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SALIVARY GLANDULAR CHANGES IN AVITAMINOSIS "A" IN RATS

by

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UNEDITED ROUGH DRAFT TRANSLATION

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ABSTRACT: In summing up what has been expounded, one should conclude that in avitaminosis-A in the salivary glands of rats ~~there are developed~~ changes of different character. There is noted a lagging in the growth and differentiation ~~and also~~ atrophy of the glands, which are most pronounced in the submaxillary gland. ~~There occur~~ degenerative-necrotic changes in the epithelium of the ducts and to a lesser degree of the acini, scaling of the epithelium cells into the lumen of the ducts. In some cases, the alteration of the walls of the ducts leads to a flow-out of the secretion into the stroma. ~~Infrequently one observes~~ inflammation, apparently connected with the accompaniment of infection. ~~Often one notes~~ proliferation and metaplasia of the epithelium of the ducts into a multilayer plane cornifying epithelium. In one case ~~there were formed~~ stones in the lumen of the ducts of the parotid gland, along with stones in the bladder with the presence in the parotid gland of metaplasia of the epithelium ~~of inflammation~~ and change in the composition of the secretion. The formation of stones, apparently, depended on the combination of a number of causes and conditions, both of a general and local character. No description in the literature of experimental production of stones has been found by us, i.e., in avitaminosis-A, although the theoretical premises of this phenomenon have been discussed by many authors. English Translation: 11 pages

U. S. BOARD ON GEOGRAPHIC NAMES TRANSLITERATION SYSTEM

Block	Italic	Transliteration
А а	*А а*	A, a
Б б	*Б б*	B, b
В в	*В в*	V, v
Г г	*Г г*	G, g
Д д	*Д д*	D, d
Е е	*Е е*	Ye, ye; E, e*
Ж ж	*Ж ж*	Zh, zh
З з	*З з*	Z, z
И и	*И и*	I, i
Й й	*Й й*	Y, y
К к	*К к*	K, k
Л л	*Л л*	L, l
М м	*М м*	M, m
Н н	*Н н*	N, n
О о	*О о*	O, o
П п	*П п*	P, p
Р р	*Р р*	R, r
С с	*С с*	S, s
Т т	*Т т*	T, t
У у	*У у*	U, u
Ф ф	*Ф ф*	F, f
Х х	*Х х*	Kh, kh
Ц ц	*Ц ц*	Ts, ts
Ч ч	*Ч ч*	Ch, ch
Ш ш	*Ш ш*	Sh, sh
Щ щ	*Щ щ*	Shch, shch
Ъ ъ	*Ъ ъ*	"
Ы ы	*Ы ы*	Y, y
Ь ь	*Ь ь*	'
Э э	*Э э*	E, e
Ю ю	*Ю ю*	Yu, yu
Я я	*Я я*	Ya, ya

* ye initially, after vowels, and after ъ, ь; e elsewhere. When written as ё in Russian, transliterate as yё or ё. The use of diacritical marks is preferred, but such marks may be omitted when expediency dictates.

SALIVARY GLANDULAR CHANGES IN AVITAMINOSIS "A" IN RATS

I. Khudoyarov and A. G. Bobkov

Chair of surgical stomatology (Dir. Prof. A. A. K'yandskiy) and Chair of pathological anatomy (Dir. Prof. M. A. Zakhar'yevskaya) I. P. Pavlov Leningrad Medicinal Institute.

The morphological changes in avitaminosis A in the organs of animals and man are described by many authors (Wolbach, Howe, Ye. Ya. Gertsenberg with co-authors V. G. Garshin, 1944 and 1946; D. I. Golovin, 1953 and 1956; and Ye. A. Popova). They show that the specific process in avitaminosis A is the so-called keratinization (horn formation) of the epithelium, and also the degeneration of the epithelial cells. V. G. Garshin deals with the proliferation and metaplasia of the epithelium in avitaminosis A as regenerative, arising in connection with the destruction of the differentiated cells. Judkin and Lambert connect the metaplasia with inflammation. Other authors (Wolbach, Howe, D. I. Golovin) consider that the first metaplastic changes occur in the absence of some expressed inflammation.

Many investigators (A. M. Gasparyan and N. M. Ovchinnikov and N. M. Lebedeva) observed in avitaminosis A in rats the formation of stones in the kidneys and the bladder. M. I. Ilinich established that along with this there occurs a breakdown of the calcium exchange

and a sharp increase in the elimination of calcium through the kidneys and the intestines. A. V. Klementov (1957, 1960) and S. N. Ugulava point out that along with the other factors a substantial role in the etiology of sialolithic illness can be played also by avitaminosis A.

The formation of stones in animals deprived of vitamin A is explained in various ways. McCarrison (cit. K. M. Leutskiy) considers vitamin A as "fortifying" the epithelium. With an insufficiency of it the existing epithelial cells in the kidneys and urine channels can be the center around which there stratifies the salts. In the opinion of K. M. Leutskiy the basic cause of the formation of stones lies in the change of the biochemical process of the tissue itself in the breakdown in the first place of the calcium-magnesium-phosphorus exchange. However, any information in the literature about experimental production of sialolithic stones in laboratory animals has not been met with by us. One should note that the authors who point to changes in the salivary glands in avitaminosis A do not give it a detailed description.

Material and Procedure. Experiments were set up for 45 white rats (35 males and 10 females) of the age around 2 months and weight of 75—100 g. Out of this number, 14 rats died; the rest were killed by decapitation. The avitaminosis developed in 33 animals. Histologically there were investigated 25 rats with external indications of avitaminosis and 6 up to the approach of the latter to the early periods of the experiments. The duration of the experiments was from 13 days up to 7 1/2 months. The animals were kept on an avitaminosis-A diet taken by the Leningrad Vitamin Institute and the vitamin laboratory VIP (All-Union Scientific-Research Institute of Plant Growing) (D. S. Sarkisov and P. I. Remezov). This diet was used in their work also by V. I. Pigarevskiy, L. I. Moskvina, D. I. Golovin, T'ang Su-en, and Ye. A. Popova.

A mixture of the products was worked into the form of a dough. From it little cakes were baked which were given to the rats without limit. All the rats received fresh water every day. Twenty rats (15 males and 5 females) served as the control and received regular food.

All the animals were dissected with careful examination of the urogenital system and the salivary apparatus. For the histological investigation, there were taken submaxillary, parotid, and sublingual glands. These were fixed in 10-percent neutral formaldehyde, over them was poured paraffin, and they were stained in accordance with the van Gieson method with haematoxylin-eosin and "mucicarmine." The "ShIK" reaction was performed, as well as that of "Koss." The average diameter of the acini and ducts of the glands was calculated on the basis of measurements with the aid of an ocular micrometer.

The rats have four pairs of large salivary glands — one pair is the submaxillary, one pair the parotid, and two pairs the sublingual (large and small). The parotid gland is the serous one, and the large and small sublingual ones are the mucous ones. The submaxillary gland is considered serous by some authors; others say it is sero-mucous; a third class consider it to be mucous, and there is a fourth group which used the term "special serous" (Jacoby, Leeson).

In order to take into account the age changes, we studied the glands of the control animals of the ages from 2 to 7 1/2 months. These changes are basically reduced to increase in the average diameter of the acini and ducts and to the intensifying of the secretion activity. In the submaxillary gland of the two-month-old rats, the epithelium of the granular (curved) tubes and the striated sections of the ducts does not have substantial differences. The characteristic granularity of the cells in the first and the basal striated character

of the latter do not appear. The organotypical differentiation of the epithelium of the cited is observed in rats of the age of 3 months.

Beginning with the 55th day of the experiment, in the case of some rats there were noted the first signs of the avitaminosis-A. Distinct avitaminosis in the case of most of the animals showed up on the 70th to the 80th day; for part of the rats it was the 80th to the 100th day, and in some cases it was the 160th to the 180th day. The outer signs of the avitaminosis-A were a hunched pose, ruffled scanty fur, exhaustion, adhesion, suppuration of the eyelids, discharge of a glasslike body, or covering of the eye with a scum.

In all the cases with avitaminosis A there was noted a lessening of the dimensions and weight of the submaxillary, parotid, and large sublingual glands of the rats, up to 40—60%, as compared with the control animals. In the case of 8 out of 33 of the rats with visible signs of avitaminosis A on dissection there were found in the bladder stones of a yellow or grayish color, numbering from 2 to 7, and of the size of from half of a pinhead to a big grain of millet.

In the histological investigation of the salivary glands as an early sign of the avitaminosis A one should count the lagging in growth, which shows up strongly in the submaxillary gland. The organotypical differentiation of the epithelium of the granular tubes of the latter actually does not occur. The nuclei preserve the central position. Granules of secretion are absent. Only in the case of one rat in which the avitaminosis showed up weakly, on the 55th day of the experiment a part of the cells of the granular tubes contained in the cytoplasm fine granules and the nucleus was located in the basal part. But, in the other cells, the granules were absent. In the acinous cells noticeable changes in the secretion ordinarily could not be found.

Up to 2 1/2 months, when there appeared distinctly signs of avitaminosis, one noted some atrophy of the acinous cells and of the epithelium of the ducts which stood out most in the epithelium of the granular tubes and the striated sections of the ducts of the submaxillary salivary gland.

At the same time, there were observed degenerative-necrotic changes in the epithelium. They were most distinctly expressed in the interlobule ducts of the submaxillary gland. They rarely are met with in the acinous submaxillary gland and only in two cases were noted in the ducts and acini of the parotid gland. In this situation ordinarily in the surface series of cells of the epithelium of the interlobule ducts there are visible cells or their groups with a dark pyknotic nucleus. The cytoplasm of these cells is stained darker. There is noted a scaling off of the cells into the gap. More rarely the nucleus and the cytoplasm undergo lysis. In this situation sometimes there are formed small intra-epithelium vacuoles.

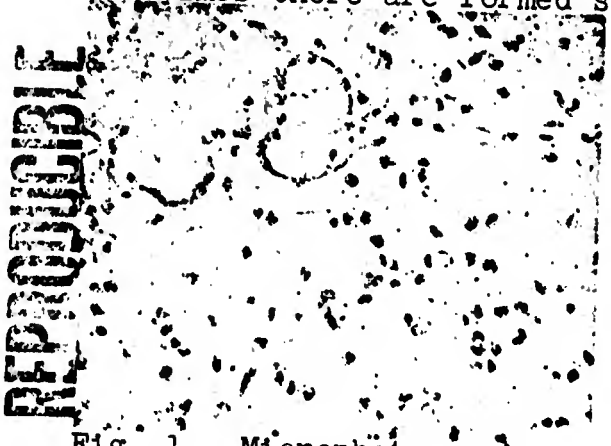

Fig. 1. Microphotograph. Submaxillary gland. Stroma with outflow in it of mucous secretion. Resolution of mucous by macrophages.

Staining by mucicarmine and haematoxylin. Magnification 400X.

In most of the cases the necrosis takes up only a small part of the epithelium cells without breaking down the continuity of the epithelial layer. But in the case of some mice, there were observed distributed necroses of the epithelium of the ducts. There is observed a swelling and fibrination of the enclosing sheath itself, and not seldom at places a breakdown of the wall of the duct with the issue of secretion from the lumen into the stroma. The layers of the stroma impregnated with mucous secretion rarely show thickened places; in it there were

visible numerous macrophages resolving the flowed-out secretion (Fig. 1). The outflow of the secretion into the stroma of the gland was noted in five cases; in one case in the sublingual gland, in two cases in the submaxillary, and in two cases in the parotid.

In the case of 3 rats there was discovered inflammation of the submaxillary gland and in the case of 1, the parotid. With one rat it had an intense character; the lumen of the ducts of the submaxillary gland was filled with hyoid exudate. The layers of the interlobule connecting tissue were edematous infiltrated with leukocytes. In the case of 2 animals, the inflammation was less intense; in the exudate there predominated lymphocytes and histiocytes with admixtures of leukocytes. Inflammatory edema was not noted. With one rat inflammatory infiltration was found in the parotid gland in connection with the outflow of secretion. In this situation, besides the resolution of the secretion by macrophages, there were noted focal accumulations of leukocytes and lymphocytes in the stroma and in the lumen of the ducts.

The proliferation and metaplasia of the epithelium into the multilayer plane was noted for the first time after 2 1/2 months from the beginning of the experiment in large interlobule ducts of the submaxillary and sublingual glands.

The epithelium of the ducts as a result of the dedifferentiation and proliferation becomes two-layer and three-layer and consists of comparatively large cells with light nuclei. Sometimes in them one meets with mitoses.

With the appearance of indications of vertical anisomorphism, the epithelium takes on the structure of a single-layer plane. In this situation in the basal layer there are located smaller cells with dark nuclei. Above, they have larger dimensions and lighter nucleus. In the surface layers, the cells are compressed; the nuclei

are subjected to pyknosis; the cells are turned into nucleus horny shells (Fig. 2). The latter form a layer on the free surface of the epithelial stratum and scale off into the lume of the ducts.

Fig. 2. Microphotography. Large duct of the submaxillary gland. The proliferation of the epithelium with the formation of a two-layer system. Focal metaplasia of the epithelium into a multilayer plane with weak cornification.

Staining per van Giesen. Magnification 400X.

The formation of two-, three-, and multi-layer flat epithelium has a focal character and more often appears in ducts of larger section. In this situation one does not note changes in the underlying connecting tissue with the aid of the ordinary histological procedures. Inflammation is absent.

Out of 25 rats with outer signs of avitaminosis during periods of experimentation of from 2 1/2 to 7 1/2 months, areas of multilayer plane epithelium in the ducts of the sublingual gland were found in 12 instances: in the submaxillary in 9 cases, and in the parotid in 3 cases. Two-, three-layer epithelium without metaplasia into the multi-layer plane was found in the ducts of the sublingual gland in two cases, in the submaxillary in six, and in the parotid in one.

Thus the proliferation and metaplasia of the epithelium of the ducts most often are met with in the submaxillary and sublingual glands and less often in the parotid. In most of the cases, they are observed in the absence of inflammation and without expressed degeneration of the epithelium of the ducts.

These observations agree with the results of the work of Wolbach, Howe, and D. I. Golovin, in the opinion of whom the formation of a multi-layer plane epithelium in the case of avitaminosis-A is not connected with inflammation or regeneration.

With the macroscopic investigation of the salivary glands and ducts, stones were not discovered once. Histologically, however, in the case of one of the animals experimented on with a pronounced form of avitaminosis A put to death on the 77th day of the experiment, there were found some small stones in interlobule ducts of the parotid gland. They had the appearance of homogeneous of concentric stratified found solid masses intensely stained by haematoxylin-eosin, lying in the lumen of the ducts (Fig. 3). The interlobule ducts are laid out at places by a two-row, and at places by a multilayer flat epithelium with cornification. Some stones were distributed among the exfoliating cells and horny shells. The bands of the stroma at places were impregnated by secretion which gave a weak reaction to the mucus with mucicarmine. In the stroma there were discovered focal inflammatory infiltrates from the leukocytes, lymphocytes, and macrophages. In the case of this rat, however, there were found many stones in the bladder.

Fig. 3. Microphotography. Small stones and scaled-off epithelium cells in the duct of the parotid gland. Staining by haemotoxylin-eosin. Magnification 400X.

The observation done shows in principle the possibility of the formation of stones in the salivary glands with avitaminosis-A; and, apparently, it turns out to be the first communication about their experimental production under the conditions of avitaminosis-A. Apparently the formation of stones in the given case depended on several causes. It is known that with insufficient vitamin A in the organism there is a breakdown of the overall calcium exchange (B. A. Shmukler, M. I. Ilinich, and K. M. Leutskiy). In our case by this there can be explained the

formation of stones not only in the ducts of the parotid salivary gland, but also in the bladder.

In the parotid gland the stones were formed with the presence in the lumen of the ducts of scaly epithelium cells and cornifying shells, which can serve as the basis for the deposit of salts. There is noted a change in the character of the secretion. Ordinarily the secretion of the parotid gland of a rat is not stained by mucicarmine, but in the given case its staining was observed. The change in the secretion could be connected with inflammation.

Conclusions

In summing up what has been expounded, one should conclude that in avitaminosis-A in the salivary glands of rats there are developed changes of different character. There is noted a lagging in the growth and differentiation and also atrophy of the glands, which are most pronounced in the submaxillary gland. There occur degenerative-necrotic changes in the epithelium of the ducts and to a lesser degree of the acini, scaling of the epithelial cells into the lumen of the ducts. In some cases, the alteration of the walls of the ducts leads to a flow-out of the secretion into the stroma. Infrequently one observes inflammation, apparently connected with the accompaniment of infection. Often one notes proliferation and metaplasia of the epithelium of the ducts into a multilayer plane cornifying epithelium. In one case there were formed stones in the lumen of the ducts of the parotid gland, along with stones in the bladder with the presence in the parotid gland of metaplasia of the epithelium of inflammation and change in the composition of the secretion. The formation of stones, apparently, depended on the combination of a number of causes and conditions, both of a general and local character. No description in the literature of experimental production of stones has been found by us, i. e., in

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