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Epithelial Tumors of the Rat Pancreas[1]

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SUMMARY—During routine necropsy of 1,252 rats of the Chester Beatty stock albino strain between January 1962 and October 1965, we saw 10 epithelial pancreatic tumors. Eight were in males and 2 were in females. Five were single or multiple exocrine adenomas, 3 were exocrine adenocarcinomas, and 2 were islet-cell tumors. A search through the literature revealed 3 reports of exocrine adenomas, 11 of exocrine adenocarcinomas, and 19 of islet-cell tumors. Histological criteria for distinguishing between adenomas of exocrine and islet origin and between benign and malignant variants of each are discussed. An association between islet-cell adenomas and adenomas of other endocrine glands in rats has been recorded by several authors; its significance is unknown.—J Nat Cancer Inst 39: 18–32, 1967.

FROM JANUARY 1962 to October 1965, we found 10 epithelial tumors of the pancreas during routine postmortem examination of rats of the Chester Beatty stock albino strain (CB) used in carcinogenicity tests. There was no reason to suspect a causal relationship between exposure to the test material and the development of a pancreatic tumor in 8 rats. The remaining 2 received no treatment.

Five tumors were single or multiple benign exocrine adenomas, 3 were adenocarcinomas, and 2 were islet-cell tumors. In searching the literature, we have been unable to find a detailed description of such tumors in rats and have been impressed by the absence of any pancreatic tumor in 7 large surveys of spontaneous tumors in various strains of rats (table 1). However, we have been able to trace 3 reports of exocrine adenoma, 11 of adenocarcinoma, and 19 of islet-cell tumors, as shown in tables 2 and 3. The "pancreatic adenomas" described by Hoch-Ligeti (*1*), Lamson *et al.* (*2*), and Tannenbaum *et al.* (*3*) have been omitted because the histological type was not indicated. Some of the reports in these tables were discovered by chance while the literature was being searched for another purpose; it is almost certain that others have been overlooked. Except for the experiment of Hendry *et al.* (*4*) with 4′-fluoro-4-aminodiphenyl, which produced a high yield of tumors at various sites including the pancreas, exocrine tumors listed in these tables were regarded by the authors as incidental findings. Some of the islet-cell tumors in rats exposed to ionizing radiation may have been induced (table 3).

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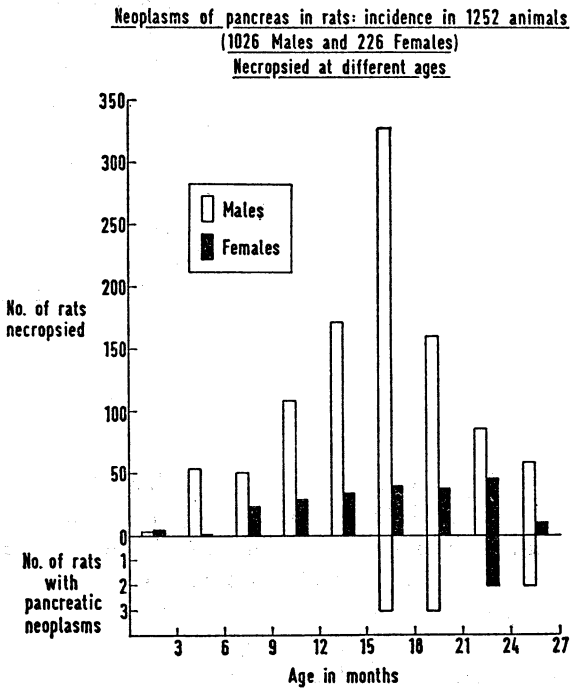
TABLE 1.—Occurrence of spontaneous neoplasms in groups of rats in which no pancreatic tumors were found

Author	Year	Strain	Remarks
McCoy (*5*)	1909	Wild rats (*Mus norvegicus*)	103 tumors in 100,000 rats
Woolley and Wherry (*6*)	1911	Wild rats (*Mus norvegicus*)	22 tumors in 23,000 rats
Bullock and Curtis (*7*)	1930	Stock	521 tumors in 489 rats; population at risk about 33,000
Ratcliffe (*8*)	1940	Wistar	320 tumors in 273 of 468 rats
Saxton *et al.* (*9*)	1948	Albino Osborne-Mendel	234 tumors in 498 rats
Davis *et al.* (*10*)	1956	Sprague-Dawley	57% tumor incidence in 150 female rats; 80% tumor incidence in 100 female rats
Crain (*11*)	1958	Wistar	200 tumors in 189 of 786 rats

MATERIALS AND METHODS

The present study began with the discovery of multiple exocrine adenomas of the pancreas at routine necropsy of 2 CB rats (#3 and 4) early in 1964. A retrospective search was made through our postmortem records as far back as January 1962 and further cases were collected in 1964 and 1965. The survey was completed in October 1965. Several reports were excluded from the study because postmortem decomposition made macroscopic examination inaccurate and microscopic examination impossible. A total of 1,252 rats, including the 10 pancreatic tumor bearers, was suitable for analysis. Eight of the affected animals were males (1,026 males in population) and 2 were females (226 females in population), an incidence of 0.79% for males and 0.88% for females. If only animals of 12 months or older are considered, the percentage of pancreatic tumor bearers is 0.99% for males and 1.18% for females. The age and sex distribution of our sample are summarized in text-figure 1.



TEXT-FIGURE 1.—Incidence of pancreatic tumors in Chester Beatty rats.

Technique of necropsy.—Most rats were subjected to experimental procedures, though some were members of control groups which received either no treatment or treatment with solvents or other vehicles only. Necropsy procedure varied in extent, depending on the nature of the experiments. However, the basic examination to which all rats were subjected included the deliberate examination of the pancreas and the recording, on a necropsy sheet, of the presence or absence of abnormality of that organ. Necropsies were carried out by various members of the technical staff of the department but always under the immediate supervision of the Senior Technical Officer, Mr. B. C. V. Mitchley. Nonetheless, as the pancreas was not a special object of study in any of these experiments, we cannot exclude the possibility that small lesions or minor changes

TABLE 2.—Reports of spontaneous exocrine pancreatic tumors in rats

Author	Year	Strain	Sex	Age (months)	Comment
Exocrine adenoma: Hendry *et al.* (*4*)	1955	Wistar	M (3)	—	3 of 23 rats treated with 4'-fluoro-4-aminophenyl in arachis oil; these may have been induced tumors
Koletsky and Gustafson (*12*).	1955	Wistar	M (2)	—	1 of 123 irradiated rats; 1 of 36 control rats
Rosen *et al.* (*13*)	1961	Sprague-Dawley	M (2)	—	2 of 141 irradiated rats
Exocrine adenocarcinoma: Loeb (*14*)	1902	White rat: strain unspecified.	F	—	Carcinoma
Wilson *et al.* (*15*)	1941	Slonaker	F	—	Carcinoma
Scott *et al.* (*16*)	1949	Curtis-Dunning	—	—	Poorly differentiated carcinoma
Elson (*17*)	1952	Albino	M	18	Carcinoma; 1 of 130 rats in aminostilbene feeding experiment
Hodge *et al.* (*18*)	1952	Not stated	F	24	Carcinoma; 1 of 200 rats treated with methoxychlor
Walpole *et al.* (*19*)	1954	Wistar	M	12	Anaplastic carcinoma; 1 of 91 control animals; no pancreatic tumor in 446 test animals given ethyleneimine derivatives
Griem (*20*)	1957	Not stated	F	18	Case report; carcinoma with metastases to local nodes, peritoneum, omentum, liver; also one intrathoracic deposit
Gilbert and Gillman (*21*)	1958	Wistar	M	—	In a survey of 1,114 tumors in 1,342 untreated rats (0.17%)
Ambrose *et al.* (*22*)	1960	Albino	F	—	Carcinoma; 1 of 240 rats treated with biphenyl
Rosen *et al.* (*13*)	1961	Sprague-Dawley	M (3)	—	3 of 141 in irradiation experiment; all in treated group
Snell (*23*)	1965	M 520	F	30	Acinar cell carcinoma

were overlooked. Similarly, the adrenals, thyroid, and testes were examined macroscopically and appeared normal.

The pancreas was fixed in 10% formol saline and samples were blocked in paraffin wax. Sections were stained with hematoxylin and eosin, van Gieson's, mucicarmine for intracellular mucin, and Gomori's aldehyde-fuchsin for islet β-cell granules.

RESULTS

The main features of the pancreatic tumors in 10 affected rats are given in table 4.

Five animals had multiple or solitary adenomas. The lesions in rats 1 and 2 were discrete, non-encapsulated adenomas in an otherwise normal pancreas. Each tumor was composed of tightly

TABLE 3.—Reports of spontaneous nonmetastasizing islet-cell tumors in rats

Author	Year	Strain	Sex	Age (months)	Comment
Bagg and Hagopian (*24*)...	1939	Wistar.....	F	26	92 rats at risk in rapid breeding experiment without suckling
Guérin (*25*).....	1954	Not stated.....	M	24	Castrated aged 2 months; later grafted with mother's ovary
Walpole *et al.* (*19*).....	1954	Wistar.....	M	22	1 of 91 control animals; 446 test animals without pancreatic tumor
Hueper (*26*).....	1955	Wistar.....	—	—	1 of 100 rats given intrafemoral nickel
Hueper (*27*).....	1955	Wistar.....	M	—	1 of 25 rats given intrafemoral chromium
			M (2)	—	2 of 25 rats given intraperitoneal chromium
Koletsky and Gustafson (*12*)	1955	Wistar.....	M (9)	—	12 islet-cell tumors in 8 of 123 irradiated rats; 1 other rat had an islet-cell carcinoma without metastasis
Ives and Dack (*28*).....	1957	Sprague-Dawley.....	(3)	—	3 of 540 rats in negative experiment with canned food; 224 tumors mostly in control group; incidence of islet-cell tumors 1.34%
Gilbert and Gillman (*21*)..	1958	Wistar.....	M (17)	—	1,342 untreated rats with 1,114 tumors; 16 adenomas (2.77% of all tumors in males) and 1 carcinoma without metastasis in males; 6 adenomas (1.12% of all tumors in females); no carcinoma in females
Berdjis (*29*).....	1960	Sprague-Dawley.....	(3)	—	Multiple adenomas in 3 irradiated rats, 1 associated with a papillary cystadenoma of the pancreas of uncertain nature
Jasmin (*30*).....	1961	Sprague-Dawley.....	—	—	1 of 100 rats; 80, including this animal, given carboxymethylcellulose
Rosen *et al.* (*13*).....	1961	Sprague-Dawley.....	M (22)	—	22 of 141 rats (15.6%) in irradiation experiment; 18% in treated group, 9.8% in control group
Thompson *et al.* (*31*).....	1961	Sprague-Dawley.....	.....	.....	1 of 125 untreated rats
Morris *et al.* (*32*).....	1962	Buffalo.....	.....	.....	Papillary adenoma in 1 of 79 rats; 59, including this animal, given *N,N'*-2,7-fluorenylenebisacetamide
Rosen *et al.* (*33*).....	1962	Sprague-Dawley.....	M	—	Multiple adenomas of islets in 49% of 115 irradiated rats and in 17% of controls
Barron (*34*).....	1963	Charles River.....	M	—	1 of 90 rats; 60, including this animal, treated with 3-phenyl-5β-diethylaminoethyl-1,2,4-oxadiazole
Berdjis (*35*).....	1963	Sprague-Dawley.....	(10)	—	Islet-cell tumors in 8 of 37 irradiated rats (21.6%) and in 2 of 36 controls (5.4%)
Warren *et al.* (*36*).....	1964	Deac-Slonaker.....	Parabionts	.....	715 pairs of irradiated parabiotic rats with 113 control pairs; 40 adenomas in irradiated partner, 2 adenomas in nonirradiated animal, 1 adenoma in control group
Snell (*23*).....	1965	WN.....	M	20	Adenoma
		ACI.....	F	21	Adenoma
Baker and Tucker (*37*)....	1966	Wistar (ICI).....	M (9)	29–38	Adenoma in 6 male rats and nonmetastasizing carcinoma in 5 rats (3 male, 2 female); 1,200 untreated rats at risk
			F (2)	29 and 32	

TABLE 4.—Spontaneous pancreatic tumors in Chester Beatty rats

Autopsy No.	Sex	Age (months)	Experiment	Macroscopic findings in pancreas (measurements refer to maximum dimension)	Microscopic findings
Exocrine tumors					
8560.....	M	19½	No treatment.....	Several nodules up to 7.0 mm	Multiple exocrine adenomas (fig. 1a)
10803.....	M	19½	0.5% 4-aminoantipyrine in drinking water	Two nodules, the larger 9.0 mm	Multiple exocrine adenmas
7231.....	F	23½	2 mg tetryl daily in drinking water	Enlarged; no tumors seen.	Multiple exocrine adenomas (fig. 2)
7122.....	M	25½	No treatment.....	Several nodules up to 5.0 mm	Multiple exocrine adenomas
6991.....	M	16½	500 μg benzo[e]pyrene in 2 ml polyethylene glycol by stomach tube once only	Discrete, 5.0 mm nodule..	Solitary exocrine adenoma (fig. 4)
8420.....	M	18	0.2% lead phosphate weekly, subcutaneous, then intraperitoneal injection	Solitary, large, hard mass in lower left flank	Well-differentiated adenocarcinoma (fig. 6)
4448.....	F	24	0.1% zinc acetate in high protein diet	Large abdominal mass attached to liver and spleen; nodules in pancreas and mesentery	Poorly differentiated adenocarcinoma
10750.....	M	17	0.75 ml Imferon subcutaneously weekly	Huge, soft, partly hemorrhagic tumor replacing pancreas	Poorly differentiated adenocarcinoma (fig. 7)
Endocrine tumors					
8593.....	M	25½	Polyvinyl sponge implanted subcutaneously into right flank at 6 weeks of age	Solitary 6.5 mm nodule..	Islet-cell adenoma (fig. 1b)
6721.....	M	20	2 mg tetryl daily in drinking water	Solitary 15.0 × 10.0 × 10.0 mm nodule	Nonmetastasizing islet-cell tumor

packed, regular, well-defined acini, the component cells of which were arranged around a small central lumen. The nuclei were large and vesicular with a prominent nucleolus. The cytoplasm was abundant, basophilic, and granular. Mitotic figures were present but infrequent and of normal pattern.

In rat 3, a cluster of discrete, round, nonencapsulated adenomas, separated from each other by compressed pancreatic lobules, was present in one branch of the pancreas (fig. 2). The stroma was more abundant than in the previous cases, accentuating the acinar pattern, and contained a few iron pigment-containing macrophages. There were partial fatty replacement of the gland as a whole and a generalized, mild, low-grade chronic inflammatory-cell infiltration.

Each nodule in rat 4 was an exocrine adenoma. The largest adenoma was well encapsulated and all the nodules had more internal connective tissue than in the previous animals. Thin-walled blood vessels were present in the stroma mainly toward the center of the nodules. Mitotic figures were numerous. Hyperplastic lobules were present among normal acinar tissue elsewhere in the pancreas.

The solitary nodule in rat 5 was a discrete, nonencapsulated exocrine adenoma in an otherwise normal gland. It resembled the other adenomas histologically except that in the center was a pale-staining area in which the regular acinar pattern was disturbed. In this area, the cells had less cytoplasm, and mitoses were more frequent than elsewhere in the tumor.

Three rats had exocrine adenocarcinomas of varying degrees of malignancy. In rat 6 the tumor was a locally invasive, well-differentiated adenocarcinoma arising in the exocrine pancreas and extending into the mesentery (fig. 6). It was mainly solid but had a cystic component into which there had been both old and recent hemorrhage. A collagenous stroma was prominent, particularly around the tumor lobules. In some fields, the pattern was remarkably like that of a simple adenoma, and the transformation of regular acini into clusters of more haphazardly arranged cells could be traced. Mitotic figures were common throughout the tumor.

In rat 7, the tumor was a poorly differentiated, focally necrotic, infiltrating adenocarcinoma composed mainly of sheets and columns of cells in a collagenous stroma. Poorly formed tumor acini were seen in some fields. The nuclei varied considerably in size, some being huge; the nucleolus was often large and the cytoplasm relatively sparse. Normal and abnormal mitotic figures were frequent.

The abdominal mass in rat 8 was a poorly differentiated tumor completely replacing the pancreas and beginning to infiltrate the spleen at the hilum. Much of the tumor was necrotic or had undergone myxomatous degeneration. Many blood vessels were occluded by intravascular thrombosis. The tumor cells had indistinct cytoplasmic margins, a pale-staining nucleus, often without a definite nucleolus and with fragmented chromatin. There was considerable variation in nuclear size and shape; mitotic figures were numerous. Part of the tumor was of epithelial origin, the cells being arranged in rows but not in acini (fig. 7). This primitive tumor was considered to be arising from the pancreas by inference only.

Two animals had tumors arising from the islets of Langerhans. The solitary nodule in rat 9 was round, discrete, not truly encapsulated but bordered on one side by a false capsule of compressed pancreatic tissue. A few exocrine acini were incorporated at the periphery. The tumor was subdivided by a delicate vascular stroma into alveolar masses. Some of the thin-walled sinusoids were dilated; pigment-laden macrophages were present in the stroma. The individual cells resembled those of a normal islet, having faintly eosinophilic cytoplasm and a small, round nucleus with an indistinctly staining chromatin network but a definite nucleolus. Hydropic degeneration of the cytoplasm was fairly common. Mitotic figures were present but not numerous. There were small areas of fat necrosis elsewhere in the pancreas.

The tumor in rat 10 was surrounded by a thick, fibrous capsule. Tongues of cells invaded this capsule in several places and at one point had penetrated it. Most of the tumor was composed of columns of cells separated by sinusoids, but in some areas, mainly toward the center of the tumor, this orderly pattern was replaced by irregularly arranged cells in a myxomatous stroma. Here the sinusoids were distended to form lakes; hemorrhage was common and tumor cells were present in the lumen of even fairly thick-walled vessels. In the bulk of the tumor, the cells resembled those of normal islets, having faintly eosinophilic cytoplasm and a vesicular nucleus with a clearly defined nucleolus, but cytoplasmic hydropic degeneration was common. Mitotic figures, though present, were infrequent and nuclear pleomorphism was not marked.

DISCUSSION

Some animals such as the dog (*38*), cat (*39*), and ox (*40*) develop nodular hyperplasia of the pancreas as a normal aging change. Each nodule is formed of acinar tissue without islets and can resemble an adenoma closely. Aging changes in the rat pancreas follow a pattern of proliferation and squamous metaplasia of ductal epithelium, locule formation, and compression of adjacent acini (*41*). However, a condition very like nodular hyperplasia can be induced by *N*,*N*′-2,7-fluorenylenebisacetamide or *N*-2-fluorenylacetamide (*42*), and naturally occurring inflammatory lesions may be accompanied by hyperplasia of surviving pancreatic lobules. We know of no way of distinguishing a hyperplastic

(giant) islet from a small islet-cell adenoma, other than an arbitrary criterion of size.

True exocrine adenomas may be single or multiple, and are usually rounded and often encapsulated. The tumor may be clearly visible or may increase the bulk of the pancreas without presenting as a focal lesion at necropsy. Because the tumor is composed of solid acini with little intermediate vascular stroma, the cut surface is white or creamish. In our experience, adenomas arise from acinar cells and apparently not from ductal epithelium. A papillary cystadenoma described by Berdjis (*29*) is the only report of such a lesion that we have been able to trace, but other reports may exist in the literature.

The cells of an acinar adenoma are arranged around a central lumen. The cytoplasm contains basophilic zymogen granules which stain darkly with hematoxylin or with Masson or Mallory's trichrome dyes. The nucleus lies at the end of the cell distant from the central lumen. It is vesicular with a coarse chromatin pattern and a prominent nucleolus (fig. 4). Mitotic figures may be frequent.

The point at which a rapidly enlarging adenoma may be considered to have become carcinomatous is a matter of opinion. In rat 5, one area of the adenoma was paler and contained more mitotic figures than elsewhere and may represent the first stage in transformation to a malignant tumor. In rat 6, although parts of the tumor were cystic, a transition from a regular acinar pattern to invasive tumor could be traced. In animals 7 and 8, there was no evidence that the tumor arose from an adenoma, and the cells of origin, whether acinar or ductal, could not be determined as is often the case in man (*43*). These larger, poorly differentiated tumors were soft, necrotic, hemorrhagic, and myxomatous. Fibrous stroma was not abundant as in dogs (*44*). Metastases were absent in our 3 rats with adenocarcinoma but present in local nodes, peritoneum, omentum, liver, and within the thorax in the animal described by Griem (*20*) though not in the animal reported by Loeb (*14*). The remainder of the reports in the literature did not mention the presence or absence of metastases.

Islet-cell adenomas may be distinguished from those of exocrine origin by architecture and staining properties. The lesions, which may be single or multiple, often possess a well-defined capsule and are reddish or brown on section. They are probably derived from β cells as in man (*45*). The cells are arranged along sinusoidal, thin-walled blood vessels which ramify throughout the tumor (fig. 5). Hemorrhages occur often, as shown by the presence of hemorrhagic cysts or stromal collections of macrophages distended with hemosiderin (fig. 3). The nuclei and cytoplasm stain less darkly with hematoxylin and eosin than do those of an exocrine adenoma; because of this, the type of pancreatic adenoma can often be guessed before the slide is put under the microscope (*compare* 1a and 1b). Cytoplasmic granules may be identified and β-granules can be stained specifically with Gomori's aldehyde fuchsin. Hydropic cytoplasmic degeneration is common in islet-cell adenomas.

We have been unable to find any record of clinical hypoglycemia due to hypersecretion of insulin in rats with islet-cell tumors.

An islet-cell adenoma is considered by some pathologists to become a carcinoma when invasion of its capsule takes place. By analogy with similar tumors in man (*45*), we are inclined to regard distant metastasis as a more reliable indication of malignancy because invasion and the presence of tumor cells in the lumen of quite large tumor blood vessels cannot always be correlated with subsequent distant spread of the tumor. Histologically, a nonmetastasizing islet-cell tumor resembles a benign adenoma in that it maintains a sinusoidal pattern, but cytoplasmic hydropic degeneration, stromal overgrowth, often with myxomatous change, and interstitial hemorrhage are much more marked. All degrees of cellular atypims may be present.

Various authors have noted the possible association of tumors of other endocrine glands with hyperplasia or tumors of the islets. The skull is not opened routinely in our laboratory so we have, at present, no data on the incidence of spontaneously occurring pituitary tumor in our rats. Baker and Tucker (*37*) of Imperial Chemical Industries, Alderley Park, Cheshire, England, tell us that 14 of 600 specific pathogen-free rats and 600 breeder rats in their laboratory, aged 29 months or over, had hyperplastic islets or islet-cell tumors. Ten of these animals (71%) also had a pituitary chromophobe adenoma and some a pheochromocy-

toma. Berdjis (*29*) has suggested that a pluriglandular syndrome involving several endocrine glands including the pancreatic islets exists in rats and can be induced in greater numbers by whole-body or partial-body irradiation. In Koletsky and Gustafson's series (*12*), endocrine adenomas were the only type of tumor not significantly more frequent among irradiated than control rats except in the number of neoplasms in each rat. Gilbert and Gillman (*21*) found a high incidence of endocrine tumors in different combinations in 1,342 untreated rats, but believed there was no evidence that neoplastic change in one gland influenced the occurrence of neoplasia in another.

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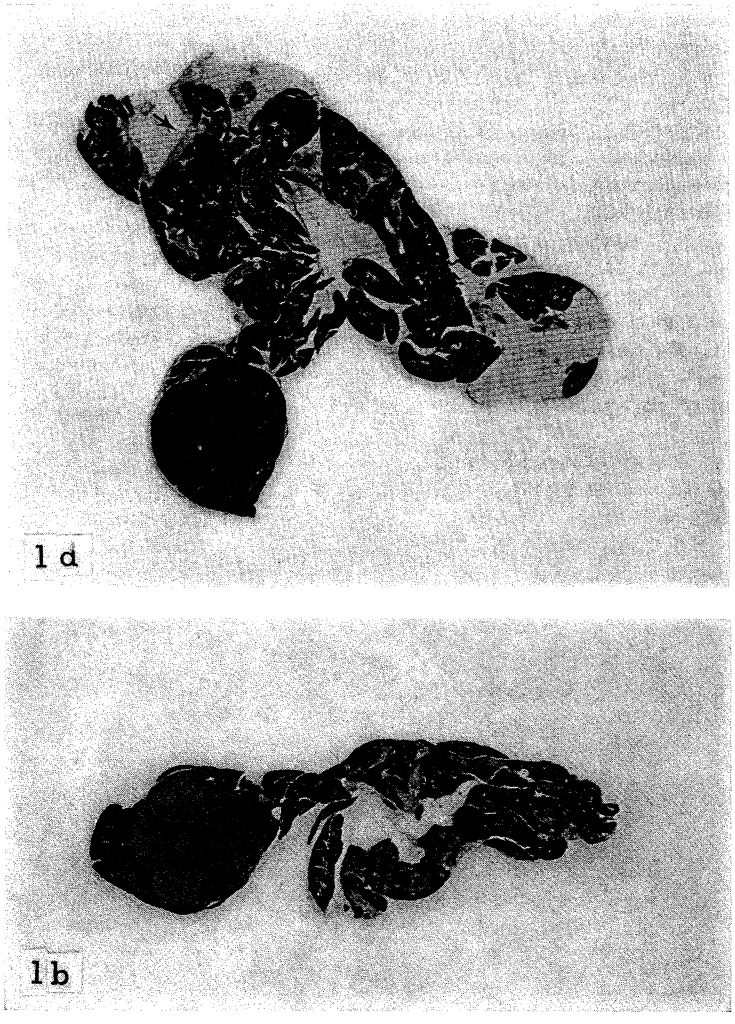

FIGURE 1A.—Rat 1. Exocrine adenoma. Smaller, similar tumor nodule is near *top left corner* (*arrow*). Hematoxylin and eosin. × 6

FIGURE 1B.—Rat 9. Islet-cell adenoma. *Note* paler (more acidophilic) staining with hematoxylin and eosin than in figure 1a. × 4

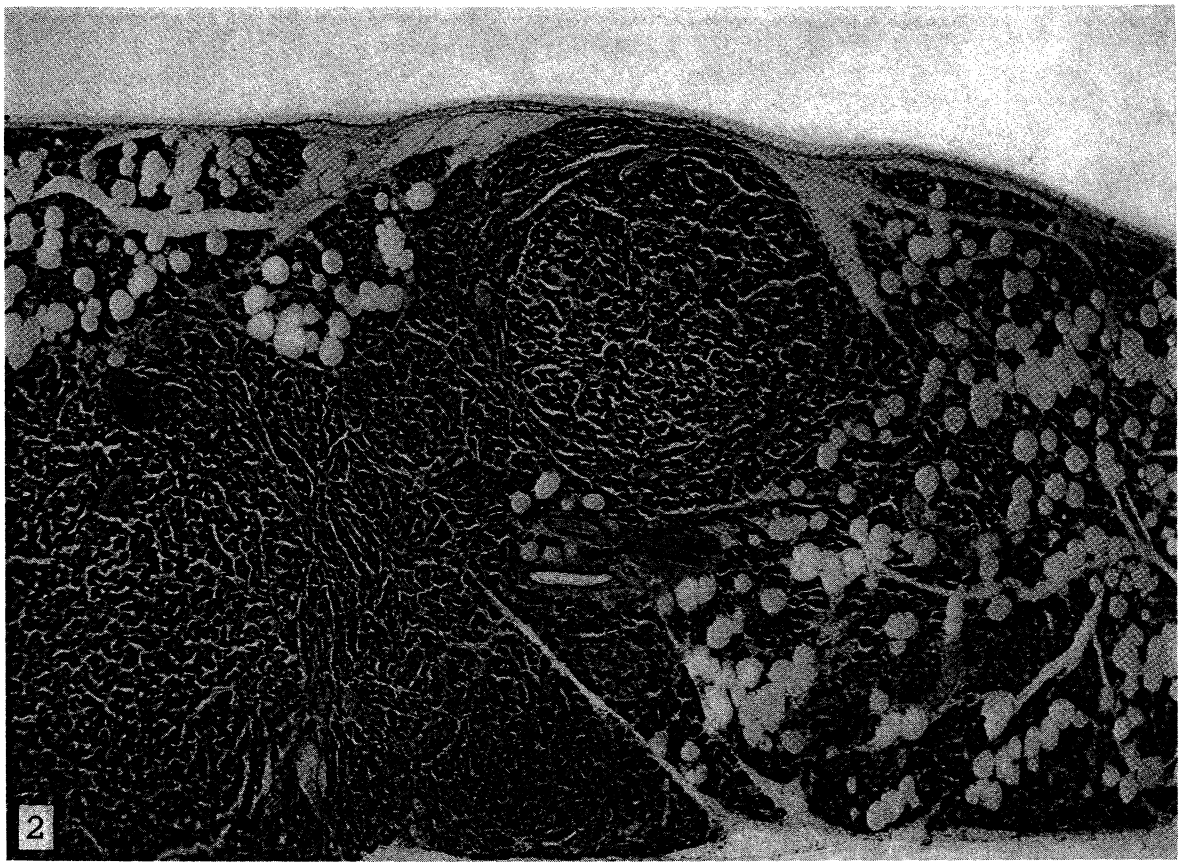

FIGURE 2.—Rat 3. Multiple exocrine adenomas. In lesion at *upper right*, there is compression of adjacent pancreas to form a false capsule. Hematoxylin and eosin. × 60

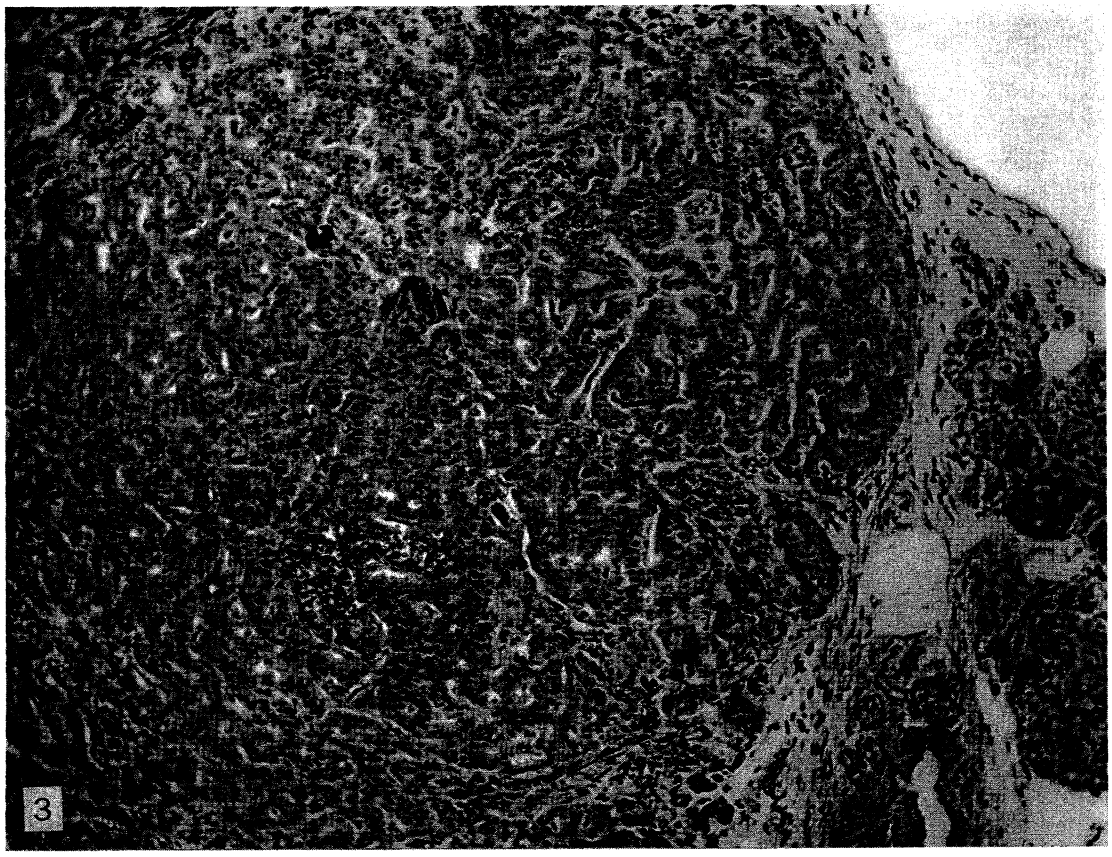

FIGURE 3.—Islet-cell adenoma. *Note* numerous thin-walled blood vessels giving the tumor a lacelike pattern. The darkly staining granular deposits are composed of iron pigment. Hematoxylin and eosin. × 160 (By kind permission of Baker and Tucker; *see* table 3.)

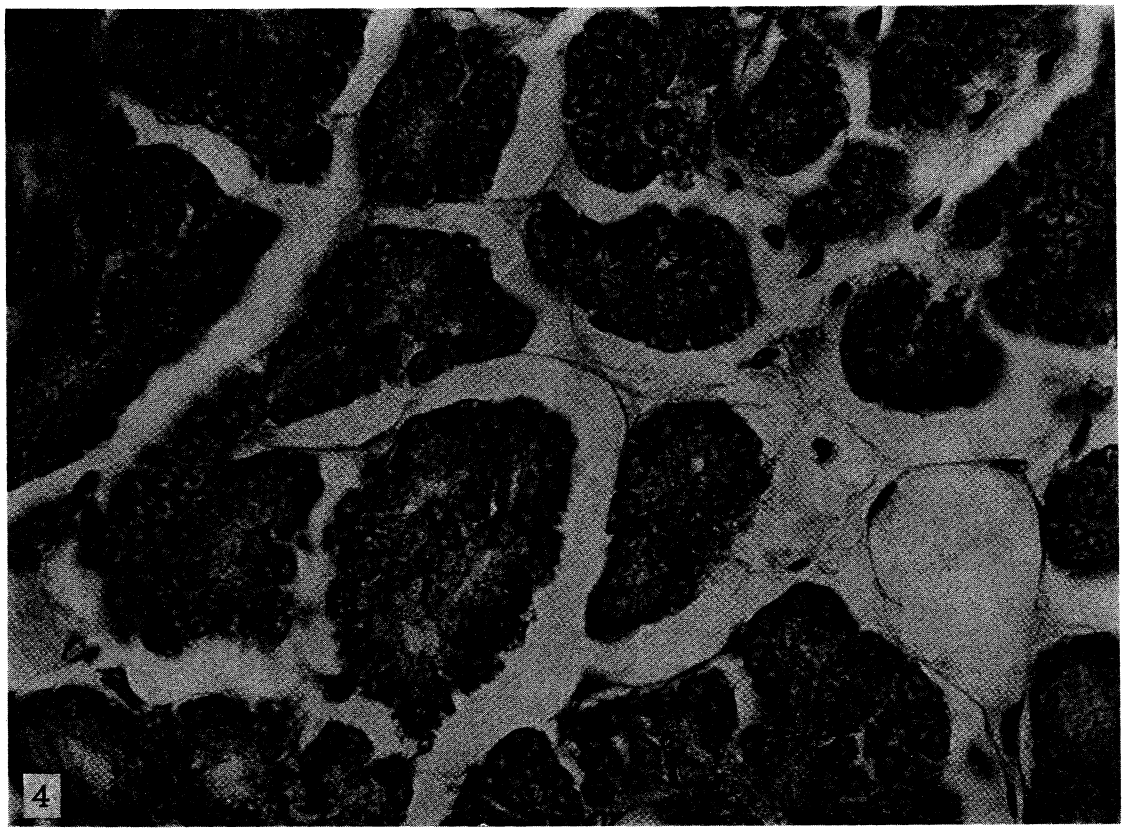

FIGURE 4.—Rat 5. Exocrine adenoma to show arrangement of acinar cells around a central lumen. Hematoxylin and eosin. × 675

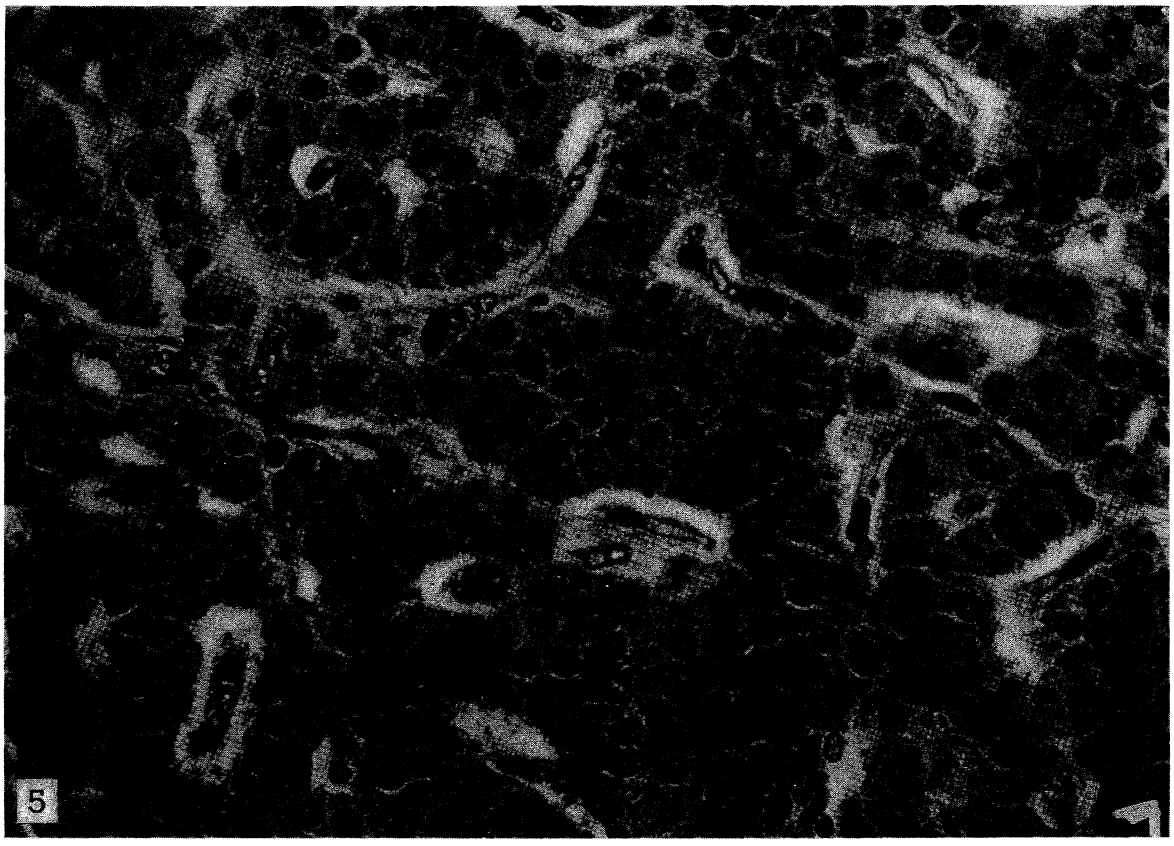

FIGURE 5.—Higher power of figure 3 to show arrangement of islet cells along sinusoids. Hematoxylin and eosin. × 675

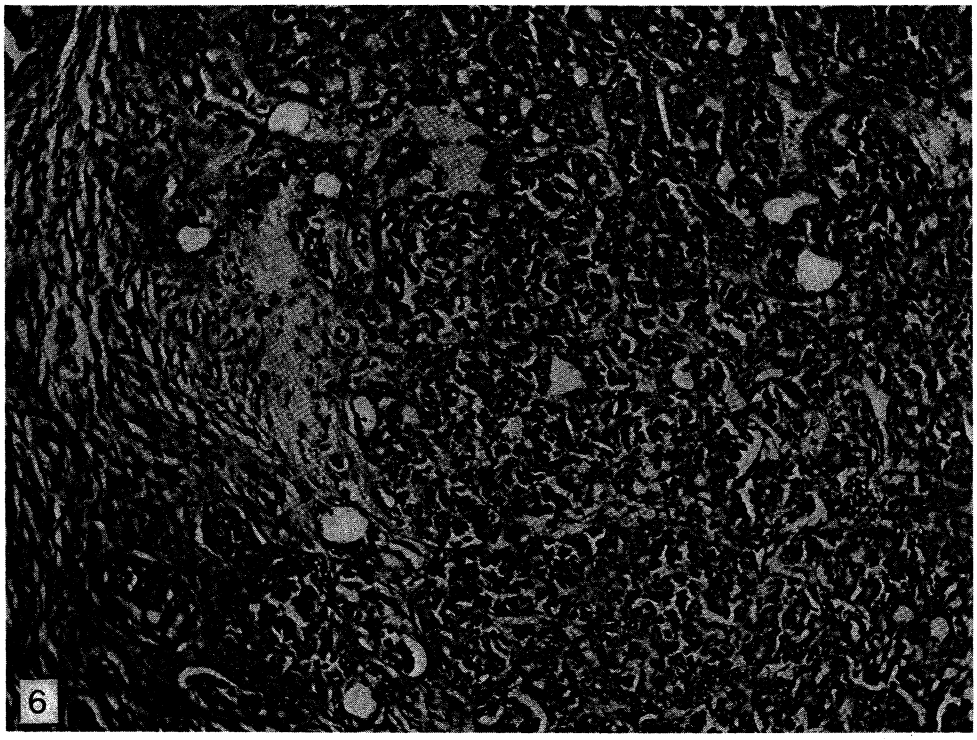

FIGURE 6.—Rat 6. This exocrine adenocarcinoma in places retains an acinar pattern. Hematoxylin and eosin. × 160

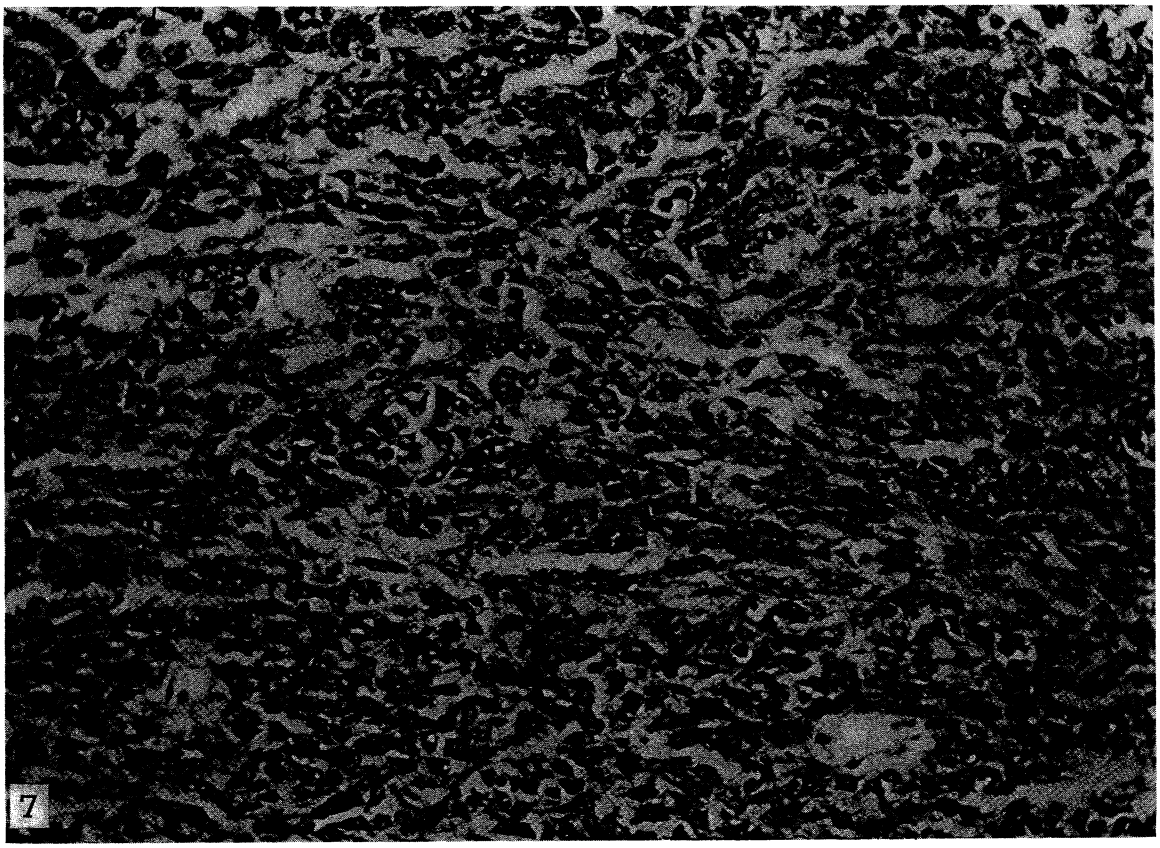

FIGURE 7.—Rat 8. Cellular area of a poorly differentiated, largely necrotic carcinoma occupying the position of the pancreas. Hematoxylin and eosin. × 200