Hyperplasia and Cystic Dilatation of Extrahepatic Biliary Tracts in Mice Bearing Grafted Pituitary Growths*

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Pituitary growths can be readily induced in mice by thyroid-destructive doses of I^{131} (3, 8). The primary growths are readily transplantable in mice rendered athyroid in a similar way but not in normal mice (3). In the course of transplantation, some such growths gain autonomy, acquiring the capacity to grow in euthyroid animals (3, 4). These pituitary grafts grow progressively in I^{131}-pretreated mice and metastasize to regional lymph nodes, and the animals die when the tumor weighs approximately 3–6 gm. The pituitary tumor cells are usually chromophobic or occasionally slightly basophilic; acidophilic cells are invariably absent.

At autopsy of the I^{131}-pretreated tumor-bearing mice, the most conspicuous findings were (a) stimulation of the gonads and secondary sex organs similar to that observed after injections of large quantities of gonad-stimulating hormones and (b) cystic dilatation of the extrahepatic biliary tract, often with rupture. The latter changes are described in the present report, and evidence is presented indicating that they are due to pituitary stimulation. In mice not pretreated with I^{131} there was tremendous hyperplasia of the thyroid gland often with numerous adenomas. Bioassays in tadpoles and guinea pigs indicate the presence of large quantities of thyroid-stimulating hormone (TSH) in the tumors and blood of tumor-bearing mice. Stimulation of the adrenal glands has not been noted in tumor-bearing hosts.

The procedures of induction and transplantation of these tumors have been described (3, 4).

Morphologic changes in the biliary tracts.—The changes in the biliary tract observed at autopsy are sketched in Chart 1 in approximately increasing order of severity. Observed after injections of large quantities of TSH in the tumors and blood of tumor-bearing mice. Stimulation of the adrenal glands has not been noted in tumor-bearing hosts.

The gallbladder was usually transparent, filled with green clear bile, and was of normal size or only slightly dilated. The extrahepatic portion of the hepatic duct was only occasionally thickened or very slightly dilated, and its intrahepatic portions showed no change. The cystic duct was usually thickened.

Microscopic examination disclosed a hyperplasia of the wall of the extrahepatic ducts, most marked in the region of the ampulla and at the junction of hepatic and cystic ducts. Figure 3 is a longitudinal and Figure 4 a transverse section of the region of the ampulla of Vater. The hyperplastic ampulla projected into the lumen of the duodenum (Fig. 3), as evident on gross dissection. There were a few mitotic figures (Fig. 8), and, in places, mucus-secreting cells are numerous. The wall of the extrahepatic duct system was thickened, with some proliferation of stromal cells and deposition of much metachromatic material in the ground substance (Fig. 5), which does not take the mucicarmin stain. This change occurred early and was noted also in one animal in which no gross changes were detected in the biliary tract. The content of the cystic dilatations was usually clear.

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slightly green, and only slightly viscous. Occasionally, they contained some white, flaky material. Fluid injected post mortem into several dilatations readily entered the duodenum after distention of the cysts. Thus, anatomically the ducts were patent; it remains uncertain whether their dilatation was due to a physiological obstruction at the ampulla, or atonia, or both.

In numerous mice the cystic dilatations were found collapsed at autopsy, and thin viscous bile filled the peritoneal cavity. In some animals killed when moribund, the entire abdominal wall and even the subcutaneous tissue in juxtaposition to the dilatation were bile-stained, indicating that rupture had occurred at least several hours before death. Peritonitis was not noted at autopsy, even though the volume of free intraperitoneal fluid was estimated at 2-3 ml. In one mouse hemorrhage into the cyst was the immediate cause of death.

In several mice there was a mild to moderate edema, with acute interstitial pancreatitis in the region of the ampulla (Fig. 7). Pancreatic fat necrosis was not seen on gross inspection but was found in sections.

Although the morphogenesis of these changes requires further study, it seems that the primary change is a hyperplasia of the duct, and that dilatation either accompanies or follows the hyperplasia. The anatomical picture is not that of biliary obstruction, and consequences of the latter were invariably absent.

Relation of tumor size and radio-thyroidectomy to common duct stimulation.—The data detailed in Table 1 indicate that these changes in the common duct are frequent only when the tumor is large. They were not seen at autopsy in mice bearing primary $^{131}I$-induced tumors or in those bearing graft-dependent tumors less than about 1 cm. in diameter. The incidence of cysts in mice with such tumors of about 1 cm. across (+) was 11 per cent; in those with tumors of about 1.5–2 cm. across (+ +), 56 per cent; in mice with larger tumors (+ + +), 85 per cent. In the course of numerous subpassages, the dependent tumor line retained ability of both to elaborate thyrotropic hormones and to cause the development of common duct cysts; but the autonomous tumor line carried in normal hosts never gave rise to such dilatations. Autonomous tumors are carried in both normal and radio-thyroidectomized mice, and the data in Table 1 indicate that the autonomous tumors lost capacity to elaborate the factor causing these

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**Chart 1**—Sketches of extrahepatic biliary ducts and gall-bladder; (a) normal; (b) common bile duct, dilated at distal end; (c) common bile duct dilated at proximal end; (d) common bile duct slightly dilated throughout its entire length; (e) duct moderately dilated throughout, with slight constriction at midpoint; (f) duct greatly dilated, forming large cyst.
changes, with two exceptions which deserve special comment. Both occurred in radio-thyroidec- tumized animals in the second subpassage (that is, soon after isolation) of the autonomous line. None was seen in later passages.

Ability to elaborate TSH was retained after acquisition of autonomy. It is possible that this dichotomy is only apparent and is due to a quanti- tative decrease in hormone production by the estrogenic hormones over periods longer than 400 days. The changes in our mice could not be attributed to estrogens alone, since they were present in males with large seminal vesicles and prostates (Fig. 2). Furthermore, they were not seen in mice bearing grafted granulosa-cell tumors dis- charging large quantities of estrogen (1) or in mice bearing grafted luteomas with secondary changes of masculinization (5, 9). Common duct cysts

**TABLE 1**

<table>
<thead>
<tr>
<th>TUMOR SIZE</th>
<th>Cystic Dilatations</th>
<th>SIZE OF CYSTIC DILATATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. per cent Small</td>
<td>Medium</td>
</tr>
<tr>
<td>+</td>
<td>88</td>
<td>5</td>
</tr>
<tr>
<td>+ +</td>
<td>89</td>
<td>52</td>
</tr>
<tr>
<td>+ + +</td>
<td>55</td>
<td>47</td>
</tr>
</tbody>
</table>

Dependent strain; host radiothyroidectomized

Autonomous strain; hosts radiothyroidectomized

++ 4 0
++ + 26 2 8 1 1
++ + 60 0
++ + 65 0

*For explanation, see text.

**TABLE 2**

<table>
<thead>
<tr>
<th>NO. AND SEX OF MICE</th>
<th>AT GONADECTOMY</th>
<th>AT DEATH</th>
<th>COMMON DUCT CYSTIC DILATATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRAIN</td>
<td>Tumor</td>
<td>Duct</td>
<td>No. of days*</td>
</tr>
<tr>
<td>M 70 S D</td>
<td>+ N.E.†</td>
<td>+</td>
<td>55 + +</td>
</tr>
<tr>
<td>M 76 S D</td>
<td>+ N.E.</td>
<td>+</td>
<td>76 + + +</td>
</tr>
<tr>
<td>M 77 S D</td>
<td>+ + N.E.</td>
<td>+</td>
<td>84 + + +</td>
</tr>
<tr>
<td>M 69 S D</td>
<td>+ + N.E.</td>
<td>+ +</td>
<td>23 + +</td>
</tr>
<tr>
<td>M 233 S D</td>
<td>+ + + Small</td>
<td>+</td>
<td>15 + + +</td>
</tr>
<tr>
<td>M 65 S D</td>
<td>+ + + N.E.</td>
<td>+ +</td>
<td>45 + + +</td>
</tr>
<tr>
<td>F 19 P 101</td>
<td>+ Small</td>
<td>+</td>
<td>90 + + +</td>
</tr>
<tr>
<td>F 90 P 101</td>
<td>+ + N.E.</td>
<td>+</td>
<td>71 + + +</td>
</tr>
<tr>
<td>F 13 P 168</td>
<td>+ + + N.E.</td>
<td>+</td>
<td>68 + + +</td>
</tr>
</tbody>
</table>

* After gonadectomy.
† N.E. = Not established.

autonomous tumors. This possibility will be ana- lyzed by quantitative bioassays.

**Relation to gonadal stimulation and to estrogens.**—

All tumor-bearing female mice with cystic dilata- tion of the common duct also had morphologic changes indicative of stimulation by gonadal stimulating hormones, with rare and questionable exceptions. On the other hand, numerous mice with tumors of medium size had gonadal stimulation without any gross cystic changes in the duct.

Gonadal stimulation was evident in numerous normal mice bearing autonomous pituitary tumor grafts exceeding 1 cm. in greatest diameter, but none of these had common duct dilatation.

Gardner, Allen, and Smith (7) described the presence of similar cysts in mice that had received occurred also in the presence of seminal vesicle atrophy.

In order to study further the role of gonadal hormones in the development of dilatation of the common duct, tumor-bearing mice of both sexes were gonadectomized. Data on such mice living after gonadectomy for 18–90 days are shown in Table 2. All mice tabulated exhibited at autopsy slight to advanced castration atrophy of seminal vesicles or uterine horns, respectively; nevertheless, all but one had some cystic dilatation of the common duct. This series includes two mice gonadectomized when the animals had a slight common duct dilatation. One of these mice died 18, the other, 90 days after gonadectomy, with large and medium cystic dilatation, respectively,
and with atrophy of the secondary sex organs. These observations suggest that gonadal hormones play a minor role, if any, in the development of the cystic dilatation of the common duct.

DISCUSSION

It is highly probable that the change in the common duct here described is caused by hormones related to TSH or by their metabolites. Transplantable tumors in mice have now been investigated for well over half a century, and among those studied are various hormone-secreting tumors, including nonsecreting chromophobe adenomas of the pituitary (6). None but the hormone-secreting pituitary tumors here described were capable of causing a cystic dilatation of the common duct. Two features are common to tumors which cause this change: discharge of tremendous quantities of TSH and absence of normally functioning thyroid glands.

During fasting, the entrance of bile into the duodenum is blocked by the sphincter of Oddi which remains tonically contracted; therefore, the gallbladder becomes gradually distended with retained bile (cf. 2). The cysts formed in our mice were not due to fasting; evidence of starvation was not noted at autopsy.

The mechanism of evacuation of the gallbladder has been the subject of some debate. Emptying of the biliary tract occurs after the introduction of fat into the duodenum when all nervous connections between the biliary and gastrointestinal tracts and between the former and the central nervous system have been severed. This suggests a hormonal or humoral mechanism (cf. 2). Ivy and Oldberg (10) obtained a hormone-like substance related to secretin, which they named "cholecystokinin," that caused contraction of the gallbladder when injected intravenously into animals. Smith, Pomaranc, and Ivy (11) found that intravenous injection of 0.5 mg. "cholecystokinin" produced prompt and efficient emptying of the gallbladder of the nonpregnant guinea pig, but a delayed and much less effective emptying of the gallbladder of pregnant animals. The small differences in the direction of decreased reactivity of the sphincteric mechanism appear to be responsible, in part, at least, for the impaired emptying of the gallbladder of the pregnant guinea pig. Most investigations on the emptying of the biliary tract concern man and dog. Rats do not have a gallbladder, but mice have; it is possible, however, that in the mouse the extrahepatic ducts behave as the gallbladder in higher mammals. If there is a "choledochokynetic" hormone, the effect here described may be attributed to inhibition of this hormone.

The evidence presented here indicates that cyst formation is unrelated to the gonadal hormones. All our mice with such cystic dilatations were athyroid or had but rudimentary, poorly functioning thyroids. Lack of TH alone cannot be the cause of this change, since it is absent in thyroidectomized animals not bearing grafted pituitary tumors. Animals bearing such tumors are subject to excessive gonadal stimulation, and estrogens can cause a similar change, as Gardner et al. (7) have shown. The liver metabolizes both estrogens and androgens, and, since common duct cystic dilatations occur in mice of both sexes bearing pituitary tumors, their genesis could be attributed to a common metabolite of male and female gonadal hormones excreted by the liver. However, since this common duct change occurs in the absence of the gonad, its genesis is better attributed to a pituitary hormone. The causation of similar dilatations by long continued administration of estrogenic hormones by Gardner et al. (7) could possibly be attributed to secondary stimulation of the pituitary.

The pituitary tumors here described secrete in large quantities only thyrotropic hormones. Secretion of gonadal-stimulating hormones is assumed on the basis of morphological changes in tumor-bearing hosts, but has not yet been demonstrated by bioassays. The possibility that a hitherto unknown pituitary hormone is responsible for the common duct hyperplasia and cyst formation and the pathogenesis of this phenomenon deserve further study.

SUMMARY

Hyperplasia and cystic dilatation of the extrahepatic biliary ducts is a usual secondary change in mice bearing large grafts of dependent pituitary tumors which secrete thyroid-stimulating hormones (TSH) and probably also gonad-stimulating hormones. Occasionally, rupture of the common duct following excessive dilatation is the immediate cause of death. Autonomous pituitary tumors (those not requiring for growth absence of the thyroid) do not cause these changes in the common duct, even though such tumors secrete TSH and possibly gonad-stimulating hormones.

The available evidence suggests that this change in the biliary tract is related to some hormone of the pituitary.

REFERENCES

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Fig. 1.—Female mouse bearing grafted tumors in both thighs. The thin-walled common bile duct is greatly dilated. Arrows point to the extrahepatic biliary tract. The ovaries are enlarged and contain hemorrhagic and cystic follicles, and the uterus is hyperplastic.

Fig. 2.—Male mouse (grafted tumor not shown). The common bile duct is dilated, and the seminal vesicles are hypertrophic. Arrows point to the extrahepatic biliary tract.

Fig. 3.—Longitudinal section of the ampulla of Vater. The mucosa of the common duct is hyperplastic, and the papillary elevation of the ampulla is exaggerated. (Hematoxylin and eosin.) ×50.

Fig. 4.—Transverse section of the ampulla of Vater. There is marked hyperplasia of the mucosa, and cystic dilatation of the adjacent part of the duct. (Hematoxylin and eosin.) ×50.

Fig. 5.—The wall of the common bile duct is thickened by increased fibrous connective tissue. (Hematoxylin and eosin.) ×100.

Fig. 6.—Normal gallbladder and cystic duct with liver. (Hematoxylin and eosin.) ×50.

Fig. 7.—Pancreatic portion of the common bile duct: with edema and acute inflammation about the duct and adjacent pancreas. (Hematoxylin and eosin.) ×150.

Fig. 8.—Terminal portion of common bile duct with mitotic figures in the hyperplastic mucosa. (Hematoxylin and eosin.) ×500.


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