

2. Case 14 is of exceptional interest in that the increase in serum-globulin consistently involved only the pseudoglobulin I fraction as determined by Howe's method (*Cf.* Gros¹¹). The fact that this serum formed an opaque gel within 5 minutes after treatment with formol is contrary to the view that the formation of an opaque gel is dependent solely upon hypereuglobulinemia. Our data would suggest that a positive formol-gel reaction is obtained in the presence of "abnormal" globulins irrespective of whether their solubility characteristics with respect to sodium sulfate correspond with those of euglobulin or pseudoglobulin.

3. We find the formol-gel reaction a convenient preliminary test for the detection of gross hyperglobulinemia in lymphogranuloma inguinale. Its reliability for this purpose in other conditions is being investigated further.

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Experimental Production of Exophthalmos Resembling that Found in Graves Disease.

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Experimental production of exophthalmos has been accomplished repeatedly by stimulating the sympathetic innervation of the eye. MacCallum and Cornell,¹ Code² produced, by electrical stimulation of the cervical sympathetic ganglion of dogs and cats, a contraction of the smooth muscle elements in the orbit which caused exophthalmos. Schockaert,³ Loeb,⁴ Friedgood,⁵ and Marine^{6, 7} have reported exophthalmos resulting from the injection of thyrotropic anterior pituitary extracts into ducks, normal and thyroidectomized guinea pigs, and by the injection of methylcyanide into normal and thyroidectomized rabbits. Loeb and Schockaert noted that the exophthalmos

¹¹ Gros, W., *Deutsches Arch. f. klin. Med.*, 1935, **177**, 461.

¹ MacCallum, W. G., and Cornell, W. B., *Med. News*, 1904, **85**, 732.

² Code, C. F., and Essex, H. E., *Am. J. Oph.*, 1935, **18**, 1123.

³ Schockaert, J. A., *Am. J. Anat.*, 1932, **49**, 379.

⁴ Loeb, L., and Friedman, H., *PROC. SOC. EXP. BIOL. AND MED.*, 1932, **29**, 648.

⁵ Friedgood, H. B., *Bull. Johns Hopkins Hosp.*, 1934, **54**, 48.

⁶ Marine, D., and Rosen, S. H., *PROC. SOC. EXP. BIOL. AND MED.*, 1933, **30**, 901.

⁷ Marine, D., and Rosen, S. H., *Am. J. Med. Sci.*, 1934, **188**, 565.

produced was functional, *i. e.*, did not persist during anesthesia or after death. Marine showed that the protrusion resulting from injection of either pituitary or cyanide was accomplished through a nervous mechanism, presumably upon the unstriated orbital muscle of Müller, and that it could be prevented by removing the cervical sympathetic ganglion.

In the following experiment exophthalmos has been produced which does not depend upon a nervous mechanism but is due to an increase in orbital structures. It is readily obtained by the injection of beef anterior lobe extracts in thyroidectomized, but not normal, guinea pigs of both sexes. Twenty-six guinea pigs were injected with a thyrotropic anterior pituitary extract for 3 to 9 weeks with a daily dose equivalent of 250-2000 mg. of acetone dried beef anterior lobe powder. Loss in body weight and intense stimulation of the thyroid, as indicated by high epithelium, almost complete loss of colloid, and gross enlargement of 6-7 times, occurred. Of these only 3 showed slight indications of exophthalmos. Besides these questionable cases the eyes remained normal or became slightly enophthalmic.

The thyroids and left cervical sympathetic ganglion were removed from 26 guinea pigs which then received daily the equivalent of 250 mg. dry anterior lobe powder of the same preparation as the earlier experiment. Definite and, in a number of instances, extreme exophthalmos developed in all but 3 animals. Exophthalmos was usually noted 12-20 days after the first injection, although in one exophthalmos was not definitely established until 53 days after the first injection; it then became extreme.

In guinea pigs removal of the cervical sympathetic ganglion produces an enophthalmos and ptosis in the affected eye, and as a result exophthalmos produced in such eyes is less marked than it is in eyes with normal innervation, however, the protrusion is clearly demonstrated by comparison with the sympathectomized eye of a control.

The eyes of exophthalmic animals remain quite open postmortem, whereas those of normal guinea pigs partially or completely close. In many cases the sympathectomized eye is more protuberant than in life, a wide scleral band showing completely around the cornea.

The fat and connective tissue of the orbit appeared oedematous. The weights of the various orbital structures recorded at autopsy show that the retrobulbar tissue was increased to an average of 40% by these injections over controls consisting of normal, uninjected thyroidectomized, and thyroidectomized guinea pigs injected with extracts of thymus and liver. The control extracts were prepared in the same manner as the anterior pituitary and injected in a

daily dose equivalent to 1,000 mg. dry tissue, instead of 250 mg., for 30-62 days. An analysis of the autopsy data shows that the increase in the retrobulbar tissue was due to an increase of 100% in the fatty connective tissue, 40% in the dorsal lacrimal gland, and 22% in the extraocular muscles. It is somewhat doubtful if the ventral lacrimal is involved in this increase.

The structure of the orbital tissues, particularly the fat, was strikingly modified by an infiltration of a stainable material between the fat cells and collagenous fibers of connective tissue, so that the amount of fat is apparently reduced. This infiltrate which stains with eosin and anilin blue contains granules and droplets, presumably lipoid, as well as many lymphocytes scattered throughout the tissue. The infiltrate may be found, though to a lesser extent, between the lobules of the dorsal lacrimal and between the muscle fibres. Associated with the infiltration, in the muscles, nests of lymphocytes occurred in some cases. Small amounts of a material possessing staining properties similar to those of the infiltrate occurring in the exophthalmic animals may be found in the orbital fat of normal and thyroidectomized animals.

Because the increase in orbital tissue was as great in the eye from which the sympathetic innervation had been removed as in the normal, and since the postmortem exophthalmos was as great or greater in such eyes, it is concluded that an exophthalmos has been produced which is not dependent on a functional sympathetic innervation or the contraction of a smooth muscle, thus differing from the exophthalmos obtained by other experimental procedures.

Oedematous infiltration of the retrobulbar tissues has been repeatedly demonstrated in, and presented as the cause of, exophthalmos associated with Graves Disease. Such exophthalmos has been found associated with all ranges of B.M.R. and particularly extreme cases of progressive exophthalmos occur following thyroidectomy for exophthalmic goiter. Human biopsy specimens of muscles, orbital connective tissue, and fat obtained at operation from 2 low B.M.R. exophthalmos cases showed an infiltration indistinguishable from that obtained experimentally.