COMMENTS AND RESPONSES

# Response to Comment on: Butler et al. A Critical Analysis of the Clinical Use of Incretin-Based Therapies: Are the GLP-1 Therapies Safe? Diabetes Care 2013;36:2118–2125

I, on behalf of Butler et al. (1), thank Bjerre Knudsen et al. (2) for their comments and accept their statement that liraglutide was not withdrawn before euthanasia of the monkeys. Nyborg et al. (3) reported routine pathological examination in the pancreas of young healthy members of three species. A single transverse section of the midpart of the pancreas was stained with hematoxylin and eosin and examined unblinded in routine fashion by a toxicological pathologist at a time when no concerns had been raised about the possibility of pancreatic effects. The monkeys were presumably young as no pancreatic intraepithelial neoplasia lesions were seen, implying that exposure to liraglutide was at an age equivalent to human childhood. The findings are therefore of uncertain relevance to middle-aged overweight humans with type 2 diabetes.

With respect to the study of Vrang et al. (4), we made no reference to the three overdosed rats. Bjerre Knudsen et al. argue that stereology of pancreas sections is required to properly evaluate the morphology of pancreas. We respectfully suggest that computational analysis cannot substitute examination of appropriate material. Inspection of a single pancreatic section in young nondiabetic Sprague-Dawley rats receiving exenatide in the study of Gier et al. (5) would similarly have seen no proliferative changes, but multiple sections through the head of the pancreas in these same animals stained for Ki67 revealed marked expansion of the pancreatic duct glands due to increased replication of this putative stem cell niche of the exocrine pancreas. Increased proliferation might have been underestimated in the study of Vrang et al. because of inadequate sampling or overfixation. Vrang et al. comment that their Ki67 immunostaining must have been valid because it was observed in the exocrine pancreas, but the images of Ki67 staining provided in the article are not of a quality to confirm this.

Bjerre Knudsen et al. question the validity of immunostaining for glucagon-like peptide 1 (GLP-1) receptors in exocrine pancreas, including in pancreatic intraepithelial neoplasia lesions. The validity of staining methods may be debated, but the consequences of incretin therapy are what matter. First, we note that exenatide accelerated pancreatic dysplasia and chronic pancreatitis in Kras mutant mice in the only published study of GLP-1 mimetic therapy in a model of chronic pancreatitis (5). Second, pancreas enlargement and acceleration of pancreatic dysplasia were seen in humans treated with incretin therapy (6). Finally, a *British Medical Journal* investigation (7) noted that a regulatory review of the monkey data subsequently reported by Nyborg et al. (3) stated that "an increased pancreatic weight was observed in young healthy cynomolgus monkeys following four weeks (males only) and 52 weeks treatment. . .Further investigations of the pancreatic tissues collected in the 52 week monkey study showed that the increased pancreatic weight was due to a 67% increase in absolute duct cell mass and 64% increase in exocrine cells when compared to the vehicle group." The company response to these observations, which was not reported in the published study, can be found in ref. 8. Bjerre Knudsen et al. (2) rightly stress the importance of transparency, and Butler et al. fully endorse the call from the American Diabetes Association and The Endocrine Society for full independent review of all studies undertaken by the manufacturers.

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