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THE ROLE OF LANGERHANS ISLETS IN PANCREATIC DUCTAL ADENOCARCINOMA

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1. ABSTRACT

An intimate relationship between the exocrine and endocrine pancreas has been convincingly demonstrated in recent years. Animal experiments have shed some light into the complex dialog between the two tissues. This interaction is pronounced in diseases of the pancreas, especially in experimentally-induced and human pancreatic cancers. New evidence highlights the importance of intact islets in the development of exocrine pancreatic cancer. Although tumors arise from large and small ducts, invasive and malignant adenocarcinomas of ductal phenotype also derive from stem cells within islets. Development of cancer within islets explains the association between pancreatic cancer and impaired glucose tolerance or diabetes. Hence, the previous epidemiological studies suggesting that diabetes is a predisposing factor for pancreatic cancer are refuted. The available evidence suggests that pancreatic cancer in a large number of pancreatic cancer patients ultimately leads to diabetes, and that removal of the tumors improves or cures the diabetes. Both in the hamster pancreatic cancer model and in patients, the development of cancer is associated with elevated plasma levels of islet amyloid polypeptide, which may be used as a tumor marker.

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2. INTRODUCTION

Pancreatic cancer, which has a high incidence worldwide, is a disease with poor prognosis since it evades early detection. In the United States, the disease presently accounts for 3% of all cancers responsible for 5% of all cancer deaths (1). It is the fourth most common cause of cancer death in men (exceeded only by lung, colorectal and prostatic cancers) and the fifth cause of cancer death in women (exceeded by breast, colorectal,lung and ovarian-uterine cancers). It is estimated that, in 1997, about 27,000 new cases of pancreatic cancer will be diagnosed in the United States, and 25,900 people will die of this disease (1).

Pancreatic cancer has a very poor prognosis. The overall five-year survival rate is less than 1% (2). The principal reason for this prognosis is the inability to diagnose the disease at an early, localized, and curable stage. Approximately 85-90% of all pancreatic tumors have extended beyond the pancreas or have metastasized at the time of exploratory surgery (3). Unfortunately, the etiological factor(s) of pancreatic cancer is not known and therefore prevention of this silent killer is not yet possible. Epidemiologic and experimental studies have suggested a link between pancreatic cancer and smoking (4-6), diabetes (7-10) or a high fat diet (11-17). However, it is not clear how these factors influence pancreatic cancer.

Although it is generally believed that cancers of exocrine pancreas in humans originate from ductal cells, their derivation from acinar cells has also been considered(18). Experimental results in different species point to the differences in the cell of origin of tumors induced in pancreas (19-23). Although rats primarily

develop acinar cell tumors (21-22), ductal and ductular cells are believed to be the progenitor cells of pancreatic cancer in hamsters.

In this review, the potential sites of origin of pancreatic adenocarcinomas are discussed.

3. HISTORICAL BACKGROUND

Until the turn of this century, and probably based on the Pearce hypothesis on the neuroectodermal origin of islet cells, the endocrine pancreas was considered an independent part of the pancreas. In 1911 Bensley (24) showed that ductal/ductular structures penetrate through some islets in guinea pigs suggesting the existence of an intimate physiological and anatomical contact between the exocrine and endocrine tissues. The shape, size, and distribution of islets is rather uniform (25) in all species and is independent of the animal size. The recognition of a portal vascular system (see ref. 26) was another early step in recognizing the existence of an association between the exocrine and endocrine pancreas. Several independent researchers showed that at least part of the exocrine blood supply of pancreas is derived from the insular arteries that first pass through islets. This blood supply explained the remarkable "halo" phenomenon that is particularly accentuated in the rat pancreas. Using a hematoxylin-eosin stain, rat acinar cells in the vicinity of islets (periinsular) appear larger and have more eosinophilic zymogen granules than those remote from islets (teleinsular acinar cells) causing a "halo" around the faintly stained islets (26). This phenomenon was thought to be the result of a higher concentration of insulin (which has a promoting effect on cellular DNA and protein content) in the vessels passing through the periinsular acini than in the teleinsular region. This concept was supported by the later finding that destruction of islet β-cells by alloxan results in the disappearance of the halo phenomenon (27). Further support for the intimate interaction of the exocrine and endocrine pancreas was shown by the presence of hormones released by the islets of Langerhans in the pancreatic juice of several species, including humans (28).

4. ENDOCRINE-EXOCRINE INTERACTION

Bensley's observation (24) was confirmed in recent years in Syrian golden hamsters treated with N-nitrosobis(2-oxopropyl)amine (BOP), a potent pancreatic carcinogen in this species (29) and in guinea pigs treated with alloxan (30). In hamsters, the histologically invisible ductules surrounding some islets (periinsular ductules) and within the islets (intrainsular ductules) could be revealed in a few islets by the retrograde injection of India ink into the main pancreatic duct (31; Fig. 1). These rare intrainsular ductular structures were found by a stroke of luck at the ultrastructural level. These findings may explain how the pancreatic hormones find their way into the pancreatic ducts (28). Despite embryological recognition of the origin of islet and acinar cells from the primitive tubules (ductules), controversies have remained on the origin of new islet cells in the mature organ. Some hold the viewpoint that their origin was from the existing islets, and others claimed the ductular cells as the progenitor cells. The latter notion was recently supported by showing that ductules contain both islet β-cells and non-β-precursor cells (32).

There is also data implying that islets control the physiological function of the exocrine pancreas. It is generally accepted that islet hormones, including insulin, glucagon, and somatostatin, functionally affect the exocrine pancreas, possibly by both paracrine and endocrine pathways (26). In several disease states both endocrine and exocrine pancreas are affected. Infantile hyperinsulinemic hypoglycemia is a good example. In this disease, the characteristic focal or diffuse proliferation of islet cells (33) is often associated with proliferation of centroacinar cells and alteration of acinar cells. This response of all three cell components of the pancreas to certain pathological insults may be due to their functional dependency or reflect damage to pancreatic multipotent (stem) cells from which all pancreatic parenchymal cells arise.

5. PATTERNS OF ISLETS DURING PANCREATIC CARCINOGENESIS

The existence of an endocrine-exocrine interaction is convincingly demonstrated in some pancreatic diseases, especially in pancreatic cancer. In the hamster pancreatic cancer model, which in morphological, molecular biological, clinical, and immunological aspects mimics the human disease (29,34-43), the participation of endocrine cells in the development of exocrine cancer begins very early during carcinogenesis. In this model, various numbers and types of islet cells are found within the hyperplastic, preneoplastic and neoplastic cells forming ductal and ductular structures (Fig. 2; 29,34,37,44-48). These endocrine cells are primarily located in the basal aspect of the glands. However, they can be found scattered at different levels of the multilayered epithelium (Fig. 3). The pattern of their distribution within the malignant epithelium and the presence of exfoliated endocrine cells and material immunoreactive with anti-insulin in the lumen of these glands indicates that, like malignant ductal/ ductular cells, the endocrine cells are renewed and shed. This phenomenon could explain the higher level of islet hormones which exist in the pancreatic juice of animals with pancreatic cancer than in normal control hamsters (45). Another interesting phenomenon in this pancreatic cancer model is an exaggerated formation of periinsular and intrainsular ductules, which otherwise are rarely seen in control animals (29,34,46-48). In fact, these intrainsular ductular structures are the earliest lesions induced, whereas alterations of ductal and ductular epithelium occur later. Depending on the dose of the carcinogen, these periinsular and intrainsular ductules gradually become visible in some or many islets. Within the islets, they expand, ramify (Figs. 4,5), and ultimately form either microcystic structures resembling human serous cystadenomas (Fig. 6) or become increasingly hyperplastic

and atypical and finally transform to malignant structures which are indistinguishable from similarly altered ductal cells (Figs. 7,8). These malignant intrainsular and periinsular ductules gradually replace the islets and leave only a small group or single islet cells which can best be demonstrated immunohistochemically (Fig. 9). Similar, randomly scattered islet cells can also be found within the invasive well-differentiated cancers. With decreasing differentiation of cancer cells, the numbers of endocrine cells decrease, but they may still be found in some invasive and metastasizing tumors (45). These findings indicate that certain cells, within or around islets, possibly correspond to the "Trübe Zelle" (49), "inselpotente Zelle" (50), "nesidioblasts" (51), "immature β-cells" (52), or "islet precursor cells," which have been recognized in the pancreas of many species, including the hamster (47), and represent tumor progenitor cells. These pluripotent cells, which obviously are also distributed randomly along the pancreatic ductal system, seem to be particularly responsive to carcinogenic insult. Within the islets, where they presumably present a source of new islet cells, they lose their ability to differentiate into islet cells and resume the undifferentiated, duct-like phenotype and undergo malignant transformation the same way as do the corresponding cells within the ductal/ductular epithelium. As discussed below, the expression of tumor-associated carbohydrate antigens, such as CA 19-9, DU-PAN-2 and TAG-72, by islet cells in the immediate vicinity of pancreatic cancer (53), is in line with the differentiation failure of these precursor cells. It is, nevertheless, ironic to see that endocrine tissue "gives rise" to exocrine pancreatic cancer.

6. EVIDENCE FOR THE IMPORTANCE OF INTACT ISLETS FOR PANCREATIC ADENOCARCINOMA INDUCTION

Several studies have demonstrated that intact islet cells are a prerequisite for the induction of exocrine pancreatic cancer from within islets. Alloxan, a nitroso compound that almost selectively destroys β-cells and causes diabetes, when it was given shortly before the pancreatic carcinogen, N-nitrosobis(2-oxopropyl)amine (BOP), significantly inhibited the induction of pancreatic cancer from both ductal/ductular cells and within islets in the hamster model (54). A more dramatic effect was obtained by the pretreatment of hamsters with a more potent β-cell cytotoxic agent, streptozotocin (55). A complete destruction of β-cells by large doses of streptozotocin before BOP treatment totally prevented induction of any exocrine pancreatic lesions, although all control hamsters not pretreated with streptozotocin often had multiple cancers (56). Apparently, not only the β-cells but also the pluripotent pancreatic cells (the target of the carcinogen) are damaged by this drug. The tumor protective effect of streptozotocin was lost when it was given after BOP treatment or when the cytotoxic action of streptozotocin on the β-cells was prevented by nicotinamide (56,57). This suggests that this diabetogenic compound directly (by destroying the BOP target cells) or indirectly (by causing metabolic alterations) interferes with the initiation stage of pancreatic carcinogenesis. The indirect effect of streptozotocin on the induction of pancreatic cancer was suggested by the experiment of Bell *et al.* in a two-pancreas hamster model (58). In this technically difficult but superbly executed experiment, the pancreas of the streptozotocin-treated hamsters (SZ-pancreas) were transplanted, as a second pancreas, into the untreated host hamsters that received BOP after transplantation. The incidence of developing pancreatic tumors in SZ-pancreas did not differ from the incidence of tumorigenesis in the native pancreas of the host. In addition, there was an inverse relationship between the plasma glucose level of the host and the tumor incidence in both transplanted and native pancreata. From this study it was concluded that the inhibitory effect of streptozotocin appears to be systemic, i.e., related to diabetes, rather than to its toxic effect on the pancreas.

7. EFFECT OF EXOGENOUS INSULIN ON PANCREATIC ADENOCARCINOMA INDUCTION

The assumption that the deficiency of insulin with its growth promoting action could be the underlying mechanism of the induction of pancreatic cancer could not be confirmed in an experiment (59). When streptozotocin and BOP-treated hamsters received therapeutic daily insulin doses for life, the tumor-protective effect of streptozotocin could not be changed. Strikingly, even fewer animals treated with insulin developed pancreatic tumors than those in the streptozotocin-BOP-treated group (59). Although streptozotocin-treated hamsters recovered from diabetes after 70 days, those treated with insulin remained hyperglycemic and showed a sustained atrophy of their pancreatic islets, which could well explain the very low incidence of pancreatic cancer in this group. Nevertheless, the results indicated that the preventive effect of streptozotocin on pancreatic cancer induction is unrelated to insulin, or that the action of insulin on tumor induction and growth is local and perhaps paracrine, i.e., a direct feedback between carcinogen-initiated cells and intact β-cells is required. This assumption was supported by a study in genetically diabetic and non-diabetic strains of Chinese hamsters.Although non-diabetic hamsters with normal and intact islets developed pancreatic tumors in response to treatment with BOP, the diabetic strains with atrophic islets were resistant to the tumorigenic action of the agent (60). If intact islet cells were in fact essential for the induction of exocrine pancreatic tumors, stimulation of islet regeneration and neogenesis (nesidioblastosis) would enhance the development of pancreatic cancer. This hypothesis was verified in a recent study, where the nesidioblastosis model of Rosenberg *et al.* was used.

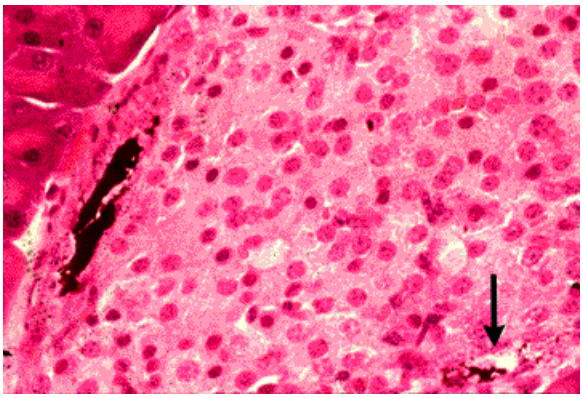

Fig. 1. Traces of india ink (*black*) in periinsular and intrainsular (*arrow*) ductules. H&E, X210.

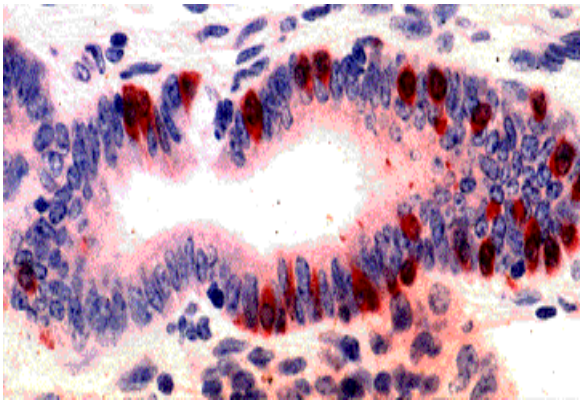

Fig. 2. Early stage in the development of pancreatic cancer. Cells immunoreactive for somatostatin (red) are seen within the hyperplastic epithelium of a ductule. X 210.

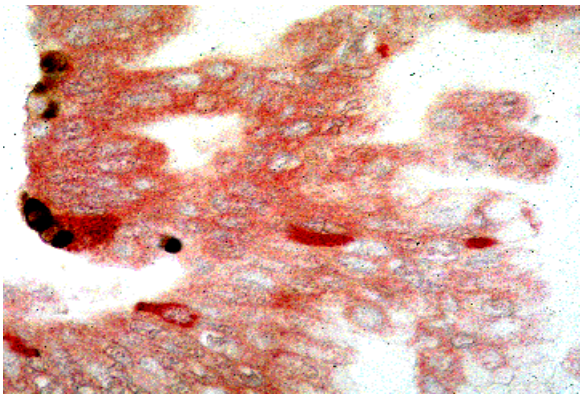

Fig. 3. Somatostatin (red) and insulin immunoreactive cells (brown) in a pancreatic cancer. Nothe the distribution of the endocrine cells in all layers of the malignant epithelium. X 210. (From reference 53, with permission).

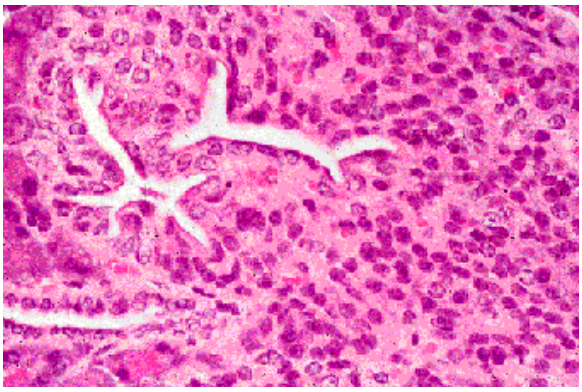

Fig 4. Distended and ramified intrainsular ductules in a pancreas of a hamster treated with the pancreatic carcinogen, BOP. This was the only microscopic finding in the pancreas of this animal. H&E, X 210.

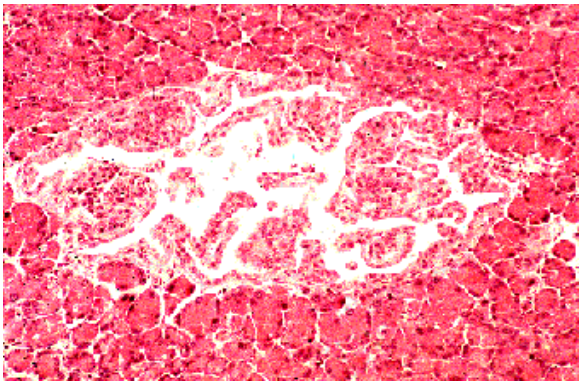

Fig. 5. Ramified and distended intrainsular ductules at early stages of pancreatic carcinogenesis. There were no changes in the exocrine pancreas. H&E, X 120.

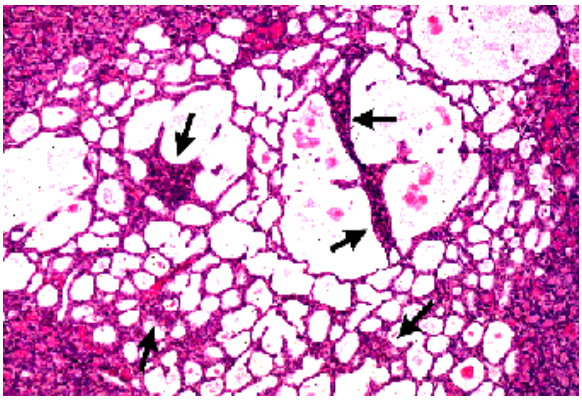

Fig. 6. Convergence of cystic intrainsular ductules of neighboring islets forming a pattern resembling microcystic adenoma. Remnants of islet cells are marked by arrows. H&E, X 75.

These investigators have shown that wrapping a segment of the hamster pancreas with a cellophane strip profoundly stimulated islet neogenesis around the wrapped area (61) to the extent that it cured the streptozotocin-induced diabetes (62). When hamsters with the wrapped pancreata were treated with BOP, significantly more tumors developed in the small wrapped region than in any other areas of the pancreas (63). However, the interpretation of the experiments performed in two independent laboratories differed significantly. Whereas Rosenberg *et al*. claimed that the tumors derive from ductal epithelium (64), our own results pointed to the derivation of most tumors from islets (63). Development of many ca *in situ* within islets and the immunoreactivity of some cancer cells with anti-insulin were reasons for our interpretation.

8. INDUCTION OF DUCTAL-TYPE ADENOCARCINOMA WITHIN ISLET TRANSPLANTS

Derivation of ductal-type adenocarcinoma from within islets could be more convincingly demonstrated if tumors could be induced in the extrapancreatic islets. This approach was achieved by transplanting the homologous pancreatic islets into the submandibular glands of hamsters (65). The submandibular gland was chosen as a site of islet transplantation because this tissue morphologically and biologically resembles the pancreas and because a pilot study demonstrated that this tissue is an ideal site for islet survival and growth (65). When hamsters with islets transplanted into their submandibular glands were treated with BOP, ductular lesions similar to those in the pancreas of these hamsters developed at the site of islet transplantation (66). However, no frank carcinoma was seen in the submandibular gland and the origin of the lesions from either submandibular gland or islets could not be determined. The small number of animals in the groups, the low dose of BOP, and the short experimental duration could have accounted for lack of cancers in these animals. To clarify these issues, in a subsequent study, islets from male hamster donors were transplanted into the right submandibular gland of female recipient hamsters who received higher doses of BOP. By transplanting male hamster islets into the submandibular glands of female hamsters, the origin of the tumor from either the male islets or the female submandibular gland could be determined by identification of the sex chromosome (Y chromosome) in the tumor cells. Six to 12 weeks after BOP treatment, 24% of hamsters developed large, aggressive, ductal/ductular type adenocarcinomas in the right submandibular gland (Fig. 10), where islets were transplanted. On the other hand, no tumors were found in the left submandibular gland, where either immortal hamster pancreatic ductal cells, fragments of hamster thyroid tissue, or cellulose powder were injected (67). As in the pancreas of BOP-treated hamsters, these islets exhibited intrainsular ductular or cyst formation (Fig. 11) and expression of blood group A antigen, which is a pancreatic-tumor-associated antigen in this species (39,40). Many tumor cells adjacent to islets reacted with anti-insulin or with both anti-insulin and anti-blood group A. Similar to the primary pancreatic cancer, tumors in the submandibular gland showed the c-Ki-*ras* mutation in codon 12 (67). A Y chromosome mRNA, identified by PCR, clearly pointed to the derivation of the tumors from male islet tissue. The possibility that tumors may have originated from a few ductular or acinar cells attached to the transplanted islets was ruled out since ultrastructural examination of many islets before transplantation did not reveal their presence. Moreover, transplantation of immortal pancreatic ductal cells that could be readily transformed *in vitro* and could give rise to invasive cancers *in vivo*, did not produce tumors in the submandibular gland (68).

9. ASSOCIATION BETWEEN PANCREATIC CANCER AND ALTERED GLUCOSE METABOLISM

These data suggest that some exocrine pancreatic cancers may be derived from islets and may explain the abnormal glucose metabolism in tumor-bearing hamsters. According to a study by Ahrén and Andrén-Sandberg, in pancreatic carcinogen-treated hamsters, the oral glucose test remained normal until the 20th-30th week, during which no tumors were produced. However, after the 30th week, the impaired glucose tolerance test occurred concomitantly with the appearance of pancreatic cancer (69). These results were confirmed by another group of investigators (70).

Similar findings are seen in patients with pancreatic cancer. The presence of malignant ductules within the human islets was first described by Warren in 1938 (71). Endocrine cells within normal exocrine pancreas and ductular structures within islets have been demonstrated by immunohistochemistry (28,29,45,47,72). The ultimate association of exocrine and endocrine cells was exaggerated in pancreatic tumors. Islet cell tumors admixed with ductular structures (73) and malignant ducts with interspersed endocrine cells are commonly found (44,53). Many ductal adenocarcinomas contain a few or a conspicuous number of different types of islet cells (Fig. 12), sometimes in a pattern consistent with the term "duct-islet-carcinoma" (44,72). The argument that the presence of islet cells within the malignant glandular structures merely represents entrapped islets was refuted by studies showing that these endocrine cells were abnormal in terms of their location, appearance, and immunoreactivity with islet hormone antibodies (44,72). Moreover, their presence in the invasive part of cancers (44) and in their metastasis (72) indicate that these endocrine cells are an integral part of the malignant exocrine tissue. Some investigators suggest that the presence of malignant ductules in islets is the result of cancer invasion. However, a thorough histological study on serially sectioned tissues did not confirm this assumption (29). Moreover, islets containing malignant glandular structures in the tail of the pancreas (Fig. 13) far from the cancers in the body of the pancreas can be found. The

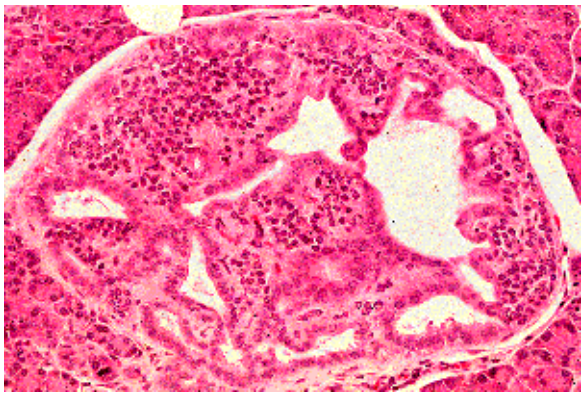

Fig. 7. Proliferation and distention of intrainsular ductules with a hyperplastic epithelium. H&E. X 120.

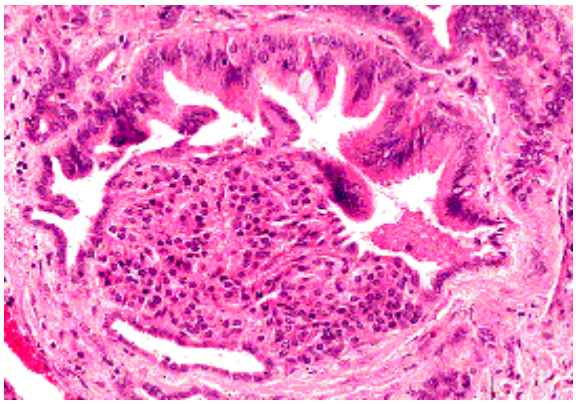

Fig.8. Malignant alterations of one segment of intrainsular ductules with invasion of the surrounding tissue. H&E, X 120. (From reference 29, with permission).

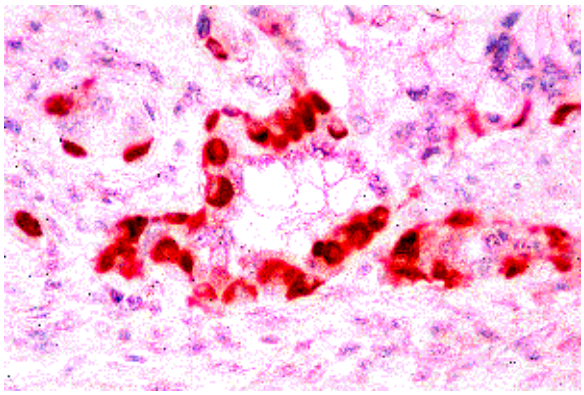

Fig . 9. A moderately - differentiated pancreatic adenocarcinoma containing cells immunoreactive with chromogranin A (red) X 210.

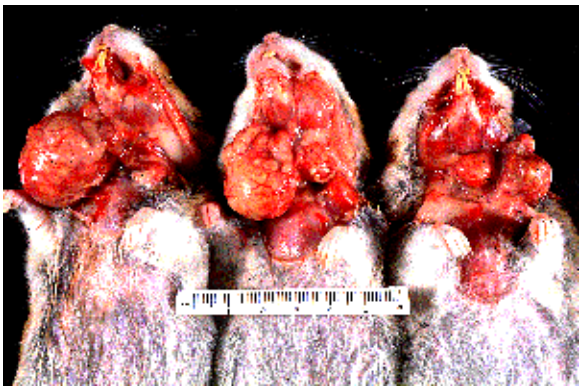

Fig. 10. Induction of tumors by BOP in the submandibular glands in hamsters, where homologous islets were transplanted. (From reference 67,with permission)

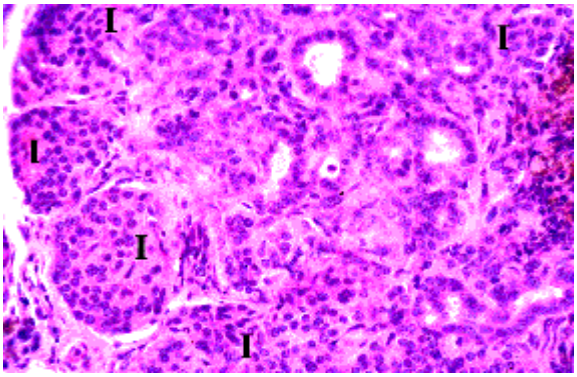

Fig. 11. Hyperplastic ductular elements are seen among islets. Some of the cells lining the ductules reacted with anti-insulin (not shown) H&E, X 210.

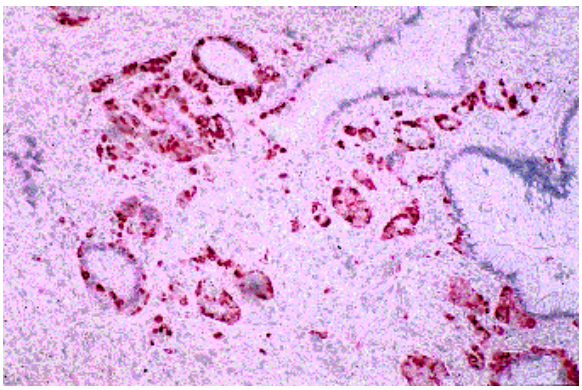

Fig. 12. A mixture of malignant glands with cells immunoreactive for chromogranin A are seen in a well-differentiated ductal adenocarcinoma. X 65.

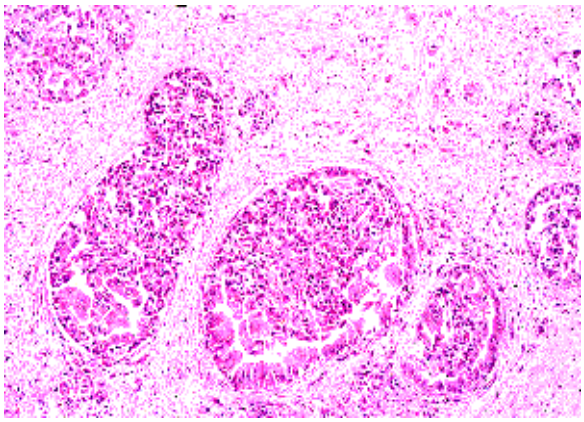

Fig. 13. Malignant mucin-producing cells are seen within islets of a patient with pancreatic cancer. H&E, X 80. (From reference 53, with permission).

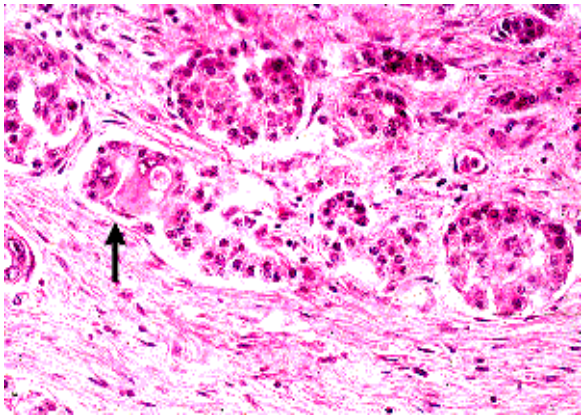

Fig. 14. A few malignant, mucin-producing cells are seen within the atrophic islets in the tal of the pancreas of a patient with pancreatic cancer in the head of the pancreas (arrow) H&E, X 120.

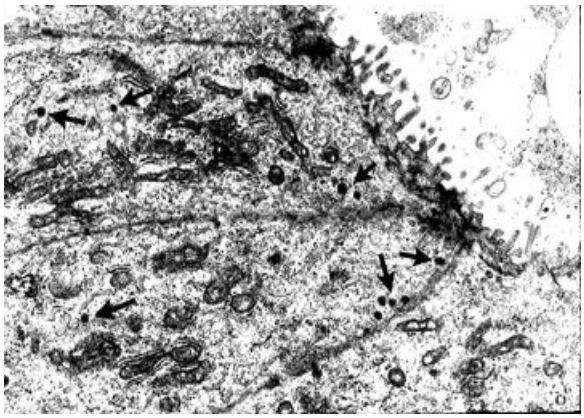

Fig. 15. A few neuroendocrine granules (arrows) are seen within cells of a well-differentiated pancreatic ductal adenocarcinoma. X 3000. (From reference 53, with permission).

patterns of a mixture of islet cells and malignant epithelial cells in atrophic areas of the pancreas suggest differentiation of islet (stem) cells to cancer cells (Fig. 14), as does the presence of neuroendocrine granules in the cells of well-differentiated ductal adenocarcinomas (Fig. 15; 29,53).

In humans, 60-80% of patients with pancreatic cancers have diabetes or an altered glucose tolerance (74-76). Epidemiological studies suggest that this may in part be due to the fact that diabetics are at higher risk for developing pancreatic cancer (7-10). Other lines of evidence imply that an abnormality seen in the glucose tolerance is a consequence of pancreatic cancer. For example, the abnormality is seen in patients with localized small pancreatic cancers (77) which are not associated with widespread parenchymal damage. In one study (77), in 25 patients with pancreatic carcinoma smaller than 2 cm, alteration of glucose metabolism was found in 9 patients (36%); in 7 patients with tumors smaller than 1 cm, a glucose tolerance test showed an abnormality in 2 (28%); and in 18 patients with tumors between 1.1 and 2 cm, impaired glucose tolerance was found in 7 (39%); in 260 patients with tumors larger than 2 cm, the prevalence of alteration was 56.1% (77). Hence, it is evident that even small and localized pancreatic cancers cause a glucose metabolic abnormality. In many patients, the altered glucose tolerance and diabetes are first detected at the time of diagnosis of pancreatic cancer (77-84). Although impaired glucose tolerance has been reported in up to 30% of patients with different types of cancer, in pancreatic cancer patients the frequency and the magnitude of impaired glucose tolerance is higher (80-84). In a study by Permert *et al.*, nearly half of pancreatic cancer patients had frank diabetes (80,81). The diabetes was seen in patients who did not have advanced disease or evidence of metastasis (80-81). In addition, in these patients the metabolic abnormality improved or was cured after tumor resection, suggesting that the diabetes was due to the presence of cancer.

Ishikawa *et al.* showed that, during an oral glucose tolerance test, the plasma C-peptide level was lower, and the proinsulin level and the total proinsulin/total C-peptide ratio was significantly higher in pancreatic cancer patients than in controls (84). Because the ratio was higher in patients with tumors, where many intact islets were left around the tumors, than in those patients with fewer islets left, the authors speculated that in the islets left in cancer stroma the activity of proinsulin converting enzymes decreases or the proinsulin production and release is stimulated (84). Because proinsulin accounts for only 5-10% of insulin activity, glucose intolerance occurs despite the higher immunoreactive insulin levels, which usually are measured by antibodies against insulin that crossreact with proinsulin. The alteration of islets around the tumor could be related directly to the neoplastic process that also affects the islets or indirectly by factors released from the nearby cancer.

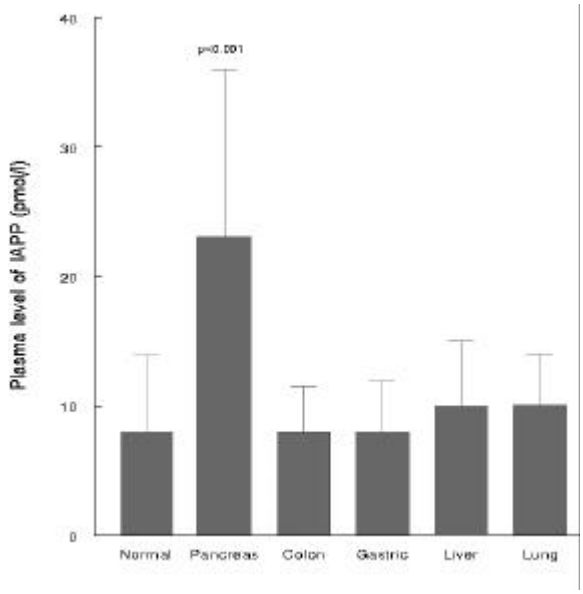

Fig. 16. Plasma level of IAPP in patients with cancer of various tissues

10. ALTERATION OF AMYLOID POLYPEPTIDE (IAPP) IN PANCREATIC CANCER PATIENTS

This question was explored by Permert *et al.* (80,81), who examined hormone levels in plasma and tumor tissue of pancreatic cancer patients. In many of their patients, the levels of islet hormones were abnormal, a finding that corresponded to the results of other investigators (78,79,83,84). Of particular interest were the elevated plasma levels of IAPP (islet amyloid polypeptide) which were significantly higher in patients with pancreatic cancer than with other forms of gastrointestinal malignancies (80; Fig. 16). In obese, noninsulin-dependent type II diabetics, a moderate increase in IAPP levels, to values of about 50% greater than controls, have been reported (85). In pancreatic cancer patients without diabetes, the plasma levels of IAPP are similar to those in obese diabetics but are significantly lower than those in pancreatic cancer patients with diabetes (85). In these patients, immunoreactive IAPP levels were lower in the pancreatic carcinoma than in the surrounding nontumoral tissue (85). In general, endocrine cells, staining for insulin, glucagon, somatostatin, pancreatic polypeptide, pancreastatin, serotonin, and islet amyloid polypeptide (IAPP), were found in well-poorly- differentiated areas, as well as in the invasive components of pancreatic carcinomas (85). The immunoreactivity for insulin, glucagon, somatostatin, and IAPP was lower or absent in the islets in the vicinity of pancreatic carcinoma (44,53). Moreover, unlike the normal islet cells, a variable number of cells within islets expressed tumor-associated carbohydrate antigens, including CA 19-9, DU-PAN-2, and TAG-72 (53). These findings pointed to fundamental alterations in the production, storage, or release of islet hormones by the islet cells in the vicinity of pancreatic carcinoma. They also suggested that, with differentiation toward ductal cells, islets lose their normal phenotypic pattern of expression. Another indication of this finding was that pancreatic cancer is not a localized exocrine disease, rather it involves both the endocrine and exocrine pancreas.

Elevated plasma IAPP levels in pancreatic cancer patients could be due to the liberation of IAPP from the islet cells surrounding the tumors by virtue of a substance(s), presumably a peptide(s) released from cancer cells. The basis for this view was the observation that, in eight of nine of these patients who underwent a subtotal pancreatectomy, the presurgically altered glucose metabolic capacity and insulin utilization rate improved postsurgically (86), and the level of plasma IAPP normalized (80,86). In three patients who required insulin before surgery, insulin was no longer needed after surgery. More strikingly, in three noninsulin dependent diabetics, blood glucose levels normalized after surgery. The results of the study by Permert *et al.* (81) are consistent with the study by Ishikawa *et al.* (84) who found that, in five out of six pancreatic cancer patients, the ratio of total proinsulin/C-peptide was high before the surgery and normalized after the surgery, whereas no such change was seen in patients with unresectable tumors. If an endocrine tissue mass was the critical factor, tumor removal should have increased the severity of diabetes and further impaired glucose metabolism rather than improve it. It should be noted that diabetes is a frequent complication of subtotal pancreatectomy for chronic pancreatitis. However, in pancreatic cancer patients, marked improvement of both whole-body and peripheral insulin sensitivity has occurred after subtotal pancreatectomy and tumor removal (80,86). These findings suggest that pancreatic cancers lead to diabetes in pancreatic cancer patients.

11. MECHANISM OF ALTERED GLUCOSE METABLISM IN PANCREATIC ADENOCARCINOMA

Several studies have addressed whether pancreatic tumors produce diabetogenic substances. In one study, extracts of pancreatic cancer tissue inhibited glycogen synthesis in the rat muscle *in vitro* (87). However, this study did not clarify whether the diabetogenic substance(s) was produced by the tumor cells, by the endocrine cells admixed with tumor cells, or by the functionally altered islets near the tumor. The study by Del Favero *et al.* indicated that the tumor cells may be the source of these substances (88). When extracts of the human pancreatic cancer cell line, MIA PaCa2, were injected into immunodeficient mice daily for 40 days, the animals became hyperglycemic (88).

The role of IAPP in the causation of diabetes in pancreatic cancer patients is suggested by its inhibition of glucose uptake and glycogen synthesis in skeletal muscle *in vitro* and *in vivo*, and in the liver *in vivo* (85,89,90). IAPP also inhibits food intake. In rats, IAPP induces nearly a 48% decrease in food intake and a 7.2% weight loss within 72 hours (90). Consequently, the high serum levels of IAPP in

pancreatic cancer patients may contribute to cachexia, profound insulin resistance, and diabetes (85).

Recent results refute the previous notion that diabetes is a risk factor for pancreatic cancer. These clinical and experimental results were confirmed by a recent epidemiological survey (91), where a correlation was made between 19 types of cancers and diabetes mellitus. The study showed a significant risk factor for liver, pancreas, and endometrial cancers. However, when the time of the diagnosis of diabetes in these patients was taken into consideration, the relative risk for liver and endometrial cancers remained elevated up to 10 years or more after the diagnosis of diabetes. In contrast, for pancreatic cancer, the relative risk for this cancer declined from 3.2 in the 5 years since diagnosis of diabetes, to 2.3 in the 5-9 years after diagnosis, and to 1.3 in the 10 or more years after the diagnosis of diabetes. Based on these data, the investigators concluded that diabetes mellitus could be a causative factor in the development of liver and endometrial cancers, while diabetes may be an early symptom rather than a direct cause of pancreatic cancer, or at least preneoplastic pancreatic lesions (91). These results parallel the clinical observations showing that development of diabetes or altered glucose tolerance occurs shortly before the clinical manifestation of pancreatic cancer (79,80,92). The lack of type I diabetic patients among the 720 pancreatic cancer patients examined by Gullo *et al*. (79) is noteworthy.

Nevertheless, the recent studies, which need further refinement and confirmation, indicate that pancreatic cancer is not merely a disease of the exocrine pancreas. The experimental results clearly show and the clinical data indicate that pancreatic ductal adenocarcinoma also arise from within islets, most probably from undifferentiated cells which also give rise to tumors that originate from ductal epithelium. However, it is noteworthy that in both the experimental model and in humans, tumors arising from large ducts, i.e., intraductal tumors, have a slow grow rate and considerably better prognosis (93), while the most common type, ductal adenocarcinoma, most probably arising from within islets, is malignant and fatal. The reason for the fast growth and expansion of tumors arising from within islets could well be related to a suitable environment within islets, where high concentrations of the growth factors, insulin, TGF-α, and IGF-1 are present.

12. PERSPECTIVE

It appears that some components of islets, most probably the pluripotent stem cells, are extremely vulnerable to malignant transformation and this tendency increases with conditions that can stimulate islet cell proliferation. This knowledge paves the way for understanding the etiology and prevention of this dismal disease.

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