latter were obtained in animals consuming a diet high in exogenous cholesterol which by itself might have interfered with endogenous cholesterol synthesis.

The unique ability of W-398 to reverse established atherosclerotic lesions and to prevent their development is of great interest. The lack of adverse effects on all major organ systems, with the possible exception of the liver, points to a specific locus of action. Little is known concerning the mechanism by which this drug brings about the observed effects. A better understanding of these mechanisms is being sought in the hope that it might lead to the discovery of even more useful agents.

*Summary.* Benzyl N-benzyl carbethoxyhydroxamate (W-398) given orally to rabbits caused disappearance of atherosclerotic lesions previously established by administration of a diet containing 1% cholesterol. W-398 also prevented the occurrence of atherosclerotic lesions when administered jointly with a cholesterol containing diet. Elevated blood cholesterol level in adult rabbits or weanling rats fed a hypercholesteremic diet were also reduced by administration of W-398. The drug was effective in doses that were well tolerated by the animals.

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## Sodium Iodide-Induced Submaxillary Sialadenitis in the Rat. (28670)

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Inflammation of submaxillary glands has been described in man(1) and in the hamster (2) in response to oral or parenteral administration of massive doses of iodide. Previous reports have concerned those species which are known from radio-autographic and biochemical studies to concentrate iodide in submaxillary gland and its saliva(3,4). Attempts have been made to correlate glandular iodide-concentrating ability with the inflammatory and metaplastic process and to relate the inflammation to chemical effects of iodide upon duct structures(2).

The rat has been shown not to concentrate iodide in submaxillary gland parenchyma or its secretion(3,5); specific glandular inflammatory changes have not been noted after iodide administration. In our studies on antithyroid effects of iodides and sulfonamides, oral administration of massive doses of sodium iodide to rats resulted in marked submaxillary sialadenitis.

*Materials and methods.* Fifty-four male Walter Reed strain albino rats initially weighing 200-250 g were randomly assigned to 6 groups. All animals received tap water and ground D & G rat biscuits* (iodine con-

* G. L. Baking Co., Frederick, Md.

TABLE I. Effects on Submaxillary Gland and Body Weights of .5% or 4% NaI Diet for 28 Days.

| Diet | No. of animals | Body wt, g | | Submaxillary gland | |
|---|---|---|---|---|---|
| | | Initial* | Final* | Total, mg† | mg/100 g* |
| .5% NaI | 6 | 238 ± 24 | 306 ± 43 | 575 | 190 ± 18 |
| Controls | 18 | 233 ± 25 | 335 ± 44 | 627 | 184 ± 16 |
| 4% NaI | 5‡ | 243 ± 21 | 238 ± 43§ | 544 | 229 ± 16§ |

* Mean ± standard deviation.
† Mean.
‡ One animal of the original 6 in this group was found at autopsy to be hydrocephalic and was excluded from the study.
§ Represents P value <.001 based on the t-test for significance of difference between means of control and 4% NaI groups.

TABLE II. Effects on Submaxillary Gland and Body Weights of .5% or 4% NaI in Combination with 2% Sulfaguanidine for 28 Days.

| Diet | No. of animals | Body wt, g | | Submaxillary gland | |
|---|---|---|---|---|---|
| | | Initial* | Final* | Total, mg† | mg/100 g* |
| .5% NaI + 2% SG | 6 | 242 ± 18 | 258 ± 15‡ | 450 | 175 ± 10 |
| 2% SG | 12 | 233 ± 22 | 310 ± 37 | 519 | 165 ± 13 |
| 4% NaI + 2% SG | 6 | 240 ± 22 | 238 ± 30‡ | 456 | 194 ± 17§ |

* Mean ± standard deviation.
† Mean.
‡ Represents P value <.001 when compared to SG mean.
§ Represents P value <.01 when compared to SG mean.

tent 800 μg/kg *ad lib*. One-half or 4% NaI and 2% sulfaguanidine (SG)† were added, singly or in combination, to the ground diets of experimental groups (Tables I and II).

Animals were weighed weekly. They were sacrificed by $CO_2$ asphyxiation at 28 days. Submaxillary glands were immediately weighed on a Mettler balance and bisected in their largest plane before processing. Portions of other salivary glands and pancreas were also obtained. Paraffin sections were stained with H & E and PAS-hematoxylin.

*Results*. Body and gland weights (Tables I and II). When compared to appropriate controls, 4% NaI, alone or with SG, resulted in complete cessation of weight gain. By contrast, 0.5% NaI significantly affected body weight only in animals getting SG. Although the submaxillary glands of animals receiving 0.5% NaI with or without SG were smaller than normal, there was no evidence of involution on a relative weight basis. With 4% NaI, the limitation of body weight so exceeded the effect on gland weight that glands were significantly larger than normal on a relative weight basis.

† Matheson, Coleman & Bell, E. Rutherford, N. J.

*Histology*. The glandular unit of adult rat submaxillary gland, as described by Jacoby and Leeson(6), consists of acini, intercalated ducts, convoluted tubules, and intralobular striated ducts, which combine to form collecting ducts lined proximally by low cuboidal and distally by squamous epithelium. Distal ducts are seen with vascular structures in loose connective tissue.

All animals which received the 0.5% NaI diet manifested the following changes in and around distal ductular structures (Fig. 1): 1. an intraluminal, ductular, and periductular, acute inflammatory response composed primarily of polymorphonuclear leukocytes and eosinophils; 2. a multilayered, metaplastic proliferation of minimally keratinizing squamous epithelium, many cells of which were anuclear and fragmented; 3. periductular vascular congestion and probable vascular proliferation; 4. slightly increased periductular connective tissue; 5. a highly uniform, virtually complete involvement of ducts by processes 1 through 4. Acini, granular tubules and striated ducts were indistinguishable from those of untreated controls.

Four per cent NaI caused a greater degree

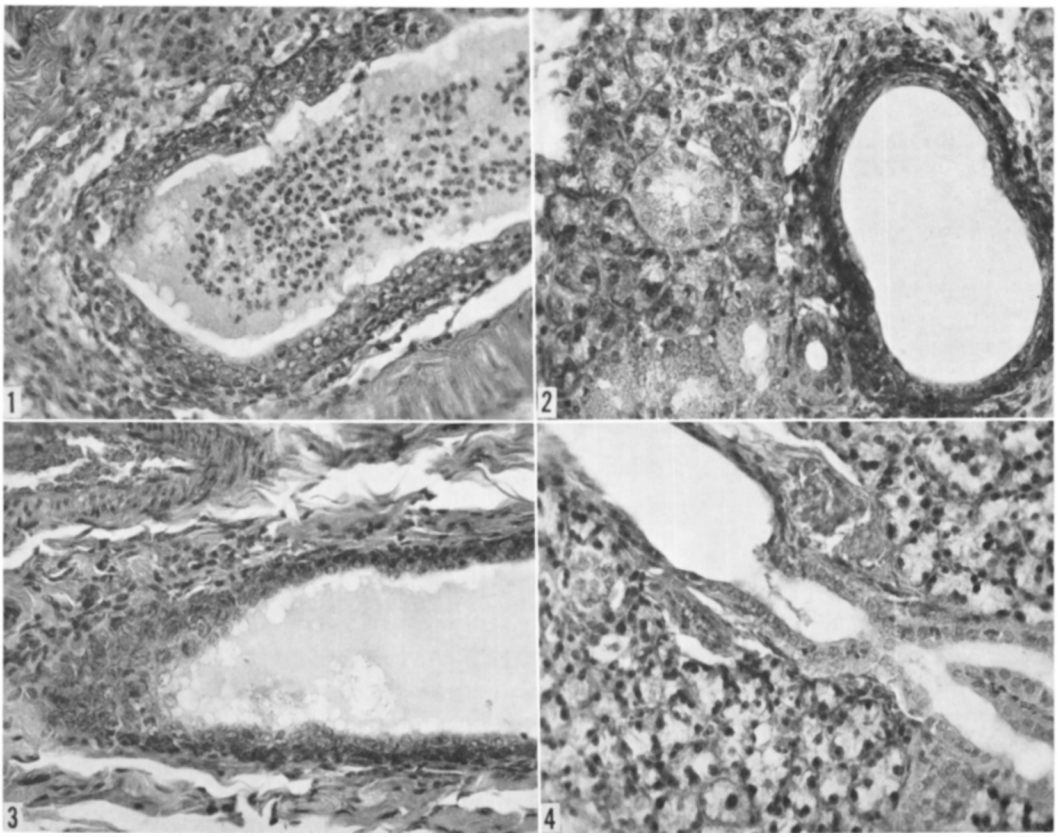

FIG. 1. Rat submaxillary gland distal duct after 0.5% NaI, showing inflammation, metaplasia, periductular vascular congestion and increased connective tissue. (H & E, ×195.)

FIG. 2. Metaplastic, chronically inflamed submaxillary duct after 4% NaI. Note intact granular tubule, left center. (PAS, ×195.)

FIG. 3. Dilated metaplastic duct, 4% NaI. Periductal fibrosis and inflammation. (H & E, ×195.)

FIG. 4. Junction of striated duct and excretory duct showing squamous metaplasia with 0.5% NaI-2% SG. (H & E, ×195.)

of ductal squamous metaplasia, a more marked periductal fibrosis, and a more chronic-type ductular inflammatory response than 0.5% NaI (Fig. 2). Ductular ectasia, vascularity, and retention of PAS-positive secretions were greater with 4% than with 0.5% NaI (Fig. 3). Glandular unit structures were preserved (Fig. 2).

Submaxillary glands of animals on 0.5% NaI and SG exhibited a ductal inflammatory response similar to those of animals given 0.5% NaI alone. With addition of SG, however, cellularity was reduced and glands contained transition zones between distal duct segments participating in the inflammatory and metaplastic response and proximal, uninvolved ones (Fig. 4).

Glands of animals given 4% NaI and SG were similar to those of animals receiving 4% NaI alone except for a focal, acute-type inflammatory response about ducts in addition to the chronic-appearing changes seen with 4% NaI alone. Other glandular structures were intact.

Sublingual glands of iodide-treated animals were unaltered. Pancreatic ductal, acinar, and islet structures of iodide-treated and control animals appeared identical.

*Discussion.* Four per cent NaI diet produces in rat submaxillary glands in 28 days a more chronic, proliferative, ductular and periductular inflammatory response, accompanied by greater vascularity, than 0.5% NaI diet.

Although sulfaguanidine and iodide are known to act synergistically on thyroid(7), addition of 2% sulfaguanidine (SG) to these high-iodide diets appears to slow the evolution of the inflammatory response in submaxillary glands. Animals receiving 4% NaI and SG reveal the combined acute and chronic glandular inflammatory response described, while those receiving 4% NaI alone show only the more chronic picture. With 0.5% NaI, animals also receiving SG show a less intense periductal inflammation and a more limited ductal epithelial proliferation, with frequent intact duct-metaplastic duct junctions.

Notwithstanding the distal inflammatory change already described, the glandular unit (acini, granular tubules and intralobular striated ducts) was intact in all groups. This suggests several possible mechanisms of action of massive doses of iodide: 1. a distally progressive concentration gradient of iodide may be produced in saliva, 2. the distal duct-structures may be more sensitive than proximal glandular areas to iodides circulating or in the saliva, 3. the effect may be mediated through some other organ, 4. the inflammatory response may be to some infectious agent activated by high iodide levels, 5. massive iodide doses in rats may produce distal salivary duct iodide concentrations obtained in other species with smaller doses. This study does not identify which, if any, of these processes is operative.

*Summary.* Submaxillary gland sialadenitis has been produced in rats on diets containing 0.5% and 4% NaI. This inflammatory and metaplastic process selectively involves distal ductular structures and is modified by concomitant administration of 2% sulfaguanidine.

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## Inhibition of T'ang Trachoma Agent by 5'-Fluorodeoxycytidine.* (28671)

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The incorporation of halogenated pyrimidines into bacterial cells was described by Dunn and Smith(1). Heidelberger *et al.*(2) reported on the anti-tumor activity of the fluorinated pyrimidines. The inhibitory effect of these drugs was studied extensively on human cell lines(3) and on neoplastic diseases in animals(4) and men(5).

Fluorinated pyrimidines interfere with DNA synthesis by inhibition of thymidylate synthetase in tumor cell systems(6) or creation of thymine deficiency in bacterial cells (7). Production of viral DNA was stopped by addition of the drugs to infected cultures as observed by plaque inhibition(8), by interference with virus propagation(9), and by alteration in function of virus infected cells (10). Addition of the fluorinated pyrimidines to cultures at intervals after virus infection offers a method by which the time course of viral DNA synthesis can be followed. Tanami *et al.*(11) studied the effect of FU and FUDR on the agent of psittacosis at various stages of the growth cycle and reported inhibition in DNA synthesis which could be reversed by uracil and thymidine. Green(12) described the time correlation be-

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