A Critical Analysis of the Clinical Use of Incretin-Based Therapies

Are the GLP-1 therapies safe?

There is no question that incretin-based glucose-lowering medications have proven to be effective glucose-lowering agents. Glucagon-like peptide 1 (GLP-1) receptor agonists demonstrate an efficacy comparable to insulin treatment and appear to do so with significant effects to promote weight loss with minimal hypoglycemia. In addition, there are significant data with dipeptidyl peptidase 4 (DPP-4) inhibitors showing efficacy comparable to sulfonylureas but with weight neutral effects and reduced risk for hypoglycemia. However, over the recent past there have been concerns reported regarding the long-term consequences of using such therapies, and the issues raised are in regard to the potential of both classes to promote acute pancreatitis, to initiate histological changes suggesting chronic pancreatitis including associated preneoplastic lesions, and potentially, in the long run, pancreatic cancer. Other issues relate to a potential risk for the increase in thyroid cancer. There are clearly conflicting data that have been presented in preclinical studies and in epidemiologic studies. To provide an understanding of both sides of the argument, we provide a discussion of this topic as part of this two-part point-counterpoint narrative. In the point narrative below, Dr. Butler and colleagues provide their opinion and review of the data to date and that we need to reconsider the use of incretin-based therapies because of the growing concern of potential risk and based on a clearer understanding of the mechanism of action. In the counterpoint narrative following the contribution by Dr. Butler and colleagues, Dr. Nauck provides a defense of incretin-based therapies and that the benefits clearly outweigh any concern of risk.

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The clinical value of new therapies for diabetes tends to be overestimated at launch, whereas the disadvantages emerge more slowly. Possible reasons include inflated expectations, marketing pressures, and the limited number of people exposed to the drug prior to launch. Full recognition of unwanted effects has also been delayed by inadequate postmarketing surveillance, especially when the unwanted effect is difficult to pinpoint or slow to emerge.

Off-target or unwanted effects pose a particular problem when a new class has wide-ranging effects. This was exemplified by the thiazolidinediones, nuclear receptor agonists with useful glucose-lowering properties but pleiotropic and unpredictable pathophysiological actions. Some undesirable outcomes such as osteopenia, redistribution of body fat, and fluid retention emerged as class effects, whereas others such as acute liver failure, increased cardiovascular morbidity, and bladder cancer appear specific to individual agents. Although the potential for unwanted effects was recognized at an early stage of development, it took years for them to be identified, analyzed, and acted upon. This meant that millions of people were exposed to agents whose potential long-term consequences were incompletely understood.

The glucagon-like peptide 1 (GLP-1)–based therapies have comparably pleiotropic actions. GLP-1 is a peptide hormone that enhances insulin secretion, inhibits glucagon release, delays gastric emptying, and suppresses appetite. Other potentially useful properties include enhanced growth and proliferation of pancreatic β-cells in immature (but not adult) rodents. GLP-1 receptors are however present in many other tissues, including thyroid, exocrine pancreas, meninges, renal tubules, and bone, and their activation results in changes entirely unrelated to glucose homeostasis. High levels of vigilance are therefore justified.

GLP-1 has a very short half-life and is therefore "seen" by its receptors in a transient and tightly regulated fashion in healthy individuals. The incretin effect is deficient in type 2 diabetes, and GLP-1–based therapy addresses this deficit. Its full glucose-lowering effect is however achieved at supraphysiological (DPP-4 inhibition) or pharmacological (GLP-1 mimetic) dosing levels. GLP-1 analogs thus achieve pharmacologic override of normal physiologic function and have the potential to produce unexpected off-target effects, whereas DPP-4 inhibition enhances the release of gastric inhibitory polypeptide (GIP) as well as GLP-1, and the long-term impact of DPP-4 inhibition upon other regulatory systems is unknown.

Regulatory authorities have expressed concerns about the potential risk of acute pancreatitis, thyroid cancer, and renal failure with some or all of the GLP-1–based therapies, warnings that are (as appropriate) conveyed in every pack that is handed to a patient. These concerns are however largely discounted by the manufacturers and those representing their views to physicians, who typically maintain that the risk of pancreatic inflammation is illusory.

Pancreatitis: Now you see it, now you don't—Exenatide, the first GLP-1–based therapy, was launched in the U.S. on April 29, 2005. A single case report of acute pancreatitis appeared in 2006 and was spotted by investment advisors who conducted their own search of the U.S. Food and Drug Administration (FDA) database and reported a potential risk of acute pancreatitis on October 2, 2006. The company made a change to its label on October 8, but the FDA did not issue its first alert until October 2007 (1). This was followed by a series of publications, mostly sponsored by the manufacturers, which reported that pancreatitis is more common in established diabetes than previously appreciated, together with pharmacoepidemiological studies using administrative databases that indicated that pancreatitis is no more common with exenatide than with other therapies for diabetes (2–4).

It is not easy to estimate the prevalence of acute pancreatitis, let alone assign a probable cause, and there are genuine difficulties in ascertaining the prevalence of acute pancreatitis in a population with diabetes. Reverse causation is an important confounder since both acute and chronic pancreatitis may give rise to

diabetes. Chronic pancreatitis may present with acute episodes of pancreatic pain. The formal criteria for diagnosis—typical pain, enzyme rises, and changes on computed tomography (CT) examination—may not be satisfied or adequately recorded in administrative databases, and unequivocal CT abnormalities may not be present. The source documentation is often inadequate and pharmacoepidemiologic analyses may reach differing rate estimates because of differing criteria. Last but not least, a plausible mechanism to explain the occurrence of pancreatitis was initially lacking. This is no longer the case.

Emergence of a mechanism—GLP-1 receptors are abundantly expressed in the pancreatic ducts as well as in the pancreatic islets, and the intense interest in GLP-1–based therapies as a potential stimulus to β-cell regeneration has overshadowed the possibility that exocrine pancreatic cells might be similarly affected. Acinar and duct cells proliferate in response to GLP-1 therapy (5) and cause an increase in pancreatic weight (6,7) (Fig. 1). Such observations attracted little attention prior to 2009 when one of eight HIP rats, a model of type 2 diabetes, developed hemorrhagic pancreatitis following exposure to sitagliptin, and some of the remaining animals showed marked acinar to ductal metaplasia, a potentially premalignant change characteristic of chronic pancreatitis (7). Gier et al. (8) noted that the pancreatic duct gland (PDG) compartment of the pancreas is particularly responsive to the proproliferative actions of GLP-1 and confirmed that GLP-1 simulates proliferative signaling in human pancreatic ductal epithelium. Two short-term studies were subsequently performed at the request of the FDA. These studies were carried out with exenatide and liraglutide in the ZDF rat model of diabetes and were reassuring with respect to possible adverse effects of GLP-1 mimetic therapy on the exocrine pancreas. Notwithstanding, pancreatic enzymes rose in both studies: one of twelve animals treated with exenatide died of massive pancreatic necrosis, and pathological findings in treated animals included acinar to ductal metaplasia and foci of ductal hyperplasia (9,10).

Some of the relevant preclinical studies are summarized in Table 1 (5–13). In aggregate, they offer a plausible mechanism for the occurrence of acute pancreatitis in patients exposed to GLP-1–based therapies since duct proliferation might lead to duct occlusion (particularly in the setting of existing dysplastic lesions), occlusion would generate back pressure, and back pressure would stress acinar cells thereby activating and releasing the digestive enzymes that they contain—a well-established causal mechanism for pancreatitis.

Human pancreatitis revisited—Animal studies do not necessarily reflect the experience in humans, but the identification of a plausible mechanism is an important step toward establishing a potential hazard and indicates a need for more detailed analysis in humans. Observational and pharmacoepidemiologic studies have suggested that acute pancreatitis is more common than expected in the diabetic population and is not increased by exenatide relative to other therapies (2–4). Although space does not permit detailed consideration here, there are some anomalies. For example, Dore et al. (2) examined the frequency of pancreatitis in a claims database comprising 25,700 patients on exenatide (past or present users) as compared with 234,500 patients on other antihyperglycemic therapies. Overall, there were more cases of confirmed pancreatitis in past or present exenatide users as compared with other therapies (40/25,719 vs. 254/234,536 = 1.56/1,000 vs. 1.08/1,000 users). The study found a reduced frequency of pancreatitis in present users of exenatide, but a propensity-adjusted RR (relative risk) of 2.8 (CI 1.6–4.7) for past use. The latter observation was discounted because those being studied were no longer taking exenatide at the time of the episode, but the exclusion would not be valid if exenatide had been stopped because of premonitory symptoms of abdominal pain or if the proposed mechanism persisted in those no longer taking the drug. Garg et al. (14) found no evidence of an increased risk of pancreatitis with exenatide, but concede that "the limitations of this observational claims-based analysis cannot exclude the possibility of an increased risk." A recent case-control study addressed many of the limitations of previous reports, including inadequate power, and found that current and recent (1 month–2 years) users of GLP-1–based therapies had a twofold risk of acute pancreatitis (adjusted odds ratio 2.24 [95% CI 1.36–3.68] for current use and 2.01 [1.27–3.18] for recent use) (15).

Studies conducted by the manufacturer under the eyes of the regulators may provide reliable information. A recent review identified 11 such reports in studies conducted by Novo Nordisk, the manufacturer of liraglutide. Seven occurred in the LEAD (Liraglutide Effect and Action in Diabetes) studies (16), two in other studies, and two in postmarketing reports. Adverse events from the FDA Serious Adverse Event (SAE) reports were not considered. The findings were considered to "implicate liraglutide as the cause in at least some of these cases" (17).

Further cause for concern comes from FDA MedWatch data. An excess of acute pancreatitis was already evident for exenatide within 1 year of launch (1), and an updated analysis in 2011 found that, as compared with other non-GLP-1–based diabetes therapies, the reporting rate for acute pancreatitis with exenatide was dramatically increased ($P < 2 \times 10^{-4}$) (18). This easily checked analysis has not been seriously challenged.

The FDA alert system was designed to identify potential safety problems, not to confirm them. Notwithstanding its limitations, to our knowledge there is no single instance in which a strong sustained signal has turned out to be entirely spurious. When Elashoff et al. (18) was published, there were 971 reported pancreatitis events for exenatide and 131 for sitagliptin. The corresponding numbers are now 2,327 and 718 (Table 2). Recognition of an adverse event undoubtedly increases the reporting frequency, but there was a signal for exenatide long before the first FDA alert was issued, and there was no reason to anticipate a similar problem with sitagliptin. Furthermore, there are now 888 reported pancreatitis events for liraglutide, 125 for saxagliptin, and 43 for linagliptin (Table 2). Every GLP-1–based therapy with sufficient market exposure has generated a signal for pancreatitis, and no other diabetes medication has done so.

We conclude that the balance of evidence does suggest an association between widely used GLP-1–based therapies and acute pancreatitis, suggesting a class effect, and that this is underpinned by a plausible mechanism.

What are the implications?—The major concern is not pancreatitis, unpleasant though this is. The concern is that acute events may be no more than the tip of an iceberg, and that these agents might cause subclinical duct proliferation, acinar to ductal metaplasia, and subclinical pancreatitis in a much higher proportion of individuals. Pancreatitis,

Table 1—*Animal studies of GLP-1–based therapy on the exocrine pancreas*

Reference	Species/age	Treatment/day duration#	Pancreas weight	Pancreas enzymes	Histology	Replication/ method
Perfetti et al., 2000 (5)	Wistar rat 22 months	GLP-1 1.5 pmol/kg · min, 5 days	↑	→	NR	↑ Ducts and acinar cells PCNA
Koehler et al., 2009 (6)	Mice 9–12 weeks	Exenatide 48 nmol/kg, 4 wks	↑	→	NR	NR
	Mice 9–12 weeks	Liraglutide 75 μg/kg, 1 wk	↑	→	NR	NR
Matveyenko et al., 2009 (7)	HIP rats 2 months	Sitagliptin 200 mg/kg, 12 weeks	↑	NR	Pancreatitis (1/8) and acinar to ductal metaplasia (3/16)	↑ Ducts, Ki67
Nachnani et al., 2010 (12)	Rats 8 weeks	Exenatide 10 μg/kg, 11 weeks	NR	↑ Amylase	Exocrine inflammation	NR
Tatarkiewicz et al., 2010 (11)	Mice 10 weeks	Exenatide 7.2 nmol/kg, 4 weeks	→	→	No pancreatitis	→ Ducts Ki67
Vrang et al., 2012 (9)	ZDF rats 7 weeks	Exenatide 0.25 mg/kg, 13 weeks	→	↑ Amylase	1/12 death pancreatic necrosis; focal acinar hyperplasia;	→ Ducts Ki67*
		Liraglutide 1.0 mg/kg, 13 weeks	→	→	3/12 death by overdose, unexplained; increased ductal proliferation and acinar to ductal metaplasia	→ Ducts Ki67*
Nyborg et al., 2012 (13)	Cynomolgus monkeys age NR	Liraglutide 5 mg/kg, 87 weeks	NR	NR	Normal	NR
	Rats age NR	Liraglutide 1 mg/kg 26 weeks	NR	NR	Normal	NR
	Mice age NR	Liraglutide 3 mg/kg, 104 weeks	NR	NR	Normal	NR
Gier et al., 2012 (8)	Rats 10 weeks	Exenatide 10 μg/kg, 12 weeks	↑	→	PDG hyperplasia;	↑ PDG and ducts Ki67
	Pdx-1 Kras mice 6 weeks	Exenatide 5 nmol/kg, 12 weeks	↑	↑ Lipase	chronic pancreatitis and advanced PanINs	↑ Ducts Ki67
Tatarkiewicz et al., 2012 (10)	ZDF rats 8 wks	Exenatide 250 μg/kg, 12 weeks	→	↑ Amylase	Normal	→ Ducts Ki67*

Preclinical animal studies reporting the effects of GLP-1–based therapies on the exocrine pancreas. *Indicates pancreas fixed in formaldehyde for 24 h or more, typically denaturing proteins to the extent that measurement of cellular replication by Ki67 is unreliable. #Maximal dose and duration of GLP-1–based therapy included in each study is shown in the summary. NR, not recorded.

whether clinical or subclinical, is well known to predispose to pancreatic cancer, and there is a signal for cancer of the pancreas for exenatide in both the FDA and German regulatory databases and for sitagliptin in the FDA database (18,19). The signal has grown stronger with 258 pancreatic cancers reported for exenatide, 63 for liraglutide, 81 for sitagliptin, 18 for saxagliptin, and 1 for linagliptin (Table 2).

Low-grade asymptomatic chronic pancreatitis with associated proliferative changes is not uncommon in the middle-aged target population for this drug class (20), making it likely that the proproliferative actions of GLP-1 therapy will at times be superimposed upon low-grade pancreatitis and its associated dysplastic changes. Some insight into this possibility was gained in the chronic pancreatitis–prone $Kras^{G12D}$ mouse model in which exenatide therapy accelerated formation and growth of dysplastic intraepithelial neoplasia (PanIN) lesions as well as pancreatitis (8). To date, this is the only study of the actions of incretin treatment in a model of chronic pancreatitis (Fig. 1). In contrast, two studies of short-term GLP-1 exposure superimposed on acute toxin–induced pancreatitis were reported to show a protective effect, but such studies do not address the mechanism of relevance (6,11).

The incidence of pancreatic cancer, as of pancreatitis, is increased in type 2 diabetes (21). Work over the past decade has established that premalignant changes known as pancreatic intraepithelial (PanIN) lesions precede and predict the onset of pancreatic cancer. PanINs are present in up to 50% of the middle-aged population, although relatively few actually progress to cancer (20). Both PanINs and pancreatic cancer express the GLP-1 receptor in humans (8). Since progression of PanINs to pancreatic cancer is via the accumulation of additional somatic mutations, any driver of increased cellular replication in PanINs is likely to increase that probability. This theoretical risk was illustrated by the progression of PanINs in the exenatide-treated

Table 2—*FDA adverse event reports for GLP-1–based drugs*

Exenatide and sitagliptin vs. controls (04Q1 to 12Q2)

Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Exenatide	2,327	1,660	19.17	(16.41–22.50)	<2.2e-16
Sitagliptin	718	411	23.89	(19.76–28.93)	<2.2e-16
Controls	207	2,832			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Exenatide	258	1,660	2.99	(2.41–3.73)	<2.2e-16
Sitagliptin	81	411	3.80	(2.80–5.11)	<2.2e-16
Controls	147	2,832			
Drug	Thyroid cancer events	Control events	OR	95% CI	*P* value
Exenatide	74	1,660	3.94	(2.56–6.20)	1.67e-11
Sitagliptin	5	411	1.08	(0.33–2.81)	0.80
Controls	32	2,832			

Liraglutide vs. controls (10Q2 to 12Q2)

Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Liraglutide	888	259	56.81	(43.52–74.71)	<2.2e-16
Controls	84	1,393			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Liraglutide	63	259	5.64	(3.80–8.38)	<2.2e-16
Controls	60	1,393			
Drug	Thyroid cancer events	Control events	OR	95% CI	*P* value
Liraglutide	57	259	17.99	(10.12–33.56)	<2.2e-16
Controls	17	1,393			

Saxagliptin vs. controls (09Q4 to 12Q2)

Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Saxagliptin	125	65	30.96	(21.33–45.35)	<2.2e-16
Controls	100	1,618			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Saxagliptin	18	65	6.04	(3.21–10.95)	6.85e-8
Controls	74	1,618			
Drug	Thyroid cancer events	Control events	OR	95% CI	*P* value
Saxagliptin	0	65	0	(0.00–5.48)	>0.99
Controls	19	1,618			

Linagliptin vs. controls (11Q3 to 12Q2)

Drug	Pancreatitis events	Control events	OR	95% CI	*P* value
Linagliptin	43	14	42.36	(20.86–90.82)	<2.2e-16
Controls	43	601			
Drug	Pancreatic cancer events	Control events	OR	95% CI	*P* value
Linagliptin	1	14	1.79	(0.04–12.72)	0.45
Controls	24	601			
Drug	Thyroid cancer events	Control events	OR	95% CI	*P* value
Linagliptin	0	14	0	(0–27.80)	>0.99
Controls	8	601			

The updated adverse event reports from Elashoff et al. (18) to include most recent available quarters and GLP-1 drugs launched since the original Elashoff report. Since rosiglitazone (Avandia) is now rarely used in the U.S., the control drugs have been increased to include insulin preparations available in the U.S. The pattern of findings is comparable with or without these added controls. Control drugs include "AVANDIA," "ROSIGLITAZONE," "STARLIX," "NATEGLINIDE," "PRANDIN," "REPAGLINIDE," "NOVONORM," "GLIPIZIDE," "GLUCOTROL," "INSULIN DETEMIR," "LEVEMIR," "INSULIN ASPART," "NOVOLOG," "HUMULIN N," "HUMULIN R," "INSULIN LISPRO," "HUMALOG," "INSULIN GLARGINE," "LANTUS," "HUMULIN 70/30," and "NOVOLOG MIX 70/30." Pancreatitis events include "PANCREATITIS." Pancreatic cancer events include "PANCREATIC MASS," "PANCREATIC NEOPLASM," "ADENOCARCINOMA PANCREAS," and "PANCREATIC CARCINOMA." Thyroid cancer events include "THYROID CANCER," "THYROID GLAND CANCER," "THYROID NEOPLASM," and "THYROID MASS." Control events include "BACK PAIN," "CHEST PAIN," "COUGH," "SYNCOPE," and "URINARY TRACT INFECTION."

$Kras^{G12D}$ mouse model (8). It is worth noting here that such a potential link between GLP-1 therapy and risk for pancreatic cancer is analogous to estrogen therapy and breast cancer. Estrogen does not initiate breast cancer, but in individuals with premalignant dysplastic ductal changes that bear estrogen receptors, estrogen accelerates growth and malignant conversion in some individuals (22). Likewise, the very high concentration of insulin delivered to the bronchial tree with inhaled insulin was as-

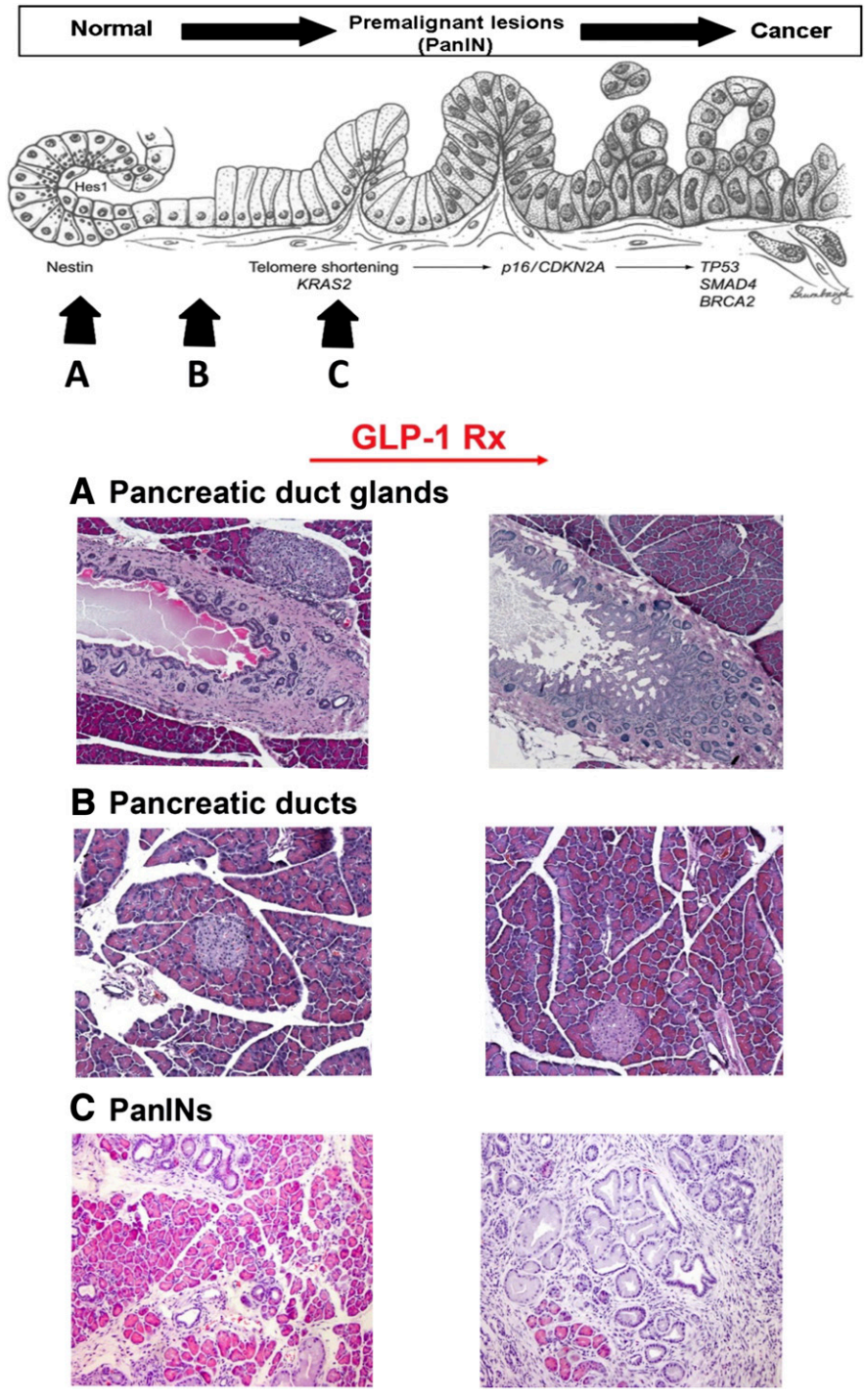

Figure 1—*GLP-1 actions on exocrine pancreas in animal studies depend on compartment studied and pancreas health. The histological characteristics of the transition from normal pancreas to premalignant changes (PanINs) typically present in the progression from asymptomatic chronic pancreatitis to cancer and, as established by human pathological and mouse genetic studies* (top panel, *modified from Maitra and Hruban* [31]). *In nondiabetic animal studies, exposure of pancreas to GLP-1 therapies has minimal discernible impact except in the pancreatic duct gland compartment where marked proliferation generates intraductal papillary projections* (A*: Pancreatic duct glands are markedly expanded in nondiabetic rats treated with exenatide 10 μg/kg daily for 12 weeks). However the pancreatic ducts show no obvious abnormalities in the same animals.* B*: In contrast, GLP-1 therapy accelerates pancreatitis and neoplasia in mice prone to chronic pancreatitis.* C*: Formation of PanINs and pancreatitis are markedly accelerated in the Pdx1-Cre; LSL-Kras^{G12D} mouse model treated with exenatide 5 nmol/kg for 12 weeks.* A, B, *and* C *used with permission from Gier et al. (8).*

sociated with an increased incidence of lung cancer (23). Are estrogen, insulin, or GLP-1 carcinogens? No, but all three can serve as growth factors, and when pharmacological stimulation of growth is imposed on dysplastic lesions, accelerated declaration of cancer is not unexpected.

Where do we go from here?—

The regulatory reflex, when presented with a safety concern, is to request further descriptive data from the manufacturers. Our view is that the request for further epidemiologic analysis misses the real point of concern and wastes valuable time. The answer lies in the human pancreas, and (until this answer is known) there are more relevant questions to ask.

One question is this: If subclinical pancreatitis is common (consistent with the episodes of abdominal pain or discomfort described by many users), we might anticipate subclinical increases in pancreatic enzymes. Anecdotally, many clinicians already know this to be the case, but there is only one published case series (24). We accept that pancreatic enzyme levels fluctuate in people with diabetes and that confirmation of increased levels in people exposed to GLP-1–based therapies does not in itself constitute evidence of subclinical pancreatitis, but if a signal is there, we need to know.

The debate has been conducted in the absence of a single report from the pancreas of a human exposed to GLP-1 therapies. This is where the answer lies (25). Most recently, the first data have become available from human pancreas following a year or more of incretin therapy; 7 individuals treated by sitagliptin and 1 by exenatide compared to 12 individuals with type 2 diabetes treated with other agents and nondiabetes (26). The pancreas was 40% enlarged with increased exocrine pancreas proliferation in incretin-treated individuals. Moreover, there was an increase in the number of PanIN (premalignant) lesions after prior incretin treatment, consistent with the findings in the Kras^{G12D} mouse model (8). A striking finding in the human pancreas after incretin treatment was marked α-cell hyperplasia with glucagon-expressing microadenomas in 3 of the 8 individuals, and a glucagon-expressing neuroendocrine tumor in 1 of the 8. Given the heavily promoted action of incretin therapy to suppress glucagon secretion, and the prior reports of α-cell hyperplasia and risk for progression to pancreatic neuroendocrine tumors (26), this finding,

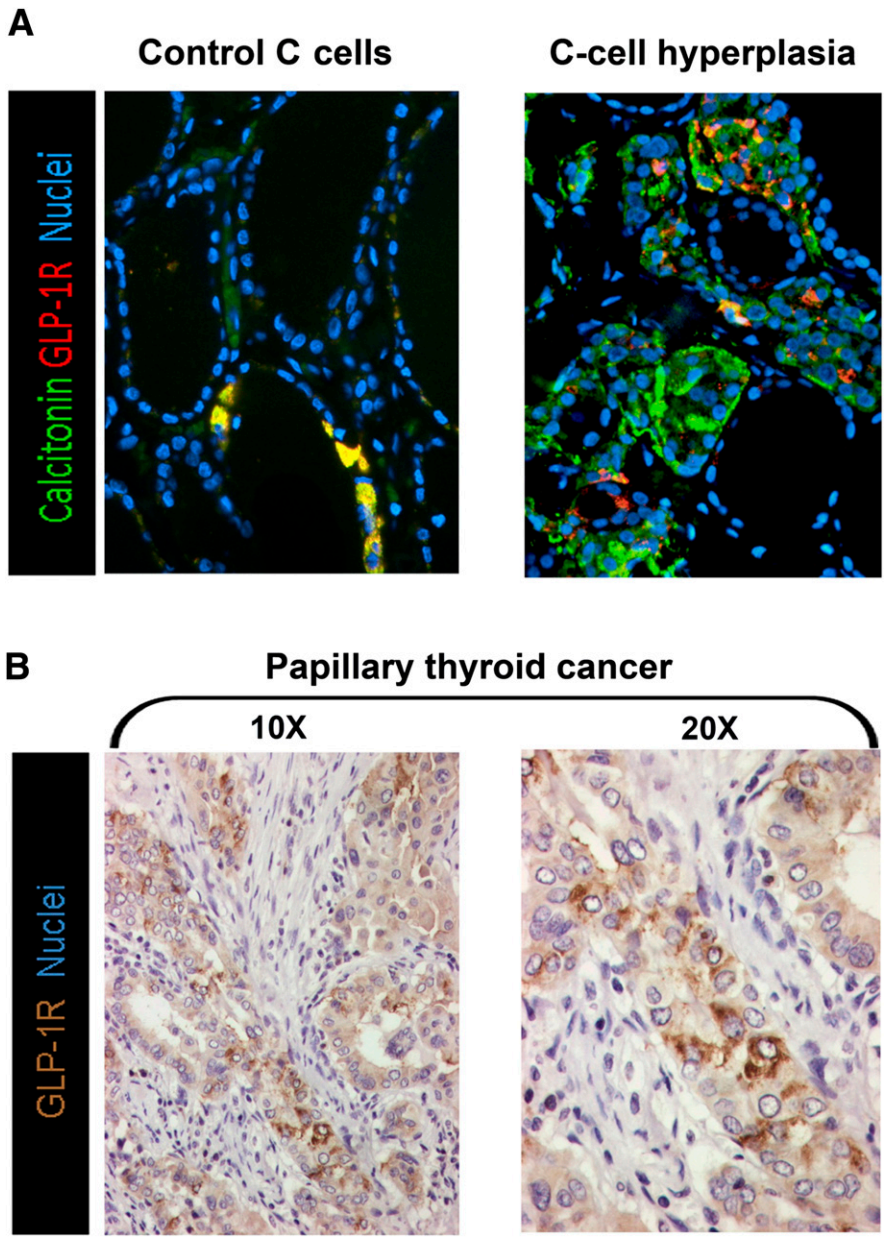

Figure 2—*GLP-1 receptors (GLP-1R) are expressed in premalignant lesions in human thyroid.* A: *Human thyroid immunostained by immunofluorescence for calcitonin (green), GLP-1 receptor (red), and nuclei (blue) in a normal thyroid* (left) *and in C-cell hyperplasia* (right). *Yellow color indicates GLP-1 receptor expression in C cells, which is present occasionally in normal thyroid and frequently in C-cell hyperplasia.* B: *Human thyroid from papillary thyroid cancer* (left *and* right panels) *stained by immunohistochemistry for GLP-1 receptor (GLP-1R) (brown). GLP-1 receptor expression is present in ~20% of papillary thyroid cancers and most medullary thyroid cancers. Used with permission from Gier et al. (28).*

while of concern, is perhaps not unexpected. No changes were reported in the exocrine pancreata of 10 monkeys that were treated with liraglutide for 87 weeks (13). Treatment was discontinued 2 weeks before the pancreata were obtained. The weight of the pancreata was not however reported (this would have been expected to increase). Long-term treatment of nondiabetic human primates with exenatide has not been published. The concerns raised in this article go well beyond the scope of routine histologic analysis conducted for regulatory purposes, and a full review by independent experts in pancreatic pathology would now seem justified (25).

In summary, a plausible mechanism links GLP-1–based therapy with acute pancreatitis—and a potential risk of pancreatic cancer—in individuals with type 2 diabetes. The model proposes acceleration of pancreatic dysplasia in the setting of low-grade chronic pancreatitis leading to sufficient ductal obstruction in a minority of individuals to provoke an episode of acute pancreatitis. Subclinical changes would be expected in a larger proportion of those exposed. The absence of pancreatitis or pancreatic dysplasia in nondiabetic models or short-term treatment of models of diabetes does not exclude the proposed mechanism. GLP-1 treatment, like estrogen in breast cancer, might promote development of pancreatic cancer in some individuals. Alternatively, periductal α-cell hyperplasia may cause duct obstruction and potentially progress to neuroendocrine neoplasia.

GLP-1 and thyroid cancer: Now you see it, now you don't—Preclinical registration studies of liraglutide found an increased number of C-cell tumors of the thyroid in rodents. Studies sponsored by the manufacturers have suggested that C cells in humans do not express the GLP-1 receptor; that humans exposed to liraglutide have, in aggregate, little or no rise in calcitonin levels; and that nonhuman primates exposed to liraglutide do not develop thyroid tumors (27). In contrast, analysis of a much larger sample of human thyroid glands and C cells established that a subpopulation of C cells in humans does indeed express the GLP-1 receptor (28) (Fig. 2). It was further established that GLP-1 receptor expression was more abundant in C-cell hyperplasia, a potential precursor of medullary thyroid cancer. Moreover, GLP-1 receptor expression is also present in 20% of those with papillary thyroid cancer, a much more common tumor for which calcitonin levels would be irrelevant. While medullary thyroid cancer is rare (29), a relatively high proportion of the population has apparently quiescent micro foci of papillary thyroid cancer (30).

Once again we must ask whether relatively short-term negative studies of GLP-1 mimetic therapy and thyroid cancer in normal monkeys provide adequate reassurance against the risk of malignancy in humans. As in the pancreas, the concern is that proproliferative actions of GLP-1 superimposed on premalignant lesions (C-cell hyperplasia or micropapillary thyroid cancer) may accelerate the progression of these lesions toward cancer. And, once again, adverse event reporting shows a clear excess of reported thyroid cancer on both exenatide (74

thyroid cancer events) and liraglutide (57 thyroid cancer events), although there is currently no similar signal for the DPP-4 inhibitors (Table 2).

Conclusions: Déjà vu all over again?—The story is familiar. A new class of antidiabetic agents is rushed to market and widely promoted in the absence of any evidence of long-term beneficial outcomes. Evidence of harm accumulates, but is vigorously discounted. The regulators allow years to pass before they act. The manufacturers are expected—quite unrealistically—to monitor the safety of their own product. We should be thankful that those responsible for aircraft safety do not operate on the assumption that the absence of evidence is evidence of absence.

The safety of the GLP-1 therapies can no longer be assumed, and there will be rapid developments in this area. Drug safety can never be assumed, and the legal principle of "innocent until proved guilty" does not apply. The case presented here does not prove that these agents are unsafe, but it does suggest that the burden of proof now rests with those who wish to convince us of their safety.

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