THE EFFECT OF AVITAMINOSIS-A ON THE PROSTATE

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PLATE 1

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Numerous experimental investigations on the effect of deficiency of vitamin A have been reported, but in only one, that of Wolbach and Howe (1), is there adequate gross and microscopic study of the sexual accessory glands in the male. In a study of the prostate in man, five cases with metaplasia and inflammation have been observed, which resembled the effects of avitaminosis A. It was therefore determined to investigate a series of rats on a deficient diet and compare the appearance with that in man.

Method

Eight prepuberal and eight postpuberal white rats from the same colony were placed on the following diet which is complete in all respects except for a deficiency of vitamin A.[1]

	gm.
Inactivated casein	20
Corn starch	50
Irradiated cottonseed oil	15
Yeast	10
Decitrated lemon juice	5
Salt mixture	5
Distilled water	45

An additional four prepuberal and two postpuberal animals were fed the same diet plus 2 drops of caritol S.M.A. every 3 days. All animals were given 0.4 cc. of wheat germ oil by mouth or hypodermically every 10 days as a source of vitamin E. The diet is similar to that used by Goldblatt and Benischek (2). The casein was

[1] We wish to thank Dr. Harry Goldblatt of the Institute of Pathology, Western Reserve University, Cleveland, for advice in the selection of this diet.

purchased in the open market under the designation technical casein. The inactivation was done with heat according to Goldblatt and Moritz (3). The cottonseed oil was the technical grade and the irradiation was carried out according to Goldblatt and Moritz (4). The salt mixture was No. 185 of McCollum (5). The lemon juice was decitrated by standing over marble for 24 hours. The corn starch was that sold under the trade name Byron brand and the yeast was labeled tested brewer's yeast–Harris, medicinal. The animals were kept in galvanized iron cages in a room with light and ventilation but no direct sunlight. The tissues at autopsy were fixed in Bouin's fluid and paraffin sections of the sexual and accessory sexual organs were stained with hematoxylin (Harris') and eosin. The diet mixture was made weekly and stored in the ice box. There was an excess of food in the cages at all times. The prepuberal animals were 30 days of age and the postpuberal 100 days of age at the start of the experiment.

RESULTS

Animals were killed or died after 85 (1), 86 (3), 99 (2), and 115 (10) days on the diet. The control animals were killed after 115 days and showed no pathological changes. All experimental animals at death showed clinical xerophthalmia.

The general pathological changes in the experimental animals are entirely similar to those described by Goldblatt and Benischek (2) and Wolbach and Howe (1) and this report will be confined to the reproductive system. Sections have been cut from the seminal vesicle, vas deferens, epididymis, and testis. Step sections (every twentieth section) of the entire prostate were prepared. As a control, sections of the lungs, bronchi, submaxillary gland, tongue, and kidneys were cut to establish the usual changes of vitamin A deficiency.

The testes from all animals were small and the tunical covering wrinkled and relatively thickened. On section the tubules were less abundant, smaller than usual in size, and did not separate as easily as the normal. The vasa deferentia and seminal vesicles showed no significant gross alteration. The prostates were slightly smaller than normal and more compact. On section the tissue was finely granular. In local areas there were foci up to 2 mm. in diameter with increased density and loss of granularity. No cysts were observed.

The seminiferous tubules microscopically are small and lined by a single, rather regular layer of Sertoli cells admixed with a few primary spermatogonia. The latter are for the most part resting but a few show mitotic figures, some of which are atypical. The lumina are

filled with a granular or fibrillar acidophilic non-nucleated debris. The limiting membrane of each tubule is not thickened. The fibrous interstitial tissue and blood vessels are not increased in number nor amount. The interstitial cells of Leydig are apparently increased, more so in the prepuberal than in the postpuberal rats. They do not contain pigment globules. In the postpuberal rats there are multinucleated cytoplasmic masses in the tubular lumina, while they are absent in the prepuberal. These cells are similar to those described in the human atrophic testes by Seecof (6). In contrast to some other types of testicular atrophy such as in cryptorchidism and in senility in man there is no thickening of the limiting collagenous membrane and the remaining cells arrange themselves in a definite single layer. The two groups differ in that the prepuberal rats show more apparent increase of interstitial cells of Leydig and the postpuberal rats show giant cells within the tubules. This testicular atrophy in rats with a sufficient supply of vitamin E has also been reported by Evans (7).

Even a cursory examination of the pelvic accessory reproductive glands shows that the changes are more striking and extensive in the prepuberal animals. In one there is atrophy of the epithelium but no cellular infiltration and no metaplasia. In the other seven the changes are similar. The prostatic acini in the middle and anterior regions are dilated and filled with a protein-poor fluid free of cells. The epithelium is low cuboidal and the nuclei are abundant, a picture similar to that of castration (Fig. 1). The large number of nuclei indicates that the cells are not low because of flattening from dilation of the acini. There is no evidence of secretory activity and the typical pale area of the cytoplasm of the normal secreting cell is uniformly absent. There is a slight to moderate increase in the thickness of the stromal collar about each acinus and under low power the lobular markings are more distinct than in the normal gland, indicative of atrophy. In focal areas, most commonly in the middle region, rarely in the anterior region, and never in the posterior region, the lumina are filled with a granular acidophilic debris and numerous polymorphonuclear leucocytes with some cellular infiltration into the surrounding stroma. The epithelium of these glands is of two types: first, a tall columnar nonsecretory cell with pseudostratification of long, slender nuclei (Fig. 2), and second, true squamous epithelium with or without

keratinization (Fig. 3). The process may involve only one alveolus of a branching gland as shown in Fig. 3.

The vasa deferentia show atrophy of both the muscular layer and the epithelium but there is no metaplasia. The intraprostatic portion also is free from metaplasia. The glands associated with this latter portion are free from pathological change. The coagulating gland of three prepuberal animals shows extensive cellular infiltration and metaplasia to the squamous type (Fig. 4).

The vesicular epithelium is atrophic and devoid of the characteristic secretion granules (Fig. 5), but the lumen is filled with a dense homogenous acidophilic mass, similar to that in the normal vesicle. The duct which connects each vesicle with the urethra shows squamous metaplasia with extensive keratinization in the three positive animals. The epididymal epithelium in three prepuberal animals is atrophic and in one there is degeneration of the cytoplasm and extensive karyorrhexis of the epithelial tubules.

The postpuberal animals show similar changes but of much less severe grade. In the prostate, areas of normal prostatic epithelium with clear areas may be found, while in others it is atrophic. Foci of exudative inflammation with metaplasia are present but small in size and not advanced. In one, the ducts of the glands associated with the ductus deferens show metaplasia. In none is there any change in the coagulating gland. In all there is metaplasia of the vesicular ducts and atrophy of the vesicular epithelium.

These anatomical changes in the accessory sexual glands in terms of physiology mean that the secretion of the male sex hormone is reduced by the feeding of a vitamin A deficient diet, markedly if the feeding is initiated before puberty, slightly, if initiated after puberty. The metaplastic and inflammatory changes in the prostate, vesicular ducts, and deferential glands are entirely similar to those recorded in other organs. The atrophy of the testis with complete suppression of spermatogenesis cannot be due to vitamin E deficiency since this was supplied in adequate amount by means of wheat germ oil.

The Prostate in Vitamin A Deficiency in Man

In a detailed morphological study of 678 prostates by the step section method, five cases of focal metaplasia with an acute exudative

inflammation were encountered. In all, there was an associated disease which produced stenosis of the esophagus; in two a carcinoma of the esophagus, in one a carcinoma of the base of the tongue, in one a bronchial carcinoma, and in one an aneurysm of the aorta. Emaciation was extreme in all cases, but no greater than in an additional four cases of esophageal carcinoma and twenty-one cases of gastric carcinoma with pyloric stenosis which did not show the prostatic lesion.

The histological appearance in the prostate is entirely similar (Fig. 6) to that found in the rats. An entire acinus or a part is lined by stratified flattened cells which at times show keratinization. The lumen is filled with a granular acidophilic material with desquamated cells, lymphocytes and polymorphonuclear leucocytes. The stroma about the acinus is edematous and infiltrated with lymphocytes and an occasional polymorphonuclear leucocyte.

Although these patients probably suffered from a complete vitamin deficiency in addition to protein, carbohydrate, fat, mineral, and water deprivation, it seems probable that vitamin A was the factor in the production of the prostatic lesion. In one of eight cases in male Chinese reported by Sweet and K'ang (8), metaplasia in the prostate was found at autopsy.

This type of metaplasia should not be confused with the metaplasia and atypical hyperplasia which is not infrequently observed in the ducts in senile prostates and commonly in small foci of benign enlargement. This latter type has been discussed by a number of investigators, notably Kasman and Gold (9). However Schmidt (10) in 1907 reported squamous metaplasia and abscess formation in a 5 months old child with keratomalacia and in a 53 year old man with an ulcerating carcinoma of the pylorus, in which it would appear that vitamin A was a factor.

SUMMARY

1. Vitamin A deficiency alone in the white rat is associated with atrophy of the testis and accessory sexual glands. This would appear to be indicative of some disturbance in the hypophyseal-gonadal-prostatic hormonal relationships. All of the known vitamins necessary for the rat, except vitamin A, were present in the diet fed the animals studied.

2. Vitamin A deficiency in the rat is associated with foci of inflammation and epithelial metaplasia in the prostatic acini and vesicular ducts entirely similar to that reported in other organs.

3. Focal metaplasia and inflammation is occasionally encountered in the prostate of patients with extreme inanition associated with stenosis of the esophagus. It seems probable that this lesion is due to vitamin A deficiency.

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EXPLANATION OF PLATE 1

All tissues were fixed in Bouin's solution and stained with Harris' hematoxylin and eosin.

FIG. 1. Cuboidal epithelial cells in the acini of the prostate from a vitamin A deficient rat. × 206.

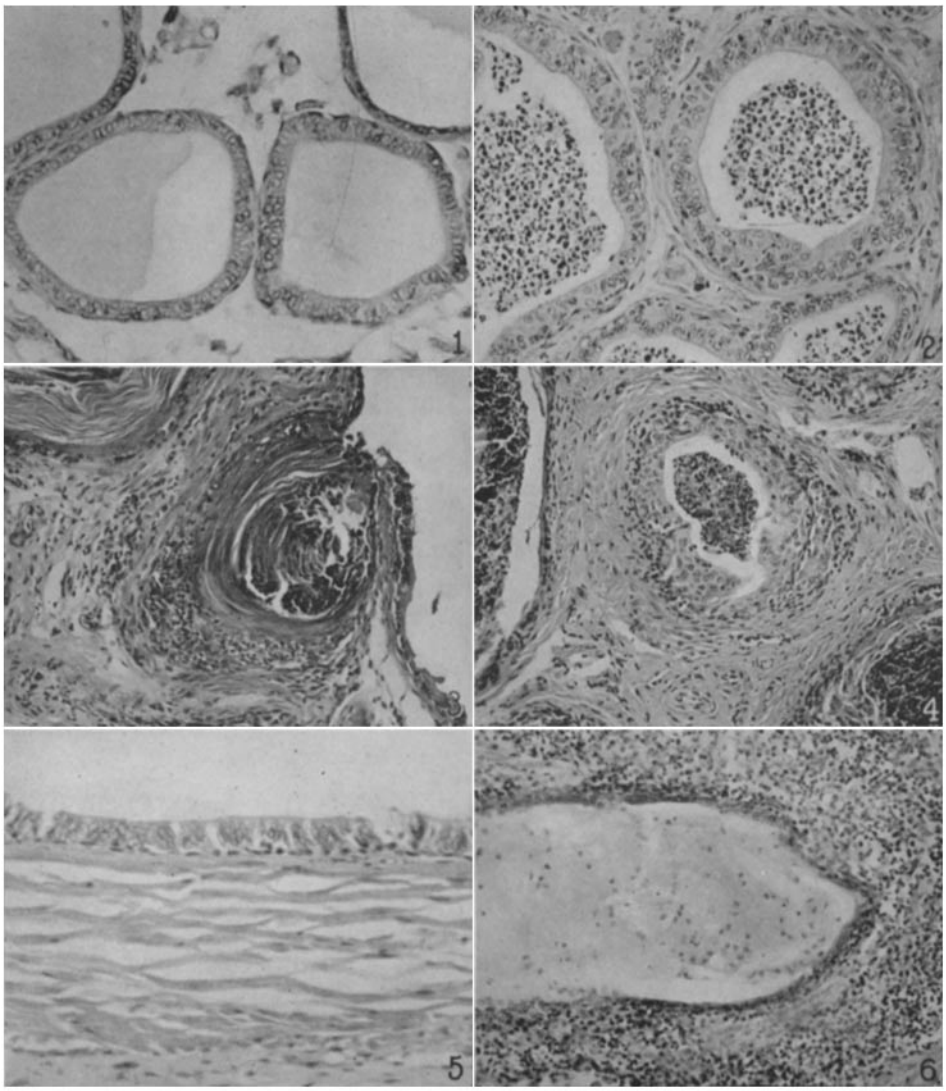
FIG. 2. Irregular tall epithelium with debris in the lumen in vitamin A deficiency. × 158.

FIG. 3. Squamous metaplasia and keratinization of one branch of an acinus in vitamin A deficiency. × 162.

FIG. 4. Squamous metaplasia and cellular infiltration of coagulating gland in vitamin A deficiency. × 128.

FIG. 5. Low nonsecretory epithelium of the vesicle in vitamin A deficiency. × 195.

FIG. 6. Squamous metaplasia and inflammation in an acinus from a case of stenosis of the esophagus from an aneurysm, possibly due to vitamin A deficiency. × 131.



(Moore and Mark: Effect of avitaminosis-A on prostate)