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354

Tumours of the pancreas

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Pancreatic tumours, whether spontaneous or induced, are rare in the rat. Apart from certain recent reports (Schoental, Fowler & Coady, 1970; Rakieten et al., 1971), no reliable method has as yet been found for inducing such tumours. This chapter is mainly based on reviews by Rowlatt & Roe (1967) and Rowlatt (1967a).

Except for the tumour illustrated in Fig. 12, we have no reason to believe that any of the tumours we discuss were of other than spontaneous origin. Details of exposure to chemical agents are given in the legends to the illustrations.

NORMAL PANCREAS

The pancreas of the rat, as in other species, is located dorsally in the abdominal cavity within mesenteric tissue close to the stomach, duodenum, ascending and transverse colons. On the left side, the tail of the pancreas lies in juxtaposition to the spleen and, on the right side, the head of the gland lies within the loop of the duodenum. It is diffusely pale pink in colour and, especially where there is abundant abdominal fat, its margins are difficult to define. It is divided into lobes of various sizes that are subdivided into lobules of similar size. Excretory ducts join the common bile duct where this traverses the pancreas before entering the duodenum. The principal histological features of the normal pancreas are illustrated in Fig. 1.

MORPHOLOGY AND BIOLOGY OF TUMOURS

Histological types of tumour

Exocrine tumours

Exocrine adenoma (including exocrine adenomatosis)
Exocrine adenocarcinoma

Endocrine tumours

Islet-cell adenoma
Islet-cell adenocarcinoma

In some cases of adenocarcinoma, it is difficult or impossible to discern whether the tumour is of exocrine or of endocrine origin.

Exocrine adenoma (including exocrine adenomatosis). The distinction between adenoma and hyperplastic nodule hinges mainly on the significance that is attached to the presence of a capsule. Adenomas, like hyperplastic nodules, may be multiple. Most lesions large enough to be seen macroscopically at autopsy have either a false capsule, formed by compression of surrounding normal tissue, or a true fibrous capsule. Irrespective of whether the lesions are classed as benign neoplasms or as hyperplastic nodules, the tendency for them to be multiple is characteristic of the rat pancreas.

Individual lesions are more or less spherical and consist of zymogen-granule-containing cells arranged in acini. The general appearance and acinar structure of the tumour tissue differs little from that of normal exocrine tissue, except for the absence of ducts and islets of Langerhans. The nuclei are usually slightly larger than those of the surrounding exocrine pancreatic tissue and there is less prominent cytoplasmic basophilia in the vicinity of the nucleus. Because of these features, exocrine adenomas usually appear slightly paler than the surrounding normal gland in haematoxylin and eosin preparations. However, this general difference in staining affinity is much less obvious than that between islet-cell tumours and normal exocrine pancreas.

The features described above are illustrated in Fig. 2–4.

It is of interest that exocrine and endocrine tumours may occur concomitantly in the same pancreas (Fig. 10 & 11).

Kendrey & Roe (1969) described a condition of "chronic relapsing pancreatitis" in rats, possibly of viral origin. The least histological sign of this condition is a decrease or loss of cytoplasmic basophilia

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in the exocrine cells in some lobules and infiltration of the interlobular connective tissue by mononuclear cells. More severe forms of the disease are characterized by flattening of the epithelium of acini, by "microcystic transformation" of the gland, and by fatty atrophy. Fibrosis of the connective tissue stroma and polyarteritis also occur. It is important to distinguish the changes that characterize the earlier stages of this disease from exocrine neoplasia. Changes due to chronic pancreatitis may be present concomitantly with pancreatic tumour. The presence of senile fatty atrophy may render exocrine adenomas prominent (see Fig. 4).

We have no information with regard to evidence of functional disturbance in rats with exocrine adenomas.

Hyperplasia of the epithelium lining a pancreatic duct is shown in Fig. 13. In other areas, changes similar to those described as chronic relapsing pancreatitis by Kendrey & Roe (1969) were seen. It is possible that the lesion shown represents the earliest stage of a neoplasm of ductal origin.

Exocrine adenocarcinoma. Carcinomas of exocrine pancreatic origin vary in appearance from well to poorly differentiated adenocarcinomas (Fig. 5 & 6). Invasion of surrounding normal pancreatic tissue, extension into the mesentery and local or metastatic spread to other organs are the hallmarks of their malignant nature. In fields not shown in Fig. 5, there is evidence of both old and recent haemorrhage; and in those not shown in Fig. 6, cells are arranged in rows but no acini are in evidence. In the case of large invasive undifferentiated tumours, origin in the pancreas may be difficult to establish.

Islet-cell adenoma. The paler staining of normal islet tissue with haematoxylin and eosin and with Gomori's chrome-alum haematoxylin-phloxin (Fig. 1) is retained when the islets give rise to neoplasms (Fig. 7 & 8). The principal diagnostic difficulty is the distinction between large normal islets, islet-cell hyperplasia and small islet-cell adenomas. For the purposes of making this distinction, the size and number of islets are the only exact criteria. A less exact, but frequently helpful criterion is the fact that in adenomas, even relatively small adenomas, the cells tend to be arranged in rows along thin-walled sinusoidal blood vessels rather than hapharzardly as in the normal islet (Fig. 9). Perhaps because of the presence of many blood vessels with only thin walls, haemorrhages, haemorrhagic cysts and groups of iron-filled macrophages are frequently seen in tumours of islet-cell origin. Some of the islet-cell tumours described by Schoental, Fowler & Coady (1970) in their rats exposed to pyrrolizidine alkaloids had regions of different degrees of differentiation (Fig. 12). They thought that one of the islet-cell tumours was probably functional. It is possible that the less differentiated regions were derived from the more differentiated by tumour-progression.

In our experience the tendency to multiplicity is less marked in the case of islet-cell adenomas than in that of exocrine adenomas. However, according to Berg (1967), multiplicity is the rule in rats of the Sprague-Dawley strain. There is apparently an association between the risk of development of benign islet-cell tumours and chromophobe adenoma of the pituitary gland (see Rowlatt, 1967a). Berdjis (1960) described a pluriglandular syndrome in which endocrine adenomas of the pancreas were featured, but his studies were of irradiated rats.

We have not observed hypoglycaemic attacks in rats subsequently found at autopsy to have islet-cell adenomas. In islet-cell tumours in mice, Like and his colleagues (1965) reported the presence of up to 12 times the normal amount of pancreatic insulin; even so the mice were hyperglycaemic.

According to Frantz (1959), most islet-cell tumours in man are derived from β-cells rather than from α-cells. The latter, which constitute the minority in normal islets, stain pink with Gomori's chrome-alum haematoxylin-phloxin. All the islet-cell adenomas that we have encountered in rats have consisted of β-cells.

Islet-cell adenocarcinoma. Islet-cell tumours of various grades of malignancy are encountered, but a well-differentiated locally invasive variety is the most common (Fig. 8). Local invasion of exocrine tissue and into the lumina of blood vessels may occur. We have encountered no case in which distant metastases were present. The tendency to haemorrhage, to haemorrhagic cyst formation and for iron-filled macrophages to be present in the stroma of malignant islet-cell tumours is the same as for benign islet-cell tumours. As in the case of benign tumours, there is an association between malignant islet-cell tumour and chromophobe pituitary adenoma (see Rowlatt, 1967a).

SPONTANEOUS TUMOURS

In no less than seven large surveys of spontaneous tumours in rats, no pancreatic tumours were listed. Our search of the literature up to 1966 (Rowlatt & Roe, 1967) revealed 3 reports of exocrine adenomas,

11 of exocrine adenocarcinomas and 19 of islet-cell tumours. Between January 1962 and October 1965 we encountered 5 cases of single or multiple exocrine adenomas, 3 of exocrine adenocarcinomas and 2 of islet-cell tumours in Chester Beatty (CB) Wistar rats (see Rowlatt & Roe, 1967). Our findings indicated an incidence of pancreatic neoplasia of about 1% for rats of that strain over 12 months of age. Since November 1965 we have encountered a further 7 cases of pancreatic neoplasia in rats, including a unique example of exocrine and endocrine neoplasia in the same rat (Fig. 10 & 11). In addition, we encountered marked hyperplasia of the epithelial lining of the pancreatic duct in one rat (Fig. 13). In the discussion of the paper by Rowlatt (1967a), Berg (1967) states that islet-cell tumours occur in about 2-3% of Sprague-Dawley rats and that they are usually multiple but unaccompanied by evidence of functional activity.

INDUCTION OF TUMOURS

Although both exocrine and endocrine neoplasms have been seen in rats exposed to exogenous chemical and other agents (see Rowlatt & Roe, 1967), in most instances it seems likely that treatment and tumour development were not associated and that the tumours were essentially spontaneous in origin. Berdjis (1960, 1963) and Rosen et al. (1962) reported the induction of islet-cell tumours in rats exposed to ionizing radiation. Schoental, Fowler & Coady (1970) reported the possible induction of benign and malignant islet-cell tumours by an alkaloid of the pyrrolizidine group given by stomach tube. Rakieten et al. (1971) recorded a high frequency of insulin-secreting islet-cell tumours in rats exposed to a combination of streptozotocin and nicotinamide. Otherwise, there is no information on how tumours of the pancreas may be induced in rats by chemical means.

COMPARATIVE ASPECTS

Basically the types of tumour that we have seen in the rat are similar in structure to some of those seen in man, but multiplicity is more marked in the rat in respect of both exocrine and endocrine adenomas.

To our knowledge no special use has so far been made of tumours of the rat pancreas as models for the study of methods of treatment of pancreatic neoplasia in man. Many of the varieties of pancreatic neoplasm in man described by Frantz (1959) have not, so far as we know, been seen in rats.

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KEY TO ILLUSTRATIONS

Fig. 1. Normal pancreas. Cells of the exocrine tissue (Ex), grouped to form acini, surround an islet of Langerhans. The nuclei of the exocrine cells are located in the strongly basophilic basal region, while the cytoplasm between the nucleus and the apex of the cells contains lightly staining zymogen granules. Typical sharply defined clefts with minimal connective tissue separate individual acini. The islet consists of centrally located pale-staining β-cells (B) and peripherally located α-cells (A). The cytoplasm of the α-cells, which appears dark in this photomicrograph, was of a typical red colour in the section. A pancreatic duct (D) and a blood vessel (BV) are also seen. Untreated 3-month-old female CB Wistar rat. Gomori's chrome-alum haematoxylin-phloxin; × 300.

Fig. 2. Pancreas in which no abnormality was observed macroscopically. Two well-circumscribed exocrine adenomas (arrows) can be seen. 14-month-old female CB Wistar rat given 6 doses, at 2-3 day intervals, of 10 mg of 1(4-dimethylaminobenzal)-indene in 0.5 ml of arachis oil by stomach tube when 6-8 weeks of age. H & E; × 7.

Fig. 3. Higher-power view of Fig. 2, showing edge of exocrine adenoma (Ex) which is separated by a thin fibrous capsule (C) from the normal exocrine tissue (N). The tumour cells show less cytoplasmic basophilia and their nuclei are slightly larger and paler than normal. The acinar pattern is well preserved, but there are no ducts or islets. H & E; × 200.

Fig. 4. Pancreas in which enlargement, but no discrete tumour, was observed macroscopically. Multiple exocrine adenomas (arrows) and extensive replacement of gland by fat can be seen. 23.5-month-old female CB Wistar rat given 2 mg of tetryl in drinking water daily from the age of 8 weeks until death. H & E; × 60.

Fig. 5. Pancreas in which was observed, macroscopically, a partly solid, partly cystic haemorrhagic mass, arising in the pancreas, attached to the small intestine and extending into the mesentery. A well-differentiated exocrine adenocarcinoma, with good preservation of acinar pattern, can be seen. Collagen formation (C) is prominent in some places and mitotic figures are frequent, though not easily seen in this photomicrograph. 18-month-old male CB Wistar rat given, by subcutaneous or intraperitoneal injection, 1 mg of lead phosphate in 0.5 ml of water once weekly over a period of 7.5 months from the age of 8 weeks. H & E; × 200.

Fig. 6. Pancreas in which was observed, macroscopically, a large intra-abdominal mass, replacing the pancreas and part of the spleen, partly soft and haemorrhagic and partly fibrous. A poorly differentiated adenocarcinoma infiltrating the spleen, with extensive areas of myxomatous degeneration and necrosis, can be seen. The tumour cells have indistinct cytoplasmic margins. Most nuclei are pale-staining and some lack a definite nucleolus. Mitotic figures are numerous. 17-month-old male CB Wistar rat given two 0.75-ml doses of iron-dextran (Imferon), by subcutaneous injection, at the age of 6-7 weeks. H & E; × 200.

Fig. 7. Pancreas in which a solitary 6.5-mm diameter nodule was observed macroscopically. A well-circumscribed islet-cell adenoma can be seen. 25.5-month-old male CB Wistar rat in which, at the age of 6 weeks, a piece of polyvinyl sponge was implanted in the subcutaneous tissues of the right flank, but which received no other treatment. H & E; × 4.

Fig. 8. Pancreas in which a solitary 5-mm diameter nodule was observed macroscopically. A locally invasive, well-differentiated islet-cell (β-cell) adenocarcinoma can be seen. Invasion of surrounding exocrine tissue is clearly apparent. In addition, extension into the lumen of a small blood vessel (arrowed) is shown. 23.5-month-old female Sprague-Dawley rat given 25-mg doses of Curetard (polymerized N-nitroso-2,2,4-trimethyl-1,2-dihydroquinoline) in 0.2 ml of polyethylene glycol 400 once weekly for 20 weeks. Gomori's chrome-alum haematoxylin-phloxin; × 160.

Fig. 9. Pancreas in which a 2.5 mm × 2 mm nodule was observed macroscopically. A well-differentiated β-cell adenoma can be seen. Note the regular arrangement of cells around sinusoids, a feature that is easier to see in an adenoma than in a normal islet. Untreated 38-month-old male ICI Wistar rat. H & E; × 675. By courtesy of Dr S. B. de C. Baker and Dr M. J. Tucker.

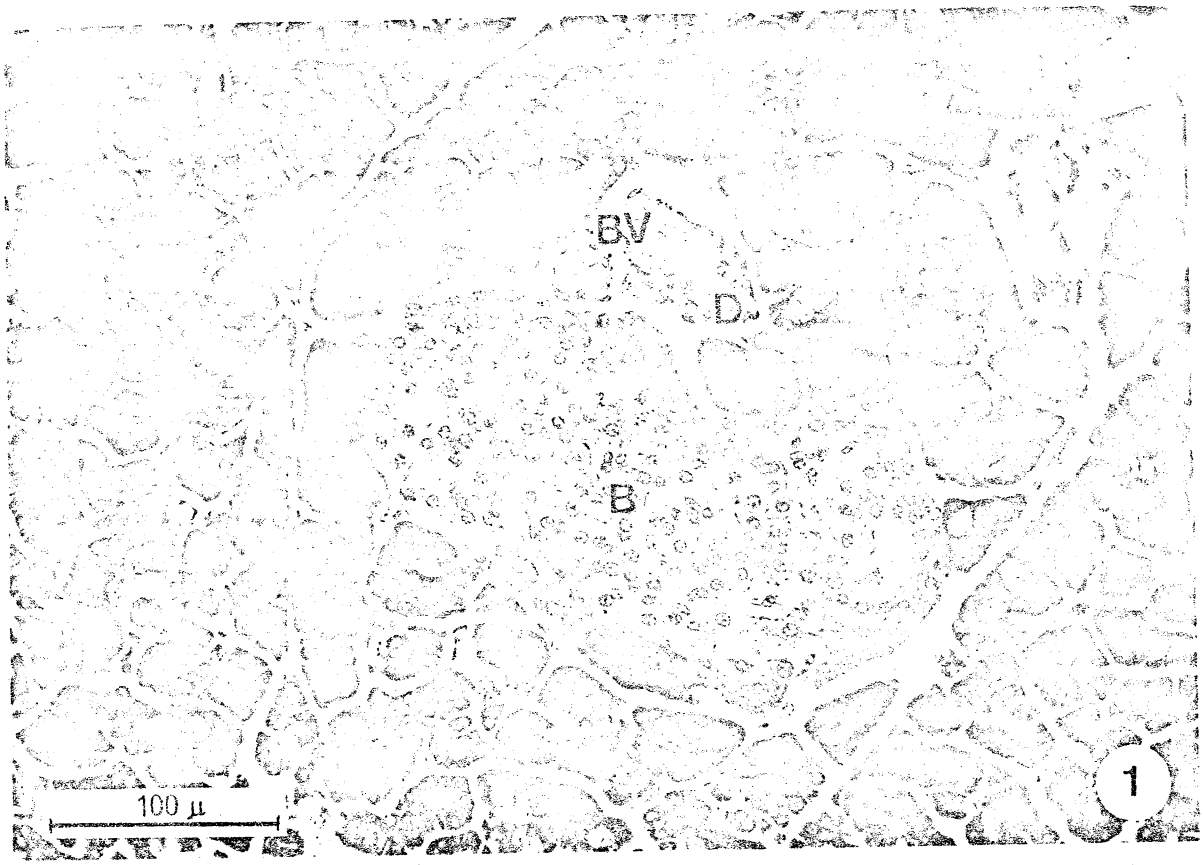
Fig. 10. Pancreas in which multiple nodules were observed macroscopically. Six exocrine adenomas (Ex) and one islet-cell tumour (i) can be seen. 15-month-old male CB Wistar rat given six 10-mg doses, at 2-3 day intervals, of 1(4-dimethylaminobenzal)-indene in 0.5 ml of arachis oil by stomach tube when 6-8 weeks of age. H & E; × 8.

Fig. 11. Higher-power view of Fig. 10: edge of well-differentiated islet-cell (β-cell) tumour showing erosion and invasion of surrounding exocrine tissue indicative of low-grade malignancy. H & E; × 160.

Fig. 12. Pancreas in which a discrete 5 mm × 3 mm nodule was observed macroscopically. An islet-cell adenoma can be seen. This tumour was of special interest because it consisted of a relatively poorly differentiated region (PD) which seemed to be expanding at the expense of a well-differentiated peripheral

zone (WD). A prominent fibrous capsule (C) separates the tumour from the surrounding normal exocrine tissue (Ex), fat cells (F) and a blood vessel (BV). 26.5-month-old male Wistar (Porton strain) rat given a single dose (600 mg per kg body-weight) of certain pyrrolizidine alkaloids from the seeds of *Amsinckia intermedia* Fisch and Mey by stomach tube when about 4 weeks of age. H & E; × 130. Reproduced from Schoental, Fowler & Coady (1970).

Fig. 13. Pancreas in which enlargement, but no discrete tumour, was observed macroscopically. Marked epithelial proliferation of the lining of a pancreatic duct (d), an area of proliferation of exocrine acini in the vicinity of the duct (p), and extensive fibrosis (f) can be seen. 18-month-old male CB Wistar rat given eight 0.75-ml doses of iron-dextran (Imferon), by subcutaneous injection, at weekly intervals from the age of 6 weeks. H & E; × 130.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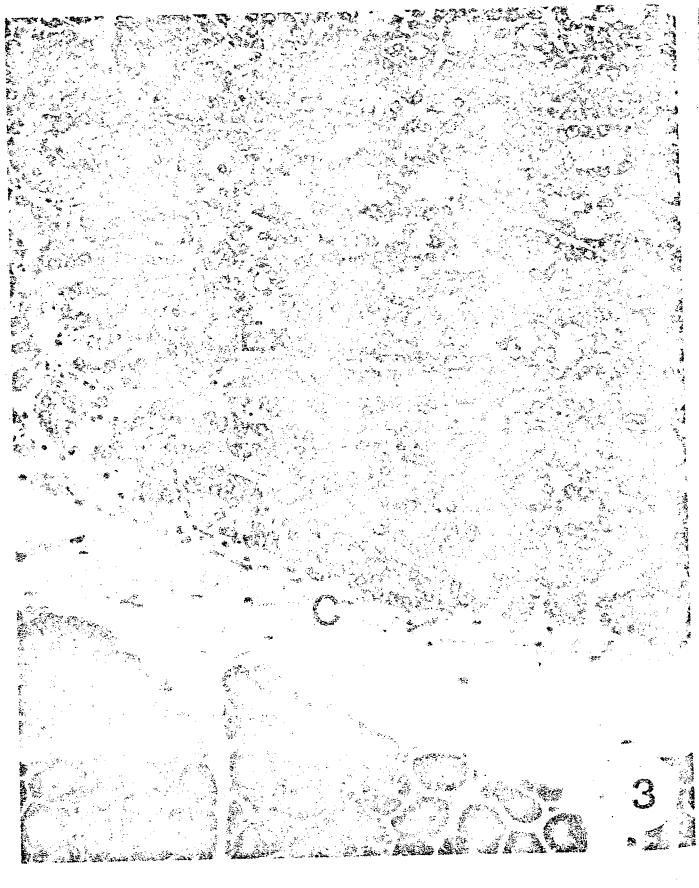
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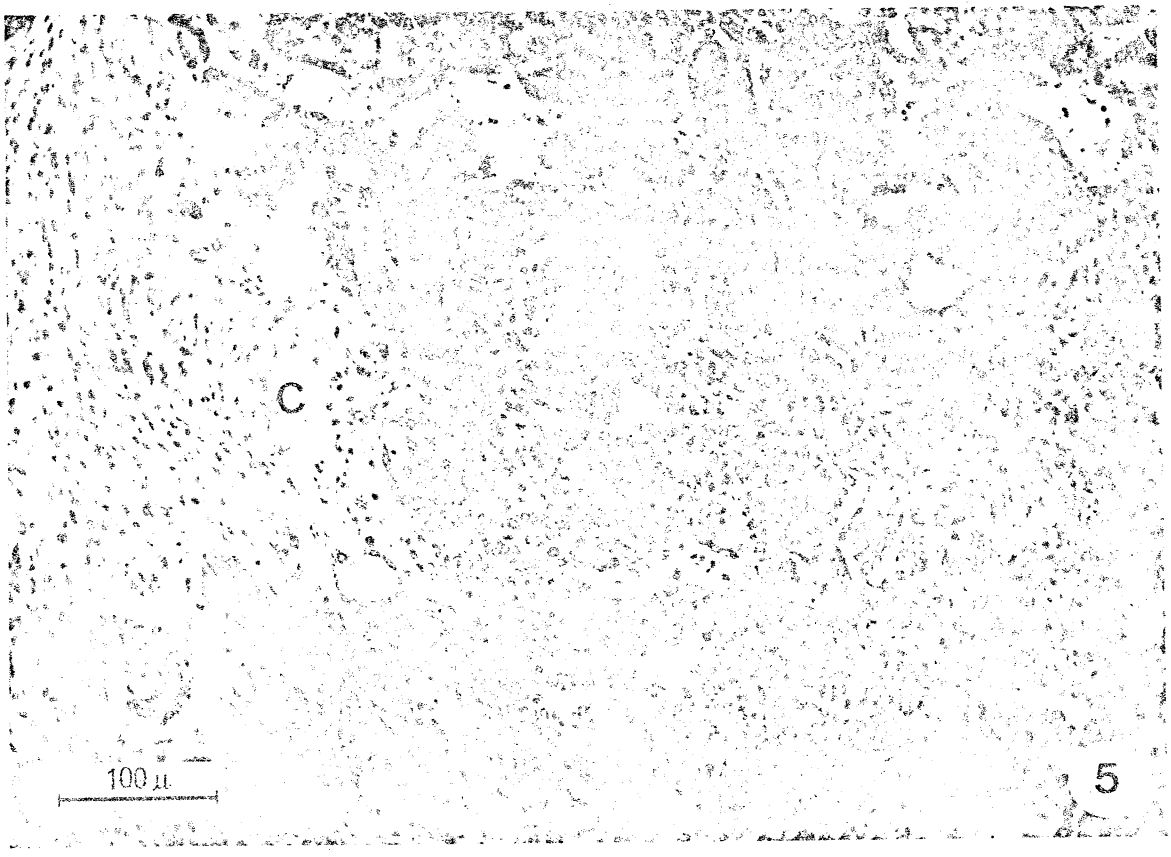
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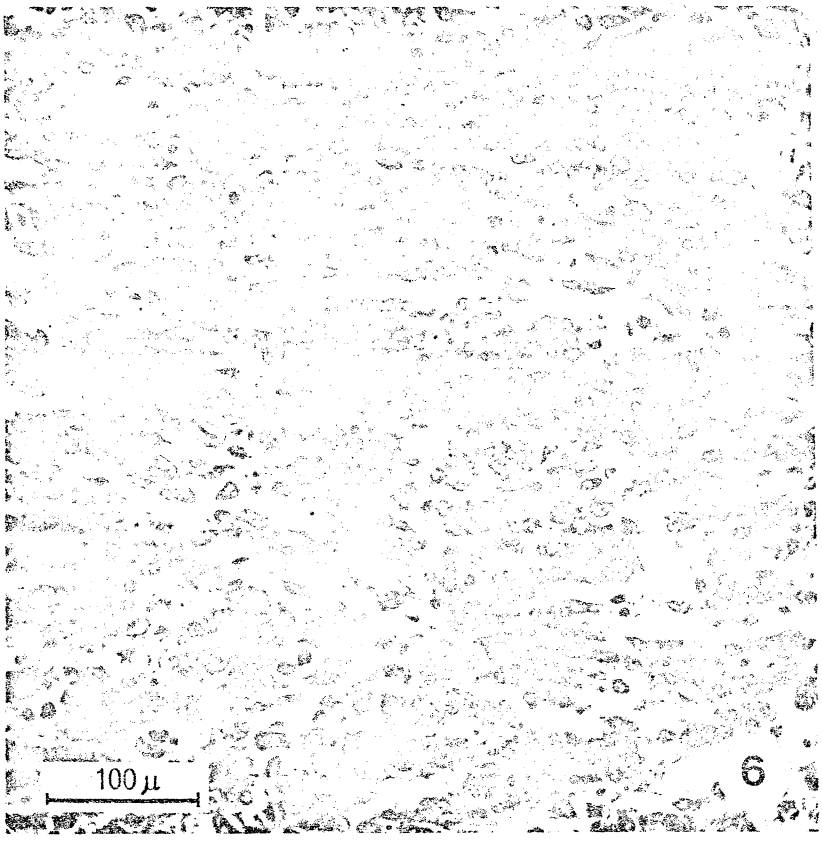

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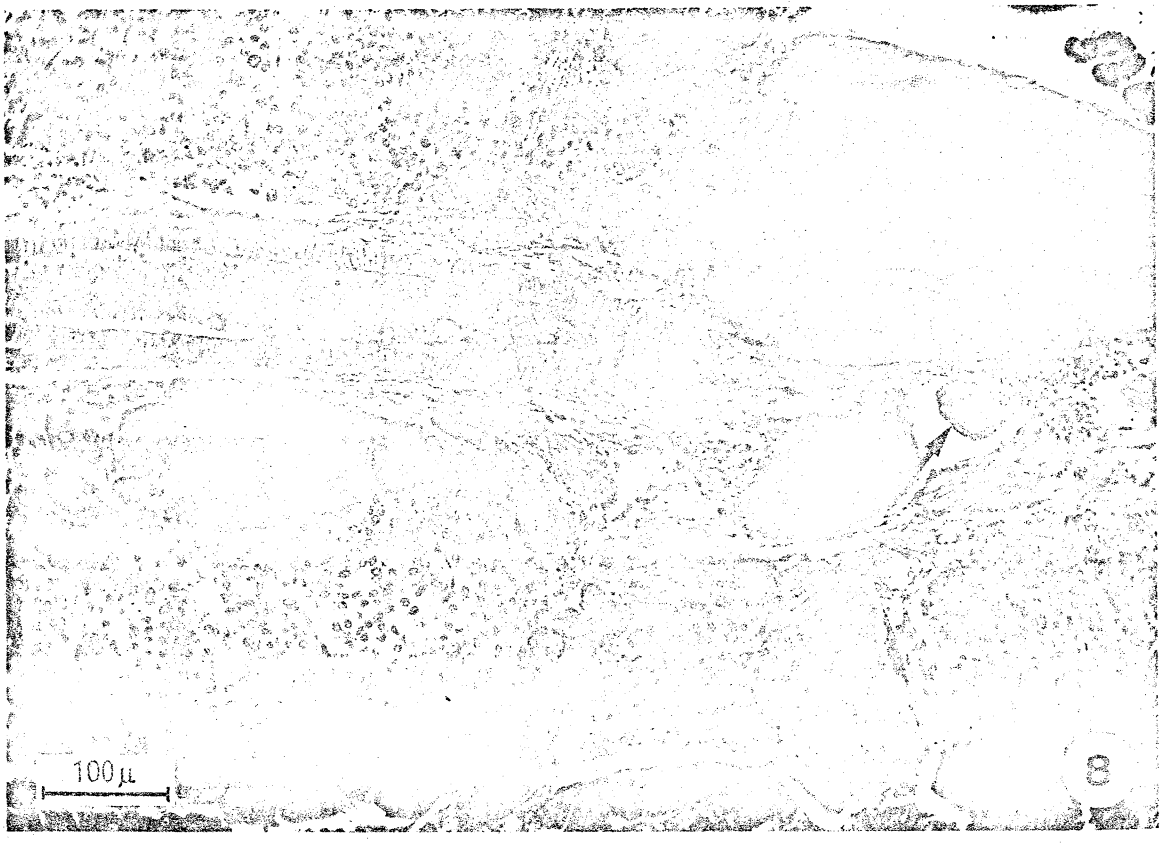

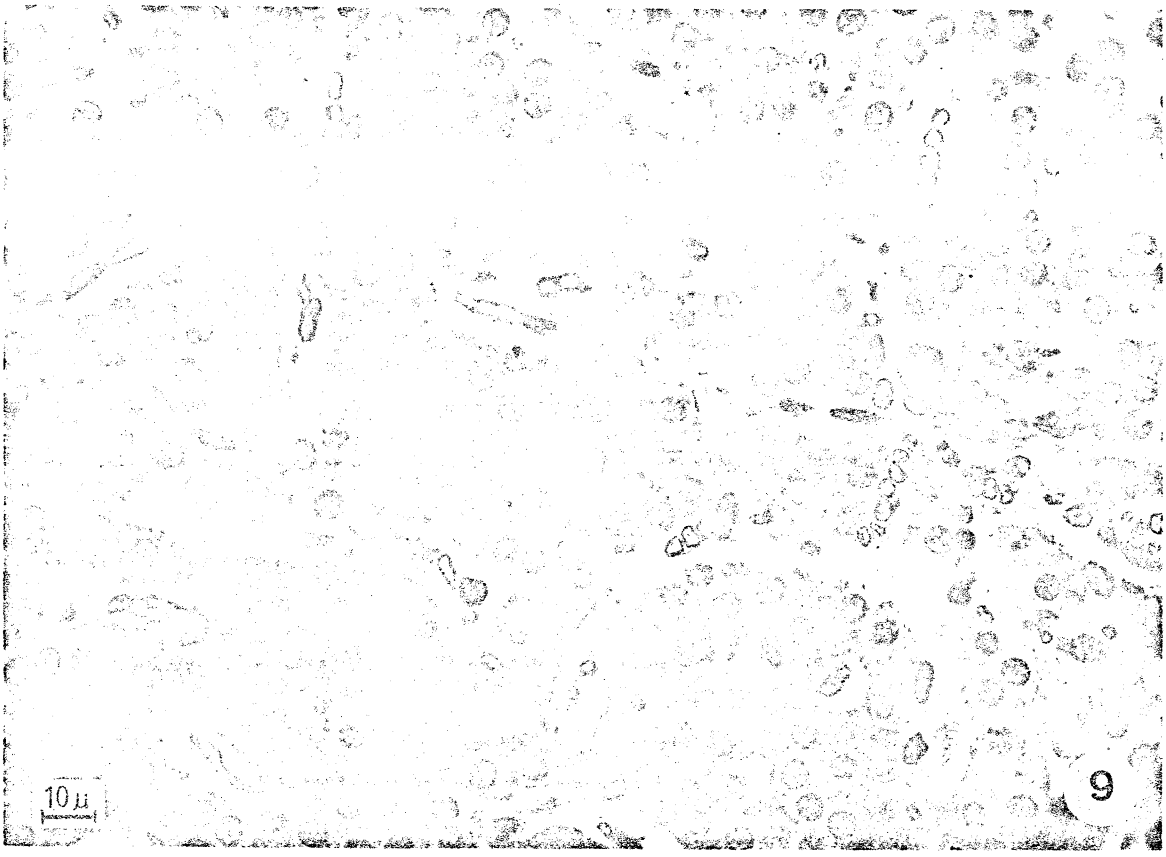
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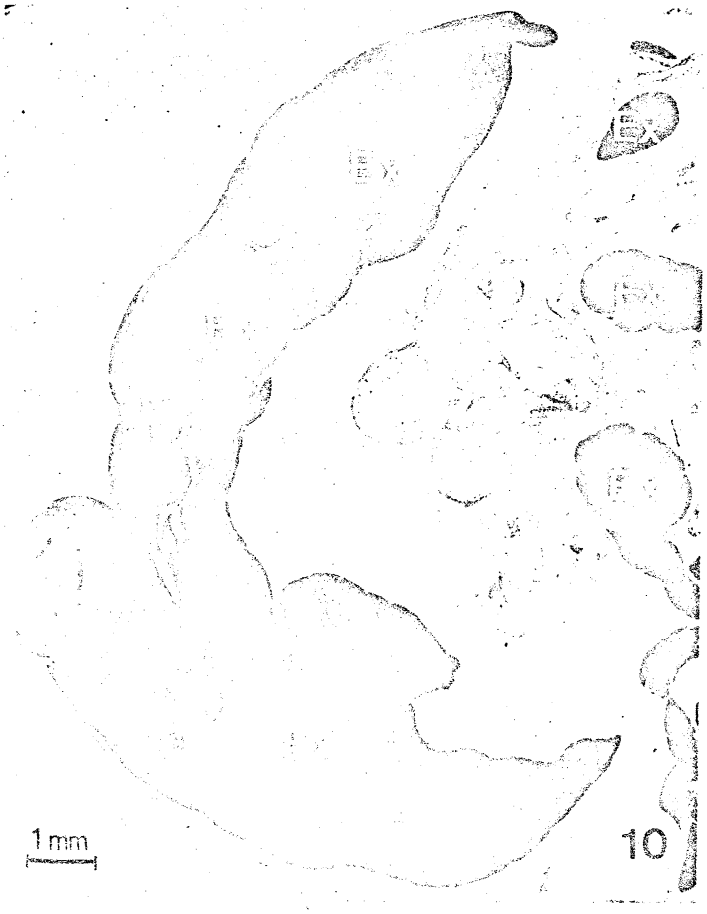
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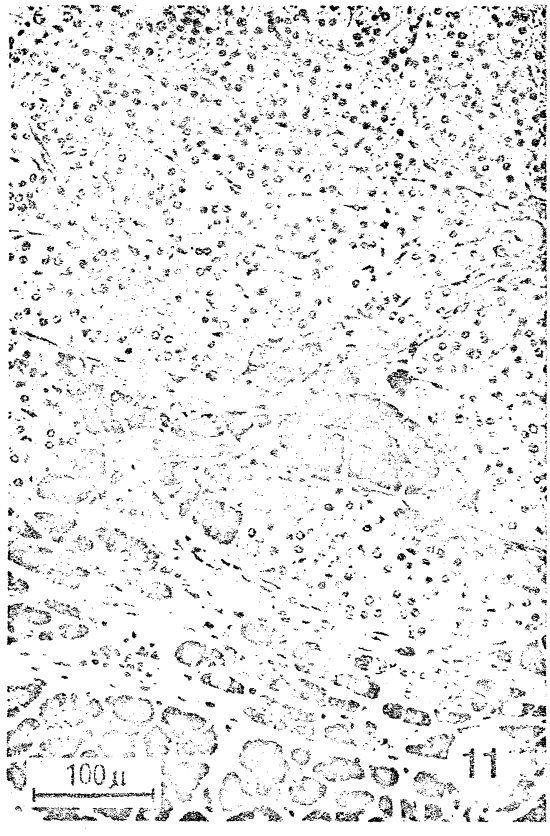
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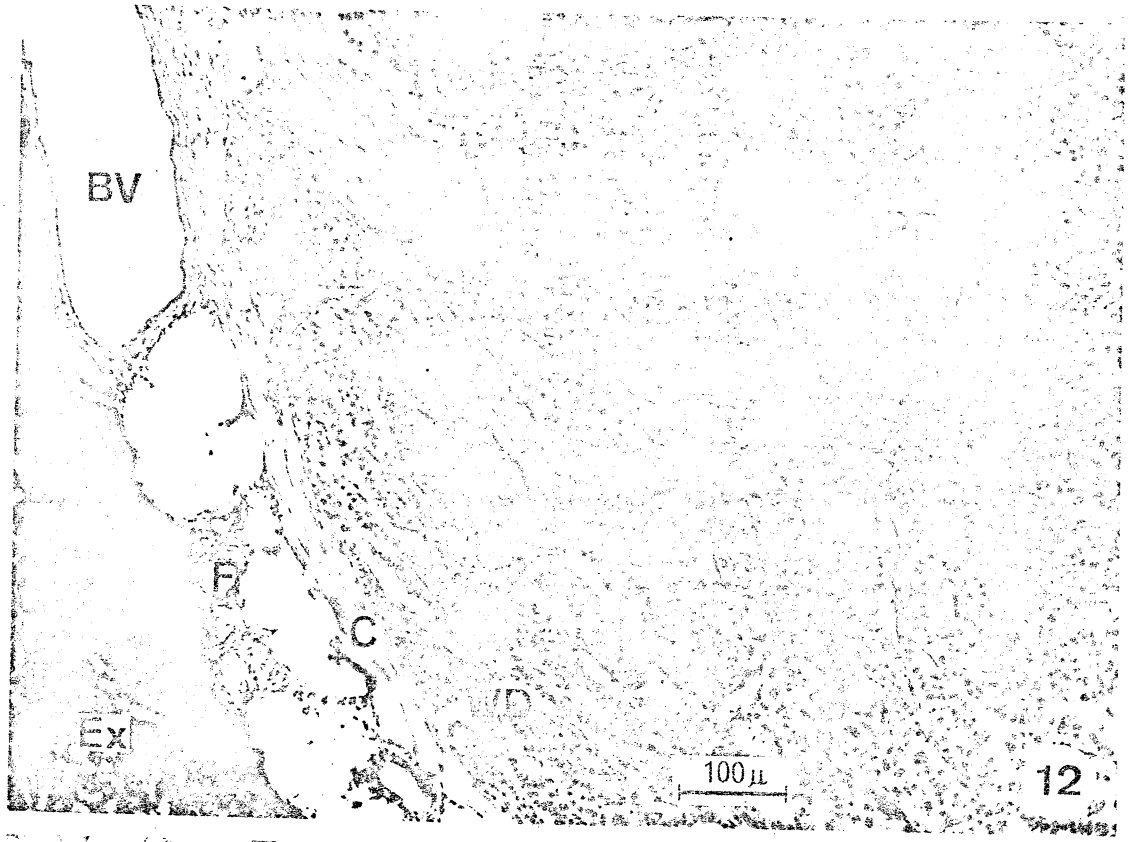

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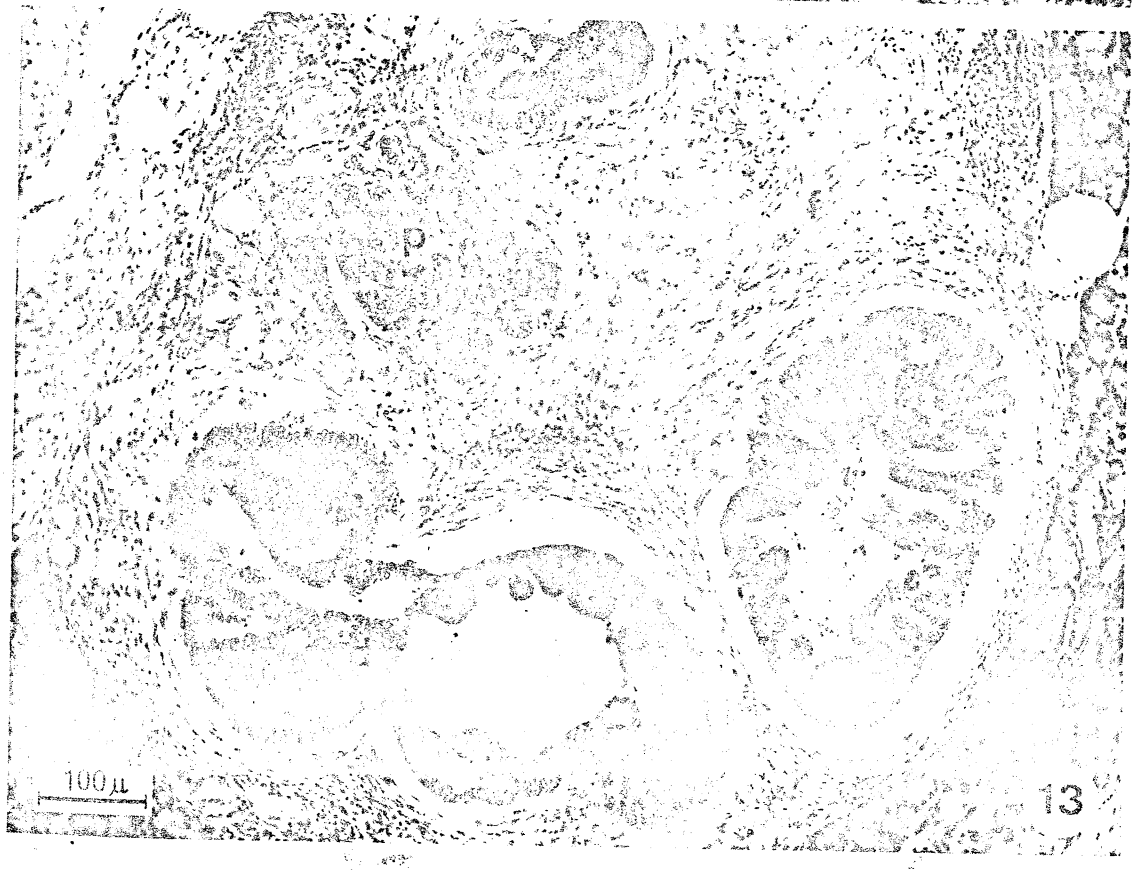

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