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Early Neoplasia of Rabbit Pancreatic Ductal Cells Induced by Dimethylhydrazine[1]

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In general, the most consistently successful tumor induction systems in the field of chemical carcinogenesis have been those that utilized methods wherein the carcinogen was delivered repeatedly and in small doses, directly to the target tissue (1).

In an effort to apply this methodology to the pancreas, techniques have been developed whereby a carcinogen-containing catheter permeation device can be placed within the mammalian pancreatic duct and remain there for prolonged periods of time without producing significant interference with normal exocrine or endocrine function of the gland. The details of the procedure are described elsewhere (R. J. Elkort, A. H. Handler, W. Cooper, D. L. Williams, P. J. Mazden, and R. H. Egdahl, submitted for publication).

Initial studies were carried out with silicone polycarbonate catheters (MEM-213; General Electric, Silicone Products, Waterford, N. Y.), but more recent studies have utilized nylon (Zytel 42; Dupont Co., Basking Ridge, N. J.) catheters, since this material markedly prolongs the duration of carcinogen exposure.

The catheters are filled with 10 μl of a 40% solution of DMH,[3] sealed, and surgically implanted into the main pancreatic duct of the New Zealand White rabbit. Histological examination of the pancreas at regular intervals thereafter shows hyperplasia, dysplasia, and metaplasia of the pancreatic ductal cells appearing 14 to 18 weeks postimplantation, progressing to periductal adenosis and adenoma formation at 34 to 48 weeks (R. J. Elkort and A. H. Handler, submitted for publication). However, with a single catheter implant, further progression of these focal abnormalities was not observed. Since the quantity of carcinogen used in these experiments is relatively small, it was felt that increasing the duration of such exposure might stimulate further progression of these ductal abnormalities toward neoplasia.

Accordingly, a group of rabbits were prepared in a manner identical to that utilized in the initial experimentation except that the 1st DMH-containing catheter was surgically removed 35 days after implantation and replaced with a 2nd identical DMH-containing catheter. The 35-day interval was selected on the basis of *in vitro* data which indicated complete release of the encapsulated carcinogen within 30 days (R. J. Elkort, D. L. Williams, S. Z. Merchant, and A. H. Handler, submitted for publication).

Fifty-six days after the 2nd implant, the animal was sacrificed and complete autopsy was carried out.

Gross observation at autopsy showed hypertrophy of the pancreas in its duodenal (head) portion. The main duct was dilated and the periductal area was shiny, gray, and indurated.

Most of the pathology appeared in the head of the pancreas. There was massive hyperplasia and dysplasia of the main ductal epithelial lining cells and goblet cells (mucus secreting). There were a few epithelial papillary hyperplastic growths into the lumen of the duct. There was some mildly invasive downgrowth of the ductal epithelial cells into the periductal connective tissue. There were atypical glands around the duct with several exhibiting hyperplasia and dysplasia. Some of the cells exhibited nuclear atypia, a few with mitotic figures. There was periductal chronic inflammation. There were several abnormally formed ducts and glands with marked proliferation (adenosis). Because of the above characteristics and since there were also many normal-appearing glands and ducts, this was thought to represent a very early well-differentiated carcinoma arising in the ductal cells. Representative histology sections are shown in Figs. 1 and 2.

In the main body of the pancreas there was focal main duct hyperplasia and some periductal inflammation. There were a few abnormally formed periductal glands. In the tail there was some mild hyperplasia of the main duct. Proliferation of the small glands and inflammatory cells was seen periductally and throughout the acini or main pancreatic substance.

Azure-eosin and phloxine stains were done to rule out the possibility of parasitic (coccidial) infestation, and these were negative.

It is recognized that this single observation must be confirmed before firm conclusions can be drawn regarding

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[3] The abbreviation used is: DMH, 1,2-dimethylhydrazine.

the value of this experimental approach. Nevertheless, spontaneous pancreatic ductal cell neoplasms have not been reported in the New Zealand White rabbit and changes similar to those described have not previously been observed in over 150 animals autopsied during the development of this model system, with the exception of the "preneoplastic" changes noted in the single catheter implant series described above. Current experimentation is directed towards confirmation of this initial observation.

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References

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Fig. 1. Section of head of the pancreas of a rabbit implanted with a 10 μl of buffered NaCl solution (0.9% NaCl) catheter in the duct for 20 weeks. There is no evidence of pathology in the duct or acinar tissue. H & E, × 40.

Fig. 2. Section of the head of the pancreas of a rabbit implanted with a nylon catheter containing DMH and 4.5 weeks later reimplanted with a 2nd DMH-containing catheter. The animal was sacrificed 13 weeks following the initial implant. The ductal epithelium is extremely hyperplastic and dysplastic. There is a papillary growth of epithelial cells (*arrow*) extending into the ductal lumen (*top*). Periductal adenosis characterized by abnormal glands and ducts (*arrows*) is evident. H & E, × 50.

Fig. 3. Section of different area of the pancreas in DMH-treated rabbit described in Fig. 2. There is marked hyperplasia and dysplasia of the ductal epithelial lining cells and secretory cells. Disorganized and atypical epithelial cells are seen invading the periductal connective tissue at certain foci (*arrows*) and extending into the ductal lumen (*arrow*). Lymphocytic inflammatory cells can also be seen in the periductal tissues. H & E, × 50.