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Influence of Gonads on Exophthalmos in Rabbits.

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The chronic progressive exophthalmos of the type seen in Graves' disease, in its uncomplicated form, is dependent upon a highly complex, though probably specific, disturbance in the balance of internal secretions which causes central stimulation of the sympathetic innervation of the muscles of Müller. It has been shown that thyroid insufficiency (either because of goiter or thyroidectomy) strikingly increases the incidence and shortens the time of production of exophthalmos in rabbits and guinea pigs.¹⁻⁵ The increase of post-operative exophthalmos in Graves' disease during the last decade is probably of the same nature. Feeding desiccated thyroid prevents it and often cures it in rabbits and guinea pigs. Thyroid insufficiency, relative or absolute, therefore, is a necessary condition in order that this form of exophthalmos may develop. Yet it does not occur in the severe thyroid insufficiencies of endemic cretinism in man, nor in spontaneous Gull's disease (*i. e.*, not preceded by Graves' disease). It is obvious that other factors than thyroid insufficiency are involved. Sex and age differences have been mentioned in earlier papers and in this report we shall present data relative to these factors.

In rabbits under 3 months and over 7 months old we have rarely been able to obtain frank exophthalmos, although maintained on a diet of alfalfa hay and oats and given daily intramuscular injections of methyl cyanide. Exophthalmos develops most frequently in puberal rabbits (4-5 months). In a general way this age factor is also seen in the exophthalmos of Graves' disease. Under our experimental conditions during the past 4 years rabbits between the ages of 3 and 7 months have shown the following incidence of exophthalmos:

1. In rabbits with intact thyroids, 63 males out of 131, or 48 %, developed frank exophthalmos; while 37 females out of 125, or

¹ Marine, D., Baumann, E. J., Spence, A. W., and Cipra, A., PROC. SOC. EXP. BIOL. AND MED., 1932, **29**, 822.

² Marine, D., Rosen, S. H., and Cipra, A., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 649.

³ Marine, D., and Rosen, S. H., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 901.

⁴ Marine, D., and Rosen, S. H., *Am. J. Med. Sci.*, 1934, **188**, 565.

⁵ Smelser, G. K., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 128.

30%, developed exophthalmos. Thus under our conditions the incidence was 18% greater in males.

2. In thyroidectomized rabbits, 47 males out of 82, or 57%, developed exophthalmos; while 19 females out of 41, or 46%, developed exophthalmos.

Thyroidectomy clearly steps up the incidence of exophthalmos but does not greatly, if at all, influence the sex difference. A similar sex difference appears in postthyroidectomy exophthalmos in Graves' disease. Thus, of 52 cases reported in the recent literature, 31, or 60%, were males and 21, or 40%, were females (data of the percentage incidence of exophthalmos in non-operated male and female cases of Graves' disease are not available.) In these human cases the average age was 53 years for males and 42 for females.

Therefore, other factors beside thyroid insufficiency and age are involved in the production of exophthalmos. We have already pointed out that those rabbits which develop the best exophthalmos also were sexually more active or frankly precocious. In the light of our present knowledge this would be explained by assuming that the intense stimulation of the anterior pituitary which follows thyroidectomy brought about the stimulation of the gonads. In view of the sex and age differences and the increased sexual development following thyroidectomy in puberal rabbits, we have studied the effect of gonadectomy in rabbits on the development of exophthalmos. Thirty-eight normal young adult male and 23 female rabbits were gonadectomized. All survived more than 2 months. No frank case of exophthalmos developed, where in a similar group without gonadectomy 50% of the males and 30% of the females should have developed exophthalmos. Two males and 2 females developed slight exophthalmos (+?) during the second and third weeks after gonadectomy, but these receded to —? at the end of the fifth week. In 3 rabbits with frank exophthalmos at the time of gonadectomy, the exophthalmos receded after gonadectomy. These experiments indicate that functionally active gonads in the rabbit greatly increase the incidence of exophthalmos and that failure of development and decline in gonadal activity may partially explain the absence of exophthalmos in cretinism and Gull's disease. What particular function of the gonads is involved is not known.

Oestrone (menformon, theelin) in doses of 100 rat units twice daily for 2 months has not influenced the existing exophthalmos in 2 male rabbits. Pituitrin-S (0.25 cc. twice daily for 12 days intramuscularly) was given to 6 rabbits without effect, and adrenalin (Parke, Davis 1-1000), beginning with 0.2 cc. and gradually

increasing to 2 cc. twice daily intramuscularly, was given to 22 rabbits over a period of 2 months without producing, or modifying existing, exophthalmos.

Summary. Male rabbits develop exophthalmos more frequently than females. This difference is independent of the thyroid gland. Exophthalmos develops most frequently in rabbits about the age of puberty (4-5 months). Gonadectomy greatly reduces the incidence even in thyroidectomized rabbits. Oestrone (menformon, theelin), pituitrin-S and adrenalin in the dosages and method of administration used neither produce, nor modify existing, exophthalmos.

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Prevention of Atherosclerosis in Rabbits. I. Administration of Potassium Thiocyanate.

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Many efforts have been made to counteract the atherosclerosis produced in rabbits by the feeding of cholesterol or cholesterol-containing foods with or without thyroidectomy.¹ These efforts have converged on a demonstration that iodides may to an extent replace the loss of thyroid in retarding the development of atheromata.²⁻⁴ Completely negative results were reported for bromides. Otherwise attempts to get effects with organic compounds, *e. g.*, chlorophyll and alcohol, have either been unsubstantiated when reported positive, or gave no conclusive results.

Good evidence exists as to the serious changes in permeability of arterial walls following both thyroidectomy and the feeding of cholesterol.⁵ It seemed reasonable, therefore, to follow out the investigations suggested by the use of ions. The Hofmeister series, although inaccurate in detail, unmistakably points to an ion which would be expected to be more effective than iodide, namely thiocyanate. At the same time it explains the ineffectiveness of the bromide ion. The relatively low toxicity of thiocyanates, coupled

¹ Anitschkow, N., in *Arteriosclerosis*, Macmillan, New York, 1938.

² Ungar, H., *Arch. Exp. Path.*, 1934, **175**, 536.

³ Turner, K. B., *J. Exp. Med.*, 1933, **58**, 115.

⁴ Turner, K. B., and Khayat, G. B., *J. Exp. Med.*, 1933, **58**, 127.

⁵ Duff, G. L., *Arch. Path.*, 1935, **20**, 81, 259.