Preliminary studies on the *in vivo* pulps of young dogs and rats have indicated the presence of at least 2 of the cell types found in tissue culture; many scattered cells throughout the pulp having membrane potentials of 5 to 10 millivolts and a few cells located along the dentinal border with membrane potentials of 25 to 45 millivolts. Work is continuing along these lines.

Summary. It has been possible to grow in tissue culture viable cells from tooth germs of young mice. Three cell types have been determined based on morphological and electrophysiological characteristics. The mouse odontoblast grown in tissue culture possesses a membrane potential which is considerably greater than that of the fibroblast and is in the range reported for smooth muscle and glandular cells. At present it is not possible to state if the physiological role of the odontoblast is sensory, glandular, or both.

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Iodine-Induced Submandibular Sialadenitis in the Hamster. (26871)

RICHARD H. FOLLIS, JR.
Veterans Administration Central Laboratory for Anatomical Pathology and Research, Armed Forces Institute of Pathology, Washington, D.C.

During the course of some studies on the pathogenesis of iodine-induced thyroiditis in the hamster(1), other tissues, particularly those which are known to concentrate this element, have been examined microscopically. Damage to the submandibular (submaxillary) glands has been found uniformly; in contrast, the parotid and sublingual glands, as well as the gastric mucosa, appear to be normal. This communication presents a description of the changes in affected glands together with comparative data on radioiodine uptake, which may help to explain the difference in reaction between the submandibular glands and other structures.

Materials and methods. Histological observations have been carried out on the salivary glands of approximately 100 normal male hamsters, each weighing about 125 g, which had received various quantities of iodide as the potassium or sodium salts for periods lasting several hours to 10 days. The iodide was administered intraperitoneally in distilled water. Animals were sacrificed at intervals from one hour after a single injection up to after 10 days of multiple doses, usually once daily. Submandibular, sublingual and parotid glands as well as glandular portions of the stomach, were studied after fixation with neutral formalin and staining with H and E, PAS, and alcian blue technics. Iodide dosages ranged from 1.0 to 200 mg, since it was found that smaller amounts were ineffective.

TABLE I. Relative Concentration of I^{131} in Tissues, Expressed as cpm/mg Wet Weight.

Time after I^{131}		Parotid gland	Sublingual gland	Submandibular gland	Stomach	Testis	Thyroid
1 hr		37.4	35.8	112.0	31.1	—	2900
2 "	1	46.3	49.8	263.0	43.3	11.1	3050
	2	44.0	41.7	165.0	—	19.1	5730
	3	62.3	90.5	620.0	—	37.0	4230
3 "	1	67.5	60.0	346.0	54.2	21.4	6060
	2	48.6	52.5	166.0	—	22.4	13100
	3	18.4	18.0	96.0	—	9.6	9450
4 "		15.8	15.7	30.6	—	—	2800

Normal animals were given 25 μc radioactive iodine, without carrier, intraperitoneally and sacrificed from 1 to 3 hours later. Samples of 3 salivary glands, thyroid, testis, and glandular portion of stomach were weighed on a torsion balance, digested in 3N NaOH and counted with a sodium iodide crystal scintillation detector.

Results. The normal submandibular gland (Fig. 1) of the hamster is composed of acini whose serous cells contain large numbers of small basophilic granules which stain by the PAS or alcian blue technics. Small, most proximal, intralobular ducts are lined by columnar cells with basal nuclei and pale cytoplasm, with faintly PAS staining granules. The cells lining the distal ducts are smaller with eosinophilic cytoplasm. The cells of the collecting ducts are more squamous in appearance. The following description of glands from treated animals is a composite of observations made after doses of iodide of various sizes. Obviously changes develop more rapidly after large than small amounts of iodide.

Following a large dose, *i.e.,* 10 mg of iodide or more, changes are seen as early as 2 to 4 hours. The lobules are spread apart by swelling of the loose interlobular connective tissue. Inflammatory cells, both polymorphonuclear as well as mononuclear types, are found in these areas. The edema and inflammatory cells are related to distinct changes in the distal portions of ducts. The walls of these structures are infiltrated with polymorphonuclear cells; the lining epithelial cells may be completely necrotic. In addition, the duct lumina are filled with leukocytes, basophilic (PAS positive) material, and desquamated cells. In these early stages, too, large numbers of leukocytes are found in and about the walls of blood vessels. No hemorrhage is seen.

By 24 hours the alterations in the ducts are more severe. The lumina of the more proximal ducts are dilated but their lining cells do not appear damaged, save that they may be smaller. Leukocytes are found between the acinar elements, which even by this time have become atrophic and have begun to lose their basophilic (PAS and alcian blue positive) contents. With increasing time, regeneration of the duct epithelium begins even though administration of iodide continues; the lining elements have a squamous appearance, more like the cells of the collecting ducts than the normal distal duct cells. The duct system is conspicuously dilated.

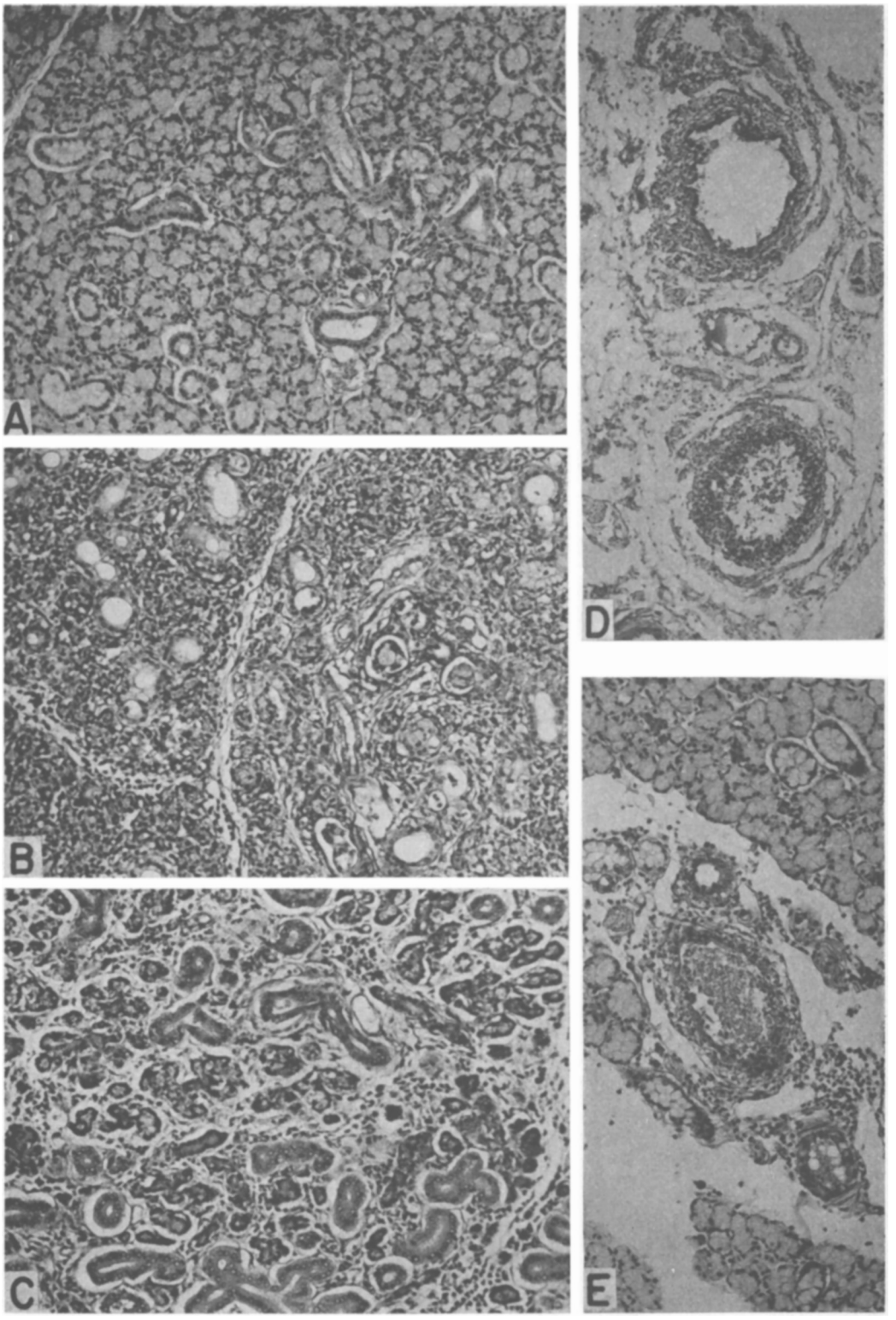
These alterations are usually diffuse. Sometimes, however, especially with lower dosage of iodine, single lobules will be involved, while neighboring ones remain normal in appearance.

If the process is followed into a more subacute phase, the regeneration of duct epithelium elements becomes more conspicuous, while the acinar elements exhibit atrophy.

No difference was found between sodium or potassium salts of iodide.

Studies of the sublingual and parotid glands as well as the glandular portions of the stomach failed to reveal any lesions.

Studies of radioactive iodine uptake of 3 salivary glands, glandular portion of the stomach, thyroid, and testis are presented in Table I. It will be noted that the concentration of iodide in the submandibular gland


A
B
C
D
E

is 3 to 5 times that of the other salivary glands in the first few hours after administration. Concentrations in thyroid and testis are high and low respectively as expected.

Discussion. Since the 1830's when iodides came to be used extensively in treatment of syphilis, clinicians have known that these compounds affect the salivary glands. Their presence in saliva(2) and the fact that painful swelling of the parotid glands ("iodine mumps") might develop when excessive amounts of potassium iodide are administered are well known(3,4). That a true sialadenitis may result from administration of large amounts of iodine to hamsters is of great interest with respect to these physiological and clinical experiences.

The distal portions of the submandibular duct system appear to suffer initial damage when iodide is administered in sufficient amounts. The other alterations described above are interpreted as secondary to the changes in the ducts. This site of injury is of great interest in view of the autoradiographic studies of Cohen *et al.*(5) who have demonstrated that radioactive iodide is localized to the proximal ducts of the submandibular glands of the hamster and is not found in the acinar portions or in the epithelial elements of the distal and collecting ducts. To explain this difference in localization between proximal portions, where presumably uptake and secretion occur, and distal portions, where injury is found, one may presume that the proximal duct cells remove the iodide from the blood and are not damaged in so doing, but that the concentration of iodide is high enough in the saliva further on to damage the lining cells of the distal portions of the ducts.

It is of interest to recall that in the therapy of syphilis with iodides patients might receive 10 to 30 g of potassium iodide each day(4). A dose of 12 g is equivalent to about 9 g of iodide, or 120 mg per kilo for a 75 kg individual. Such a dose is comparable to 10 mg for a 125 g hamster, an amount of iodide which produces marked changes in the submandibular gland.

The comparative studies of uptake of I^{131} by the 3 salivary glands of the hamster, reported above, confirm those of Myant and coworkers(5,6,7). The relative activity of the submandibular glands with respect to the others, which was found by these workers, is of the same order of magnitude, *i.e.*, about 5 times that for the parotids, as was observed here. The concentrating activity of the gastric mucosa is of the same order as that of the parotid and sublingual glands. Autoradiographic studies had previously demonstrated the uptake of iodine by glandular gastric mucosa of the hamster(8). That the submandibular glands, in contrast to the parotid and sublingual glands and glandular gastric mucosa, are the only structures involved when iodide is administered would appear to warrant the hypothesis that the concentrating ability and damage are causally related. That a certain dosage level must be reached before the alterations will appear further strengthens this hypothesis, one which could, of course, be further enhanced by studies in other species. In the rat, which does not concentrate iodine to any degree, no inflammatory change has been produced by excess iodine (unpublished observations). The species differences already reported by Cohen and Myant(7) provide data which may guide such studies.

Naturally, the production of damage in salivary gland which can best concentrate iodine is of great interest with respect to the iodine-induced thyroiditis studied in this laboratory(1). That a critical amount of iodide must be administered to produce this change in the thyroid(9) and that a high concentration of iodine must be reached in the gland if the change is to occur (unpublished observations) make most plausible the hypothesis that the inflammation is the response of a direct toxic effect of iodide on

FIG. 1. *A.* Submandibular salivary gland, normal hamster (H-532) (× 125). *B.* Submandibular gland (H-516) 3 days after administration of 20 mg iodide (× 125). *C.* Submandibular gland (H-528) 10 days after 200 mg iodide (× 125). *D.* Submandibular ducts (H-578) 4 hr after 200 mg iodide showing inflammatory reaction about and in walls of ducts (× 80). *E.* Submandibular duct showing necrosis wall and periductal inflammation 6 hr after 200 mg iodide (× 80).

the thyroid epithelial cells. Whether this hypothesis can be established with certainty remains for continuing studies to disclose.

The occurrence of spontaneous sialadenitis has been described in various species(10,11). The hamster is no exception(12). Salivary gland disease in this species is characterized by prominent intranuclear inclusions. These have not been observed in the salivary glands of any animals studied in this laboratory. Furthermore, no inflammatory changes have been observed in a large number of animals which had not received iodide. The possibility must, of course, be considered that iodide may activate a latent viral agent. If so, and such seems most unlikely, this agent is unaccompanied by inclusions and must be activated with great rapidity, *i.e.*, within 4 hours.

The sexual dimorphism of the submaxillary glands of the rat and mouse is well recognized(10). All of the observations reported herein have been in males. Whether such a change occurs in females remains to be studied. So, too, the effects of prolonged administration of iodide as well as the possible production of chronic sialadenitis are worthy of further investigation.

Summary. Administration of large amounts of potassium iodide to the hamster leads to an inflammatory reaction in the submandibular glands, but not in the parotid or sublingual structures. The primary site of damage is the distal duct system. Such selective damage by this agent may be related to the greater concentrating ability of iodine by the submandibular glands in contrast to the parotids and sublinguals.

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Establishment of Resistance to Gardner Lymphosarcoma (6C 3HED) and L#2 Lymphoma in C3H and A/He Mice.* (26872)

WILLIAM M. LARSON, JR., CHARLES R. SLATER AND RALPH W. MCKEE
Department of Physiological Chemistry, School of Medicine, University of California, Los Angels

The production of resistance to growth of Ehrlich carcinoma in C57 BL mice(1,2) and in Swiss mice(3) by intraperitoneal injections of X-irradiated Ehrlich carcinoma cells has been reported. Furthermore, Revesz(4,5) has found that if X-irradiated Ehrlich cells are mixed with non-irradiated cells in appropriate quantities there is inhibition of cancer cell growth and immunity is produced in the injected mice. However, if too few X-irradiated cells are present in the mixture there may even be an enhanced growth without immunity being produced.

We are reporting here the production of complete resistance in C3H mice to Gardner lymphosarcoma (6C 3HED) and L#2 lymphoma, and in A/He mice to Gardner tumor.

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