Summary

The study of histological sections of 406 cases of nonendocrine pancreas carcinoma at Memorial Hospital indicated that morphological patterns of pancreas carcinoma could be delineated as follows: duct cell adenocarcinoma (76%), giant-cell carcinoma (5%), microadenocarcinoma (4%), adenosquamous carcinoma (4%), mucinous adenocarcinoma (2%), anaplastic carcinoma (2%), cystadenocarcinoma (1%), acinar cell carcinoma (1%), carcinoma in childhood (under 1%), unclassified (7%).

In 195 cases of patients with pancreas carcinoma, search was made for changes in the pancreas duct epithelium and these were compared to duct epithelium in a control group of 100 pancreases from autopsies of patients with nonpancreatic cancer. The following incidences were found for pancreas cancer and nonpancreatic cancer, respectively: mucous cell hypertrophy, 39 versus 28%; pyloric gland metaplasia, 28 and 17%; epidermoid metaplasia, 6 and 12%; papillary hyperplasia, 42 and 12%; atypical duct hyperplasia, 14% and none; carcinoma in situ in 19% and none in the control group.

Mucin in the majority of pancreas cancers suggested that the cell type of origin of the common pancreas cancer is the mucin-producing duct epithelium. The association of atypias and carcinomas in situ in the patients with pancreas carcinoma implies, by analogy to other organs, that there may be a significant latent period between the appearance of carcinoma in situ and the grossly recognizable pancreas cancer.

Introduction

The morphological classification of primary pancreas carcinomas of the nonendocrine variety would seem to pose no problem to the pathologist because most of these cancers are adenocarcinomas and they span the spectrum commonly found with adenocarcinomas of other organs. Originally, Ewing (18), from this laboratory, described only 2 types of pancreas cancers, cylindrical cell adenocarcinoma arising from the ducts and carcinoma simplex arising from the parenchymal cells. In the subsequent 5 decades terms such as mucous adenocarcinoma, colloid carcinoma, duct adenocarcinoma, pleomorphic cancer, papillary adenocarcinoma, cystadenocarcinoma, and other variants, such as epidermoid carcinoma, mucoepidermoid cancer, giant-cell carcinoma, adenoacanthoma, and acinar cell carcinoma, have appeared (7, 18, 23, 47, 62). Subtypes of islet-cell tumors have been defined (27). As pointed out by Baylor and Berg (5) in discussing the limitations of their study of 5000 patients with pancreas cancer from 8 cancer registries, few pathologists precisely characterize the microscopic features of their cases.

We have reviewed cases of cancer of the pancreas at Memorial Hospital to determine whether there are definable morphological subgroups and to indicate their relative distribution in our material. The delineation of morphological patterns of pancreas cancer may eventually permit a correlation with some genetic, biochemical, endocrinological, clinical, epidemiological, prognostic, or other parameter of significance and thereby further an understanding of this neoplasm that appears to be increasing and has such a poor prognosis for the patient at the present time.

Materials and Methods

From a survey of 757 cases listed as cancer of the pancreas in the Cancer Registry, Clinical Information Center, Memorial Hospital, during the years 1949 through 1972, we have been able to examine histological sections of tissue from 503 cases. Sixty-seven were eliminated from the study for the following reasons: in 42 cases biopsy material did not show any cancer; 3 cases were reclassified as periampullary carcinoma; 7 cases were reclassified as metastatic cancer (2 cases of oat-cell carcinoma of lung; 1 case each of adenocarcinoma of the lung, breast, and colon; 1 malignant lymphoma; and 1 embryonal rhabdomyosarcoma of the retroperitoneum); in 13 cases aspiration biopsies did not furnish enough tissue for classification; 1 debatable case was of either gastric or pancreas origin; and 1 tumor was believed to be of common bile duct origin rather than of pancreatic duct. Thirty cases of malignant islet-cell tumor, recently reported from this laboratory (14), were also excluded.

Cases coded as ampullary or periampullary cancer, duodenal cancer, islet-cell tumors, or retroperitoneal tumors involving the pancreas were not examined, and the parenchymal cells. In the subsequent 5 decades terms such as mucous adenocarcinoma, colloid carcinoma, duct adenocarcinoma, pleomorphic cancer, papillary adenocarcinoma, cystadenocarcinoma, and other variants, such as epidermoid carcinoma, mucoepidermoid cancer, giant-cell carcinoma, adenoacanthoma, and acinar cell carcinoma, have appeared (7, 18, 23, 47, 62). Subtypes of islet-cell tumors have been defined (27). As pointed out by Baylor and Berg (5) in discussing the limitations of their study of 5000 patients with pancreas cancer from 8 cancer registries, few pathologists precisely characterize the microscopic features of their cases.

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Cases coded as ampullary or periampullary cancer, duodenal cancer, islet-cell tumors, or retroperitoneal tumors involving the pancreas were not examined, and
possibly a few pancreas cancers were thereby lost to our study.

In 406 cases there was an operative biopsy of a pancreatic tumor; a confirmation of a pancreas cancer in the surgically resected pancreas, or autopsy specimen; or, in association with a lesion clearly defined in the operative notes as a pancreatic tumor, there was a biopsy taken of a regional lymph node, or of a metastatic lesion, which revealed a neoplasm consistent with pancreas cancer. In 291 cases tissue diagnostic of pancreas cancer was obtained at operation, and in 115 cases the tissue was obtained at autopsy. In 99 cases surgically resected (partial or total) pancreas tissue with a lesion clearly defined in the operative notes as a tumor; a confirmation of a pancreas cancer in the surgically study. Histological slides of the primary tumor varied pancreatic tumor, there was a biopsy taken of a regional metastasis were available. Additional slides, particularly for the demonstration of mucin, were cut from the paraffin-embedded block in 53 cases.

Recently, we have obtained for electron microscopy ultrastructural studies pancreas cancer tissue removed at operation in 28 cases and from autopsy in 3 cases (not included in the morphological classification study).

In 214 cases (99 cases of partial or total pancreatectomy and 115 autopsies), additional study of the pancreas cancer material for associated hyperplasia, metaplasia, atypias, or carcinoma in situ changes in the duct epithelium was attempted. Nineteen cases were rejected because of autolysis of duct epithelium or insufficient ductal tissue present in the histological slides, leaving 195 cases with adequate material. Pancreases from 100 consecutive autopsies (performed in 1973) of patients with nonpancreatic cancers, similar in age and sex to the pancreas cancer cases, were used as controls. Patients were subjected to different regimens of chemotherapy or radiotherapy in the 2 groups, and no corrections were made for these factors. Four to 9 histological sections from each pancreas of the 2 groups were examined.

Standard fixation in 10% formalin solution and staining with hematoxylin and eosin were used for all tissues. Meyer's mucicarmine stain (45) was used to demonstrate mucin, and the periodic acid-Schiff (43) and Alcian blue stains (44) were used to indicate pyloric gland metaplasia (57, 58, 68). The tissue for electron microscopy was fixed overnight in Karnovsky fixative, rinsed in buffer (s-collidine), and post-fixed for 1 hr in 1% osmium tetroxide. The specimens were embedded in epoxy resin (Maraglas) and stained with uranyl acetate followed by lead citrate, and examined in a Siemens-Elmiskop 101 electron microscope (17). Material from one of our acinar cell carcinomas was taken from autopsy "wet" tissue kept in 10% aqueous formalin solution for 8 months. Autopsy had been performed 12 hr postmortem.

In the attempt to subclassify the cases it was required that for a case to fall into one of the groups a predominant, consistent pattern must have been present throughout most of the tissue. In the cases where both a primary and metastatic lesion were available, the same morphological features had to be present in both lesions, with few exceptions. It was fully realized that the quest for a consistent morphological structure, or for changes associated with cancer, was a difficult one involving subjective interpretation made on the small sampling of a tumor, which was sometimes restricted to only a few slides. There were some cases (7%) where admixtures of types occurred so that they were listed as unclassified. A much larger sampling might change the subtyping of cancers or the incidence of changes in duct epithelium.

Results

Nonendocrine Pancreas Neoplasms

Benign Epithelial Nonendocrine Neoplasms. We were able to examine histological material from only 7 cases of benign epithelial nonendocrine neoplasms (3 serous and 4 mucinous cystadenomas) and from 1 case containing a microscopic focus of adenomatous hyperplasia of acinar cells found incidentally at autopsy.

Malignant Epithelial Neoplasms. We have classified primary malignant lesions of the nonendocrine pancreas under the general headings of carcinomas (Table 1), sarcomas, primary malignant lymphomas, a miscellaneous group, and metastatic cancer. We estimate that over 95% of the malignant lesions of the nonendocrine pancreas are adenocarcinomas and the following appear to be distinctive types.

Duct Cell Adenocarcinoma (Adenocarcinoma, Cylindrical-Cell Adenocarcinoma (18), Papillary Adenocarcinoma (23), Pancreas Cancer (5)). In the normal duct system of the human pancreas there is variation from the flat to cuboidal epithelium of the smallest ductules to the high columnar mucous cell of the epithelium in the head of the pancreas (9, 24). There is absence of mucin in the smallest ductules, as indicated by the negative mucin stains, and the presence of mucin, indicated by a positive mucin stain, in the apical region of the columnar cell of the duct epithelium, particularly in the larger ducts (24, 46). By electron microscopy it can be demonstrated that droplets of mucigen are present in the duct epithelium (9) (Fig. 7) and not in the smallest epithelial cells of the ductules.

Our cases of duct adenocarcinomas were similar to the adenocarcinomas seen elsewhere in the biliary tract, gastrointestinal tract, lung, and other organs (Figs. 1 and 2). There was a mixture of large and small glands, often with 1

<table>
<thead>
<tr>
<th>Classification of nonendocrine pancreas carcinomas</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duct cell adenocarcinoma</td>
<td>308</td>
<td>76</td>
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<tr>
<td>Giant-cell carcinoma</td>
<td>19</td>
<td>5</td>
</tr>
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<td>Microadenocarcinoma</td>
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<td>4</td>
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<td>2</td>
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<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Acinar-cell carcinoma</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
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<td>7</td>
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<td>406</td>
<td>102</td>
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size predominating, but because of much overlapping we lumped all cases altogether (23). Areas of well-differentiated adenocarcinoma to foci of poorly differentiated glandular configurations were present. The glands were lined by tall columnar or cuboidal cells. The nucleus was usually round to oval and was located in the base of the cell. The cytoplasm varied from a watery clear to darker pink, most often resembling the cytoplasm of the cells of the large pancreatic ducts or the biliary tract epithelium. Mucicarmine, periodic acid-Schiff or Alcian blue stained the cytoplasm usually at the apical portion, or luminal border. Occasionally, goblet cells were present. Desmoplastic response was usually considerable (Fig. 2), and often sclerotic areas revealed only a few glands separated by dense bands of collagen.

Focally, mucinous cells, “signet-ring” cells, papillary carcinoma, and small tubular patterns of adenocarcinoma were observed. Some glands were so well differentiated that when they were present in the periampullary region it was difficult to distinguish the tumor from the normal glands found in this area (40). Pancreatic duct adenocarcinoma when metastatic to the lung occasionally simulated primary adenocarcinoma of the lung (37, 38).

Electron microscopic study of 28 duct adenocarcinomas showed in many cases globules of mucigen usually in the apical cytoplasm (Fig. 8), but in some cases none was present. In cases with duct obstruction and no pancreas cancer, there appeared to be mucous cell hypertrophy with more than the usual amount of mucigen in the cytoplasm (Fig. 7). Zymogen granules were not present in any case.

Giant-Cell Carcinoma [Pleomorphic (28, 35), Medullary (62), Sarcomatoid (47), or Carcinosarcoma (23, 32)]. The giant-cell carcinoma appeared to be a distinctive type (Fig. 3), although it was not specific for the pancreas. It was characterized by the presence of huge cells with very large, pleomorphic, often vacuolated nuclei, containing prominent nucleoli and abundant coarse nuclear chromatin. The cytoplasm was abundant, dense, and stained heavily with eosin. Phagocytosis was seen occasionally. The tumor cell resembled similar cells seen in melanoma, hepatocellular carcinoma, choriocarcinoma, rhabdomyosarcoma, and the giant- and spindle-cell carcinomas of the thyroid and lung. Areas of spindle malignant cells were usually present and sometimes made up a large part of the tumor. With multiple sections of these tumors, one could find in most of the cases areas of adenocarcinoma contiguous to the giant tumor cells (Fig. 4) (conversely, in some duct adenocarcinomas of the pancreas, or in adenocarcinomas of other organs, small foci of giant cells can be demonstrated). Only when the predominant mass of tissue was composed of giant cells was the case assigned to the giant-cell category. No case of carcinoma of the pancreas simulating the giant cell tumor of the bone, believed to be of acinar cell origin by Rosai (59), was present.

Microadenocarcinoma. This neoplasm usually consisted of an intimate combination of 2 types of tissue: nests of small to intermediate-sized cells without glands or intervening stroma, or intercellular substance, and small glands (Figs. 5 and 6). The mucicarmine stain was positive in many such glands. Usually, within a microscopic field both elements were recognizable, with either the solid or glandular component predominating. In most areas the microadenocarcinoma was predominant and large foci of necrosis were present. Sometimes the adenocarcinoma resembled the biliary-pancreatic duct epithelium; in other cases it resembled more the gastrointestinal types. The pattern is also seen in colon cancer and adenocarcinomas of other organs. We debated whether this should be called solid microadenocarcinoma because of the frequent presence of areas of solid masses of small cells, but because the microadenocarcinoma predominated in many of our cases we decided to name the type by its predominant component. Both components were malignant in all of our 15 carcinomas.

Adenosquamous Carcinomas [Adenocanthoma (12), Mucoepidermoid Carcinoma (23), Squamous Carcinoma (41)]. A characteristic pattern of the adenosquamous carcinoma was the presence of 2 components, an adenocarcinoma and a squamous cell carcinoma (Fig. 9). The glandular areas varied in their differentiation from well to poorly differentiated. In the 3 cases tested where there was a question as to whether mucin was present, all gave a positive stain for mucin, either in glands or in the individual adenocarcinoma cells. The squamous pattern was characterized by epithelium with whorls, keratohyalin, or “pearls.” Occasionally, intercellular bridges were present. By electron microscopy one could demonstrate tonofibrils (Fig. 10). In 1 case only squamous carcinoma was present in the metastatic lesion. The metastatic lesions had the same pattern as the primary tumor in all other cases. Both the glandular and the squamous components were malignant in all of our 14 cases.

Mucinous Adenocarcinoma [Colloid (23, 30), Gelatinous (34), or Mucoid Carcinoma (69)]. Mucinous adenocarcinoma was a distinctive type, characterized by the presence of huge multiloculated pools of mucus (Fig. 11), sometimes with very few cells being present. The cells were often flattened or compressed in the periphery against a collagen stroma, so that one found in both primary and metastatic areas large pools of mucus in a relatively acellular field separated by strands of collagen. Usually, there were small foci or individual cells of adenocarcinoma discernible (Fig. 12). In 1 case there were diffuse, isolated foci of “signet-ring” carcinoma cells in the mucus pool. A similar pattern is seen occasionally in the breast, gastrointestinal tract, and other organs.

Cystadenocarcinoma [Papillary Cystadenocarcinoma (3, 6, 55, 67)]. This appears to be a malignant variation of the benign cystadenoma with cysts of varying size and contents, separated by collagen strands and lined at the periphery with epithelium (Fig. 13). In the cystadenocarcinoma, the epithelium ran a gamut from flat cells to papillae of malignant epithelium projected into and filling the cyst (Fig. 14). Generally, the malignant epithelium showed loss of polarity, hyperchromicity, and bizarre nuclei with very heavy nuclear chromatin. Mitotic figures were present. Some cysts were empty, or more often they had serous or mucinous contents. Cystadenocarcinoma has to be distinguished from a duct adenocarcinoma with focal papillary features, or cystic degeneration, or one with duct carcinoma producing obstruction and dilation of the ducts. Our 3 cases showed mucin in the cyst contents.
Acinar Cell Carcinoma [Parenchymatous Adenocarcinoma (18, 64)]. The structure of the normal acinar cell with its basal nucleus and prominent nucleolus surrounded by extensive ergastoplasm and the apical zymogen granules is well known (9).

Our few cases showed gland formation, tubular arrangement, and somewhat random mixture of various configurations of acini (Figs. 15 and 16). Usually, in the cell there was considerable deeply staining cytoplasm, a basal nucleus, and, as in many carcinomas, nests of malignant cells that did not retain the characteristic configuration of the normal gland but appeared as sheets of smaller malignant cells. In some cells zymogen granules could be discerned, but in most of the slides there was only a diffuse, nonparticulate pink to red cytoplasm. A few foci resembled islet cells. No enzyme studies were done to confirm the presence or absence of the usual pancreas exocrine enzymes. In 1 case we were able to obtain formalin-fixed “wet” tissue and examine it by electron microscopy. There was much nuclear and cytoplasmic autolysis, but typical zymogen granules, fewer in number than in normal acinar cells and somewhat autolyzed but still recognizable (Fig. 17), were present in many cells. None of the 3 cases gave any evidence of the production of excessive amounts of enzyme activity.

Anaplastic Carcinoma [Indeterminate Carcinoma (47)]. There were 6 cases in which differentiation of a small, diffusely infiltrating cell was so limited that it was not possible to place the cell type, or pattern of growth, in any of the above groups. Because the cells grew in nests or chords of cells they were placed in the general category of carcinomas (Fig. 18). However, in view of the absence of electron microscopy and other studies, this assignment was provisional. The mucin stain was negative in 3 of the 3 cases tested.

Cancer of the Pancreas in Childhood [Infantile Type (22)]. One tumor was found in a 3-year-old child. There were areas of small-cell adenocarcinoma, squamous-cell elements, malignant spindle cells, and benign areas of mesenchymal tissue, including bone, found in a tumor of the head of the pancreas (Fig. 19). A similar case has been described by Frable et al. (22). Another case in a child, not included in this study, was seen in consultation by Dr. Frank W. Foote, Jr., who noted that the structure was that of a papillary cystadenoma resembling a case described by Frantz (Ref. 23, Fig. 13). An apparently similar case has been recorded (31). Other cases in children have been reported (49, 66).

Unclassified Cancer. There was a significant percentage of tumors (7%) of cases that were difficult to classify. Most showed poor, or partial, formation of glands or ducts. Mucin was demonstrated in some cases. In other cases the pattern was solid, or trabecular, without mucin. Some cases presented with small glands, or gland-like structures.

Metastatic Cancer (23)

In 100 consecutive autopsies of adults from this hospital with a primary cancer other than pancreas, roughly similar in age and sex to our pancreas cases, 16 showed metastasis to the pancreas. The most common primary sites were lung, melanoma of the skin, and diffuse malignant lymphoma, 3 cases of each. The primary cancers in the other 7 cases were 1 each from a variety of organs.

Miscellaneous

Although in this study no ciliated (23, 42, 62), carcinoid (52) (69), or oncocyct tumor (31) was included, these cells are normal, although rare, constituents of duct epithelium and, presumably, tumors of these cell types will appear, rarely. From this hospital there has been reported (15) a case of carcinoid syndrome the cell type of which was uncertain, being either islet-cell or of carcinoid origin. We have not included the case in this report.

Associated Duct Cell Changes

Hypertrophy of mucous cells (Fig. 7) was more prevalent in the pancreas cancer cases than in the control group (39 versus 28%, respectively). Pyloric gland metaplasia (57, 58, 68) (Fig. 20) was slightly greater in the pancreas cancer group (28 versus 17%). Epidermoid (squamous) metaplasia of duct epithelium was less frequent in pancreas cancer patients (6%) than in the patients with cancer of other organs (12%). Papillary hyperplasia (63) was seen in 42% of pancreas cancer cases (Fig. 20) and in 12% of the patients with nonpancreatic cancer. Marked atypia of duct epithelium (Fig. 21) was found in 14% of our pancreas cancer cases, but none was noted in the pancreases of 100 autopsies of patients with nonpancreatic cancer. In 19% of cases with pancreas cancer, there were associated carcinoma in situ changes of the duct epithelium. In none of the control nonpancreatic cancer cases did we find in situ lesions. Usually, the in situ changes (Figs. 22 to 25) were associated with areas of papillary hyperplasia and/or marked atypia and most often were found adjacent to the primary tumor. However, in 2 cases of cancer of the head of the pancreas, in situ changes were present in the body, and/or tail of the pancreas (Fig. 25).

Prevalence of Subtypes

The categories of carcinomas, their incidence, and the relative percentages of metastasis to the pancreas from other organs represent findings in patients of a cancer hospital and may not be representative of the general population.

Discussion

Histological Types. One may legitimately question the value of subclassification of pancreas cancer at the present time because most patients die within 1 year from the onset of symptoms. In addition, there is the possibility that 1 category might merely represent a minor variation of
another group, e.g., the giant-cell carcinoma might represent an accelerated growth rate of the duct adenocarcinoma. However, there were 19 cases of the giant-cell variety with a distinctive, fairly uniform structure and it might be instructive from a conceptual viewpoint to know why this difference occurred even if the 2 types represented essentially the same tumor. One subgroup, widely recognized as having a characteristic appearance, the cystadenocarcinoma, seems to have a better prognosis than the other types and is, thereby, different in both morphological structure and biological behavior (5, 6, 67). The acinar cell carcinoma is morphologically recognizable, particularly if electron microscopy is used, and occasionally it continues to synthesize the enzymes characteristic of the cell type (2, 11, 13, 51, 64).

It is possible that chemotherapeutic compounds will be found that have differential effects on the cancer subtypes, just as ethionine has been shown to affect the normal acinar cell more than it does the normal duct, or islet, cell epithelium (19, 21, 25), or as streptozotocin has been demonstrated to cause more damage to the β-islet cell than it does to other pancreas cell types (10).

Occasionally, as in tumors of other organs, a specific histological type will be the characteristic expression of an environmental factor, e.g., mesothelioma of the lung in asbestos workers (60) and the recently reported angiosarcoma of the liver in polyvinyl chloride workers (53). A cell type may give rise to a specific hormonal response, such as the medullary carcinoma of the thyroid C-cell and its production of the calcitonin hormone (65). Usually, there is not a clean-cut relationship between morphology and an etiological agent.

One of our adenosquamous cancer patients had 2 other cancers, as well as the adenosquamous cancer, develop in a radiated field, the latter 30 years after the radiotherapy. This is somewhat reminiscent of the thyroid cancers developing subsequent to “thymic” radiation in infancy (16, 56). One of 4 adenosquamous cancers in the population of Hiroshima appeared in a person exposed to the atomic bomb radiation (12).

The subtypes that we have listed have been noted in many cancers by many investigators, most of whom have indicated that the commonest cancer of the pancreas is an adenocarcinoma (1, 5, 7, 18, 23, 26, 30, 47, 48, 62). In contrast to our designation of duct adenocarcinoma as the principal type is the report of Baylor and Berg (5), who collected the diagnoses from 8 cancer registries. Only 4.4% of their cases were listed as “ductal adenocarcinoma.” However, 63% of the cancers were called “adenocarcinoma” and another 23% were labeled as “cancer NOS” (not otherwise specified). Essentially similar results were reported from the Connecticut Cancer Registry (48).

We have not recognized the category of “papillary adenocarcinoma,” reported by Baylor and Berg (5) to occur in 1.3% of their cases. In many duct cell adenocarcinomas there are areas of papillary carcinoma, carcinomas of the peripapillary area tend to be papillary, and cystadenocarcinomas characteristically have considerable papillary carcinomatous foci. Our incidence of 1% and theirs of 0.2% for cystadenocarcinoma and the significantly better 3-year survival figures for both groups suggest that their papillary carcinoma cases would have been classified as cystadenocarcinomas by us.

The microadenocarcinoma pattern, although present in foci of tumors from many organs, particularly the colon, has not, to our knowledge, been set aside previously as a type of pancreas cancer. It may represent a variant of the duct adenocarcinoma, or possibly carcinoid, but enough cases showed this consistent appearance to warrant the suggestion that this might be a distinct entity.

The anaplastic group of tumors also appears to be a recognizable cell type, but until electron microscopy, histoch­emical, or biochemical studies are performed its cell of origin is uncertain. This tumor type is present in many other organs.

The acinar cell carcinoma has been widely recognized. In 3 reports the incidence of this lesion has differed from our figures [15% in 1 group (37), 13% in a 2nd (47), and 11% in the 3rd (62)], higher than the 1% found in our patients. Only if very-well-differentiated acini, or acinar cells, were present in some foci would we include the cases in this category and possibly we have thereby excluded poorly differentiated acinar cell tumors. Frantz (23) and others (30, 48) remarked that the type was rare.

The extreme rarity of acinar cell adenomas of the pancreas in humans is surprising because adenomas and adenomatous lesions have been produced experimentally in animals by azaserine (39), nitrosoamines (54), and 4-hydroxyaminoquinoline 1-oxide (33, 61). Our only case of benign acinar cell lesion was a microscopic focus of adenomatous hyperplasia. Cystadenomas were more frequent in our material. Our 7 cases were fairly representative of these lesions. Glener and Mallory (24) collected 36 such cases from 6 Boston hospitals.

Whether these histological subtypes represent a spectrum of random morphological expressions of a single process or whether they are the result of multiple different carcinogenic factors, each giving rise to a characteristic type, is unknown. It is assumed that morphological aspects of a tumor have an underlying macromolecular basis for their anatomical distinctiveness, even if these patterns cannot be, at the present time, correlated with an unique phenotypic biochemical process. There probably are severe limitations to the variety of morphological patterns that a cell can manifest in reacting to carcinogenic factors. Nevertheless, the search for possible correlations should be pursued.

Cell of Origin of Adenocarcinomas. Conceivably, the duct (or ductule) cell, the islet cell, or the acinar cell could give rise to the commonest type of adenocarcinoma since it is believed by most embryologists that the duct cell gives rise to both the acinar and islet cells. By “dedifferentiation,” the latter 2 might revert to an embryonic duct cell type and then be transformed to the carcinoma, or be transformed directly to a carcinoma.

The distinctive acinar cell with its abundant ergastoplasm, a basal nucleus, and zymogen granules in the apical cytoplasm does not produce mucin. It would therefore have to lose its ability to synthesize zymogen granules and acquire a mucin-producing facility to give origin to the adenocarcinoma. The absence of zymogen granules by light or electron microscopic examinations in 28 consecutive
cases of duct adenocarcinoma does not suggest that transition between the 2 cell types occurred.

The islet cells have distinctive tinctorial and morphological characteristics that permit one to identify by light microscopy a group of tumors that fit into that category. The islet cell contains no mucin and has no zymogen granules. Further separation into different islet cell groups through the use of histochemical staining and electron microscopy examination and hormone production by the tumor is possible (27). In none of the 28 cases diagnosed as adenocarcinomas by light microscopy was there noted by electron microscopy the distinctive granules of any type of islet cell.

There appears to be no significant evidence supporting the possibility that either the acinar cell or the islet cell “dedifferentiates” and gives rise to the commonest adenocarcinoma. In situ carcinoma lesions were recognized in duct epithelium adjacent to the primary lesion, further supporting the claim of the duct cell as the cell or origin. Ductule epithelium also could give rise to the duct cell adenocarcinoma but the absence of mucin makes this cell a less likely candidate for the cell of origin.

The duct cell would also be the favorite contender as the cell type of origin for the mucin-producing microadenocarcinoma, the adenosquamous carcinoma, the mucinous adenocarcinoma, the cystadenocarcinoma, and the giant-cell adenocarcinoma.

Whether an islet cell or acinar cell gives rise to the other subgroups is not clear. Either would have to be considered, as would the ductule cell, as a potential cell type of origin in the non-mucus-producing anaplastic carcinomas and some unclassified tumors.

Duct Epithelium Changes Associated with Pancreas Cancer. Our figure of 19% of the cases showing a carcinoma in situ adjacent to the primary cancer is higher than the 3% reported by Sommers et al. (63) in 141 autopsies of pancreas cancer cases collected from 3 hospitals. Whether this represents differences in the amount of duct epithelium available for study (we concentrated on 195 cases in which considerable duct epithelium was present) or because of different criteria used for diagnosis is unknown. The results of both groups nevertheless suggest the possibility that there may be a significant latent period between the appearance of cancer in situ in duct epithelium and the grossly recognizable pancreas cancer, analogous to the long interval between carcinoma in situ of the human uterine cervix and invasive cervical cancer (4, 20). Tempering the findings is the fact that in Bell’s (7) 609 autopsies of cancer of the pancreas, collected from many hospitals, only 2 were found incidentally at autopsy; the rest were diagnosed clinically. However, it would not appear from this report that an intensive search for in situ lesions was made.

The incidence of 14% of cases showing marked atypia in the pancreas cancer group and none in the control group would appear to be significant. It is consistent with the general finding in human cancer that, with primary cancers, one frequently finds associated typical hyperplasias, marked atypia, and carcinoma in situ, the yield increasing with the amount of tissue studied.

Sommers et al. (63) found that 41% of their cases showed papillary hyperplasia, usually more prevalent in the vicinity of the cancer and the larger ducts. Similar papillary (or adenomatous) hyperplasia occurred in about 9% of nonneoplastic autopsies and in 28% of autopsies of diabetic patients. Our higher incidence of papillary hyperplasia in the pancreas cancer cases (42%) is consistent with these findings. However, there was obstruction to the pancreas duct in most of our cases, a complicating factor in the assessment of this change. Birnstingl (8), in cases with a variety of acute and chronic nonpancreatic diseases and no cancer of the pancreas, reported an incidence of 29% having hyperplastic columnar epithelium.

The greater percentage of mucous cell hypertrophy in the pancreas cancer cases is also complicated by the presence of duct obstruction and the lack of a more appropriate control group, one with duct obstruction without pancreas cancer.

It was somewhat surprising to find less epidermoid metaplasia in the pancreas cancer cases (6%) than in the nonpancreatic cases (12%) and such a low incidence of changes in both groups. Sommers et al. (63) also noted that epidermoid metaplasia was not pronounced in pancreas cancer cases. Birnstingl (8) found an incidence of 8% in patients with acute and chronic disease but without pancreas cancer. Korpássy (36) found epidermoid metaplasia of the pancreas in 12% of 500 unselected, carefully studied autopsies. This increased to 29% in patients over 70 years old.

In 2 cases of cancer of the head of the pancreas, the in situ carcinoma areas were in the body and tail of the pancreas some distance away from the primary tumor (Fig. 25). Multicentric origin of papillary carcinoma in the ducts of the pancreas was noted by Habán (29), a finding consistent with the multicentricity of other human carcinomas.

**References**


**Patterns of Pancreatic Carcinoma**

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Patterns of Pancreatic Carcinoma


Fig. 1. Duct adenocarcinoma. Fairly-well-differentiated adenocarcinoma resembling pancreatic ductal epithelium. There is desmoplastic reaction. H & E, x 136.

Fig. 2. Duct adenocarcinoma. Fairly-well-differentiated adenocarcinoma showing a variety of large and small glands and desmoplastic reaction. H & E, x 136.

Fig. 3. Giant-cell carcinoma. Bizarre tumor giant cells with huge, often irregular, sharply defined, dark nuclei and abundant deeply staining cytoplasm are present. H & E, x 250.

Fig. 4. Giant-cell carcinoma. Peritoneal implant showing a focal area of fairly-well-differentiated glands (left) in the presence of many tumor giant cells. H & E, x 148.

Fig. 5. Microadenocarcinoma. Solid configuration of cancer cells intermixed with small glands. H & E, x 54.

Fig. 6. Microadenocarcinoma. Predominantly microglandular cancer with intervening small cells. H & E, x 136.

Fig. 7. Electromicrogram of benign pancreatic duct epithelium in head of the pancreas. Cancer of ampulla giving pancreas duct obstruction was present. Hypertrrophy of mucous cell with anacical muciglobules. x 16,000.

Fig. 8. Electromicrogram of well-differentiated adenocarcinoma of head of pancreas. Mucigen globules are present in apical cytoplasm of 2 cells. No zymogen granules present. x 17,600.

Fig. 9. Adenosquamous carcinoma. Fairly-well-differentiated adenocarcinoma with a squamous cell carcinoma component. H & E, x 136.

Fig. 10. Adenosquamous carcinoma. Electromicrogram of an adenosquamous carcinoma cell showing tonofibrils (black wavy lines). H & E, x 6,720.

Fig. 11. Mucinous adenocarcinoma. Pools of mucus subdivided by collagenous septae. Only a few carcinoma cellular elements are present. H & E, x 35.

Fig. 12. Mucinous adenocarcinoma. Similar to Fig. 11 except that carcinoma cells are present (lower center and upper right cysts). H & E, x 56.

Fig. 13. Cystadenocarcinoma. Cystic areas with cyst wall lined by papillae of mostly columnar mucinous epithelium with small foci of cells running a gamut from hyperplasia to marked atypia to carcinoma. H & E, x 62.

Fig. 14. Cystadenocarcinoma. Papillary variety of cystadenocarcinoma illustrating the complex arborizing labyrinthine structure. H & E, x 54.

Fig. 15. Acinar-cell carcinoma. Metastatic nodule of mostly fairly-well-differentiated acini and acinar cells. Undifferentiated or poorly differentiated cells, left upper and left lower regions. H & E, x 54.

Fig. 16. Acinar cell carcinoma. Same as in Fig. 15, different field, showing many acini with basal nuclei and abundant apical dense cytoplasm. As is usual with formalin fixation and hemotoxylin and eosin staining, zymogen granules are not distinct. H & E, x 136.

Fig. 17. Acinar-cell carcinoma. Electromicrogram of the same case as Figs. 15 and 16. Marked postmortem autolysis. However, characteristic zymogen granules are present, although somewhat autolyzed. Specimen fixed 12 hr postmortem. x 15,600.

Fig. 18. Anaplastic carcinoma. Diffuse infiltration of varying sized cells with large nuclei and relatively little cytoplasm. There are nests of tumor cells surrounded by thin fibrous septae. H & E, x 350.

Fig. 19. Carcinoma of childhood. Tumor of the head of the pancreas in a 3-year-old boy. There are areas of anaplastic small cells, small gland formations, foci of squamous elements. H & E, x 56.

Fig. 20. Papillary hyperplasia of pancreatic duct. Tissue from area adjacent to cancer of head of the pancreas. Papillae of orderly hyperplastic epithelium showing periodic acid-Schiff-positive material (black) in apex of cell (left). Stained areas at base of papillae (black, right) represent pyloric gland metaplasia. H & E, x 62.

Fig. 21. Atypical papillary hyperplasia and carcinoma in situ. A pancreatic duct showing atypical papillary hyperplasia with a focal area of carcinoma in situ. Tissue taken from area close to carcinoma of head of pancreas. Periductal fibrosis present. H & E, x 52.

Fig. 22. Carcinoma in situ. A large pancreatic duct showing intraductal carcinoma. Note the cribriform pattern, loss of polarity, and nuclear and other cytological abnormalities. Tissue adjacent to invasive duct adenocarcinoma. H & E, x 140.

Fig. 23. Carcinoma in situ. Enlargement of lower left zone of Fig. 21 showing focus in in situ carcinoma. Variation in size and shape of nuclei, loss of nuclear and cell polarity, and increased condensation and abnormal distribution of nuclear chromatin. H & E, x 340.

Fig. 24. Carcinoma in situ. Small duct near carcinoma of head of pancreas. Lower area, cells and nuclei with marked variation in size, shape, staining, and polarity of nuclei. H & E, x 340.

Fig. 25. Carcinoma in situ. Large duct in body of pancreas in case with cancer at head of pancreas. Carcinoma in situ with papillary features. H & E, x 340.
Morphological Patterns of Primary Nonendocrine Human Pancreas Carcinoma

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