Comment on: Butler et al. Marked Expansion of Exocrine and Endocrine Pancreas With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors. Diabetes 2013;62:2595–2604

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In the July issue of *Diabetes*, Butler et al. (1) described histopathologic findings of potential concern in pancreatic tissue obtained at time of death from 8 patients who were reportedly treated with "incretin" -based therapies (sitagliptin or exenatide). A small number of pancreata from diabetes patients and nondiabetic subjects served as controls. We acknowledge the importance of questions that pertain to human safety with newer glucose-lowering agents, and we appreciate the difficult and labor-intensive nature of this study (1). There are several limitations of the reported work that warrant comment.

Firstly, the number of pancreas samples examined was very small; from 7 sitagliptin-treated patients and 1 exenatide-treated patient. A number of demographic characteristics, which might be critical to the analysis, were different between incretin-treated and control subjects. One-half of the control diabetes patients had a short duration of disease (<5 years) versus only 1 of 8 of the incretin patients; the severity of disease was also clearly different—5 of 12 control diabetes patients were receiving no antihyperglycemic therapy. The 8 incretin-treated patients were also significantly older (~18 years) than the diabetes control group. The age difference may be particularly relevant given the known correlation between older age and increased PanINs (pancreatric intraepithelial neoplasias) (2,3). In addition, 2 of 12 control diabetes patients may have had type 1 diabetes, as DKA (assumed to indicate diabetic ketoacidosis) was listed as a contributing cause of death.

Secondly, it is important to note that evidence of proliferation involving multiple islet cell types and ductal cells, the key observation of this study, has been reported in pancreata obtained from organ donors after periods of life support (mechanical ventilation) of greater than 2–3 days in duration (4). Thus, it would be relevant to control for variables relating to preterminal care in studies that examine histology of the pancreas.

Thirdly, the approach to statistical analysis in this study also raises concerns. The data are not sufficient to establish causal relationships because of the many important confounders and the absence of baseline information. For example, the original analysis of pancreas weight analysis did not adjust for any reported covariates, and the reported covariates are not balanced. When the data are reanalyzed, after adjustment for covariates including BMI, duration of diabetes, sex, and age by a linear regression model, pancreas weights are not significantly different between incretin-exposed versus -nonexposed patients with diabetes (P value = 0.119), or the incretin group versus nondiabetic subjects (P value = 0.598). Interestingly, BMI and sex effects (independent of incretin use) were significantly associated with pancreas weight. Our analysis of these data also yields a significant (P value = 0.028) increase in pancreas weight associated with metformin use per se. Furthermore, if one excludes the two control patients where DKA is listed as a cause of death or if one excludes two other possible type 1 patients (insulin-requiring where the onset of diabetes occurred at age less than 20 years), the differences (in particular pancreas weight and α-cell mass) are no longer statistically different. We also noted that data pertaining to PanINs were presented as a pooled analysis of frequency for two types—PanINs 1 and 2—without providing data for each type or individual patient data (which were provided for several other parameters).

Finally, Butler et al. (1), citing their own previous work in mice (5), suggest that chronic pancreatitis is an underlying driver for dysplasia, yet there was no evidence presented in the current study (histology or clinical history) to suggest that this disorder was present. In addition, no cases of acute pancreatitis or pancreatic cancer were reported. The authors neglect to cite other work that examined dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide 1 (GLP-1) analogs in preclinical toxicology studies. Several such studies—with both classes of agents—have failed to detect evidence of inflammation or dysplasia involving the pancreas; importantly, these studies also recently include an assessment of effects in models of type 2 diabetes (6–8). In attempting to explain the possible finding of α-cell hyperplasia, the authors cite sources (references 23–25 in Butler et al. [1]) that describe this phenomenon as a response to ablation of

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glucagon receptor–mediated signaling. Complete blockade of glucagon action is uniformly associated with marked hyperglucagonemia whereas glucagon levels are typically modestly suppressed by DPP-4 or GLP-1 analog therapy. To our knowledge, there are no reports of pancreatic α-cell hyperplasia or hyperglucagonemia as a consequence of either DPP-4 inhibition or GLP-1 analog administration in controlled toxicology or clinical studies involving any species examined to date.

Given such limitations as those discussed above, the data presented in the article by Butler et al. (1) do not adequately support the conclusion that the observed histopathologic findings can be attributed to prior therapy with sitagliptin or exenatide. The choice of therapeutic agents for the treatment of diabetes must always include a careful assessment of benefits versus risks. Data from long-term randomized, controlled clinical trials (such as the ongoing large cardiovascular outcomes trials) are necessary to adequately assess this balance.

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REFERENCES

1. Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. Diabetes 2013;62:2595–2604
2. Stelow EB, Adams RB, Moskaluk CA. The prevalence of pancreatic intraepithelial neoplasia in pancreata with uncommon types of primary neoplasms. Am J Surg Pathol 2006;30:36–41
3. Detlefsen S, Sipos B, Feyerabend B, Klöppel G. Pancreatic fibrosis associated with age and ductal papillary hyperplasia. Virchows Arch 2005;447:800–805
4. In't Veld P, De Munck N, Van Belle K, et al. β-cell replication is increased in donor organs from young patients after prolonged life support. Diabetes 2010;59:1702–1708
5. Gier B, Matveyenko AV, Kirakossian D, Dawson D, Dry SM, Butler PC. Chronic GLP-1 receptor activation by exendin-4 induces expansion of pancreatic duct glands in rats and accelerates formation of dysplastic lesions and chronic pancreatitis in the Kras(G12D) mouse model. Diabetes 2012;61:1250–1262
6. Tatarkiewicz K, Smith PA, Sablan EJ, et al. Exenatide does not evoke pancreatitis and attenuates chemically induced pancreatitis in normal and diabetic rodents. Am J Physiol Endocrinol Metab 2010;299:E1076–E1086
7. Vrang N, Jelsing J, Simonsen L, et al. The effects of 13 wk of liraglutide treatment on endocrine and exocrine pancreas in male and female ZDF rats: a quantitative and qualitative analysis revealing no evidence of drug-induced pancreatitis. Am J Physiol Endocrinol Metab 2012;303:E253–E264
8. Tatarkiewicz K, Belanger P, Gu G, Parkes D, Roy D. No evidence of drug-induced pancreatitis in rats treated with exenatide for 13 weeks. Diabetes Obes Metab 2013;15:417–426