolgus monkeys at doses of more than 400 times those used in humans showed minimal-to-mild islet hypercellularity with no increase in islet size (data on file, Amylin Pharmaceuticals). There have been no reports of recurrent, severe hypoglycemia or of nesidioblastosis in patients with type 2 diabetes mellitus during more than 2670 patient-years of exposure to exenatide. Given that neither experimental nor clinical evidence suggests that GLP-1 or exenatide induces nesidioblastosis, and given the multiple hormonal and metabolic changes that occur after bariatric surgery, we would suggest that the link between bariatric surgery and nesidioblastosis is multifactorial. Further study may lead to insights concerning the regulation of beta-cell function and growth.

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TO THE EDITOR: Service et al. suggest a causal relationship between gastric bypass and nesidioblastosis, and Cummings, in the accompanying editorial, comments on the suggestion. The most obvious explanation, however, has not been sufficiently disproved — that the immediate malabsorptive effects of gastric bypass may rapidly induce a metabolic imbalance (because of the rapid reduction of 44 percent in body-mass index [BMI; the weight in kilograms divided by the square of the height in meters]) and that these changes may interrupt the negative-feedback–controlled steady state present before surgery between obesity-related insulin resistance and hyperinsulinemia and beta-cell hyperplasia. I think the authors should have demonstrated an absence of adaptive changes before gastric bypass. The findings in Patient 1 (of insulinoma) and in Patient 5 (of preexisting symptoms) directly contradict the conclusions of Service et al. To show a cause-and-effect relationship, the total beta-cell volume should be determined in a larger number of obese controls who have not undergone gastric-bypass surgery and who are selected on the basis of matching BMI values and insulin resistance before gastric bypass, not on the basis of normal size of islets. With a BMI of 33.2 to 36.3, the concurrent controls were substantially less obese than the index subjects before gastric bypass (BMI, 44.4 to 62.5). Unfortunately, pancreatic tissue obtained from such persons is available only rarely. Therefore, further elucidation of the issue will require longitudinal studies of insulin function in patients undergoing gastric-bypass surgery.
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THE AUTHORS REPLY: Dr. Carpenter and colleagues and Dr. Kaiser make important observations germane to speculation regarding the pathogenesis of endogenous hyperinsulinemic hypoglycemia in some patients who have undergone Roux-en-Y gastric-bypass surgery. Indirect evidence led us to implicate the potential mediation of beta-cell–trophic agents such as GLP-1, which appears to be present in increased concentrations after this type of surgery. We concur with Dr. Carpenter and colleagues that a cause-and-effect relationship has not been established. Thus, if their observations prevail, GLP-1 may not be relevant in this context. Dr. Kaiser emphasizes both the importance and the difficulty of obtaining perfectly matched (according to BMI) control pancreatic tissue from obese patients who have not undergone gastric bypass and thereby brings into question whether beta-cell hyperfunction was a consequence of the surgery or persisted despite the postoperative weight loss. A recently published finding that normal insulin secretion resumes after bariatric surgery in patients who do not have hypoglycemia suggests that some as yet unidentified mechanism becomes operative after gastric-bypass surgery and results in hyperinsulinemic hypoglycemia in some patients. We agree that further studies of beta-cell growth and function before and after bariatric surgery are needed.

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THE EDITORIALIST AND COLLEAGUES REPLY: Dr. Kaiser challenges the suggestion of a causal relationship between Roux-en-Y gastric-bypass surgery and nesidioblastosis. Although this link is unproven, growing evidence supports it. Nesidioblastosis is extremely rare and almost never develops in adulthood. Among the confirmed cases in the study by Service et al., patients who had undergone Roux-en-Y gastric-bypass surgery were more likely — by a factor of 400 — to have nesidioblastosis than the general population. Another group has subsequently published similar findings, and we know of two additional centers with parallel observations. Dr. Kaiser argues that adaptive beta-cell hypertrophy in obese persons who have insulin resistance might cause hypoglycemia when postoperative weight loss improves insulin sensitivity. Although this is plausible, purely restrictive bariatric operations are not associated with nesidioblastosis and do not cure diabetes so rapidly or so often as Roux-en-Y gastric-bypass surgery, despite causing massive weight loss. Dr. Kaiser’s hypothesis would ideally be tested by longitudinally assessing islet histology after gastric bypass, or at least by measuring total beta-cell volume in equally obese controls who have insulin resistance and who have not undergone gastric bypass. Although the inaccessibility of human pancreatic tissue hinders such experiments, new animal models of gastric bypass might make such an investigation easier. Moreover, the multicenter Longitudinal Assessment of Bariatric Surgery trial will perform serial examinations of insulin secretion and action in patients undergoing Roux-en-Y gastric-bypass surgery.

Dr. Carpenter and colleagues dispute the suggestion that GLP-1 has a dominant causative role in post–gastric bypass hyperinsulinemic nesidioblastosis. We concur. GLP-1 can stimulate beta-cell growth in animals, and theoretically, GLP-1 levels might increase after gastric-bypass surgery. However, although GLP-1 increases after jejunoileal bypass and biliopancreatic diversion, recent assessments of modern, proximal gastric bypass in humans and rodents report unchanged levels. Furthermore, GLP-1 does not stimulate insulin secretion without concomitant hyperglycemia. Together with evidence provided by Dr. Carpenter and colleagues, these find-
ings suggest that factors beyond GLP-1 stimulate beta cells after Roux-en-Y gastric-bypass surgery. For example, decreased ghrelin levels could contribute, and animal studies implicate an unknown factor from the proximal intestine. This physiology, it is important to note, benefits most patients with diabetes who undergo gastric bypass, and overshoot is exceedingly rare. Even if GLP-1 occasionally contributes to beta-cell hypertrophy in persons with a predisposition — as suggested by extremely high levels in two cases of nesidioblastosis after gastric bypass — the risk associated with pharmacologic stimulation of only the GLP-1 pathway is substantially less than that due to the multifactorial effects of Roux-en-Y gastric-bypass surgery. Beta-cell overgrowth caused by GLP-1–receptor agonists has never been reported, and if it ever occurs, it should resolve with discontinuation of the drug, which is far easier than a reversal of Roux-en-Y gastric-bypass surgery.

**Lung-Cancer Screening**

TO THE EDITOR: Mulshine and Sullivan (June 30 issue) note the high proportion of cancers detected by screening at stage 1. As they acknowledge, however, this proportion cannot be used to indicate the efficacy of screening, which requires a corresponding reduction in the absolute number of advanced lung cancers. Earlier controlled trials, using standard radiography, failed to achieve this effect. Preliminary analyses of trials that used low-dose computed tomography (CT), although inconclusive, show no diminution in advanced cancers in the incidence screens as compared with controls. This failure may reflect the proximal endobronchial origin of many cancers (for which CT scanning is relatively insensitive) or the rapid growth of advanced lung cancers.

Contrary to the suggestion of the authors, overdiagnosis of clinically insignificant lung cancers remains a concern with screening. Overdiagnosed lung cancers need not differ biologically from lethal cancers: a tumor of 0.5 g with a diameter of 1 cm and a volume-doubling time of 300 days (the mean value for malignant nodules <3 cm) would require 8 years to achieve a lethal size of 10 cm, during which interval some elderly people who smoke will die from competing illnesses.

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THE AUTHORS REPLY: The issue of overdiagnosis has recently dominated discussions regarding...