the absence of the pituitary we could never induce maturation of the follicles or luteinization of the granulosa cells with A.P.L., but the luteinization of the theca cells is very conspicuous. This might suggest that the stimulation of granulosa elements is only possible in the presence of a pituitary factor which would obviously be lacking in the hypophysectomized animal and which, perhaps, cannot be supplied adequately by the immature pituitary during the first days of life.

If a thecal luteinization has been produced during the first days of life and the administration of A.P.L. is continued to the 26th day, the normal reaction of the ovary fails to develop. Whereas the control litter-mate receiving A.P.L. between the 21st and 26th day of life only shows maturation of follicles and corpus luteum formation, the ovary of the rat receiving the same amount of this hormone from the 6th until the 26th day shows nothing but thecal luteinization. Whether this phenomeon is due to an inhibition of follicular maturation by the corpus luteum hormone formed in the thecal cells is meanwhile open to discussion.

Following the formation of these thecal corpora lutea continuous oestrus has been observed both in hypophysectomized rats and in the animals of the present experimental series. As no signs of maturation could be detected in the granulosa, we have to assume that the luteinized thecal cells are responsible for the oestrus.

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Further Studies on the Exophthalmos in Rabbits Produced by Methyl Cyanide.*

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Chronic, progressive, bilateral exophthalmos has been produced in more than 150 prepubertal rabbits maintained on a diet of alfalfa hay and oats by the daily intramuscular injection of 0.05-0.1 cc. of methyl cyanide. [1, 2] Feeding fresh vegetables markedly inhibits its

* Aided by a grant from the Ella Sachs Plotz Foundation.

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[1] Marine, D., Spence, A. W., Cipra, A., PROC. SOC. EXP. BIOL. AND MED., 1932, **29**, 822.

[2] Marine, D., Baumann, E. J., *Trans. Assn. Am. Phys.*, 1932, **47**, 261.

development. Exophthalmos may appear as early as the 14th day and as late as the 60th day after beginning the cyanide injections. Males are much more susceptible and some breeds (Dutch) are more susceptible than others (Belgian). The degree of exophthalmos obtained has been highly variable in rabbits of the same age, sex and breed, but it is always proportional to the degree of thyroid hyperplasia (goiter) present.

We believe it is established that the initial cause of the exophthalmos is dependent primarily upon an increased tonicity and spastic contraction of the smooth muscles of the orbit and eyelids which are brought about by stimulation through the autonomic nervous system.

1. Dividing the cervical sympathetic trunk in 3 rabbits below the superior cervical ganglion definitely diminished the exophthalmos on the operated side when the animals were quiet, and particularly reduced the spasm of the lower eyelid. If the animal was disturbed, however, the exophthalmos became as marked as on the intact side.

2. Removal of the superior cervical ganglion permanently abolished the exophthalmos on that side in 6 animals.

3. Curetting the medulla of both suprarenals was without effect on existing exophthalmos in 3 animals, nor did it hasten or delay the onset of exophthalmos. Curetting the right suprarenal medulla and removing the left suprarenal gland in 18 rabbits was also without definite effect.

4. Thyroidectomy in 13 prepubertal rabbits hastened the onset of exophthalmos and increased it when performed after exophthalmos had developed. Thyroidectomy decreased the percentage of prepubertal rabbits resistant to the development of exophthalmos from 20-30% to 0.

Since exophthalmos develops in rabbits with intact thyroids only when they develop marked thyroid hyperplasia (goiter), one may conclude that protection against cyanide exophthalmos is in part dependent upon the presence of the iodine containg hormone of the thyroid. So far, we have not been able to abolish the exophthalmos in thyroidectomized rabbits by administering desiccated thyroid. (In several animals this drug has caused a temporary increase.) The administration of iodine to rabbits with intact thyroids, however, prevents its occurrence, as does the administration of fresh plant and fruit juice concentrates (ascorbic acid). The exophthalmos, therefore, depends in part upon thyroid insufficiency. Gley[3] noted

[3] Gley, E., *C. R. Soc. Biol.*, 1910, **68**, 858.

the spontaneous occurrence of exophthalmos in 2 thyroidectomized young rabbits. The exophthalmos of Graves' disease also appears to depend in part upon a relative thyroid insufficiency, since it may develop after and is frequently made worse by partial thyroidectomy and since the most beneficial treatment[4, 5, 6] has been with desiccated thyroid or thyroxin and iodine.

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Measurement of the Circulation Time with Saccharin

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Among the methods used for the measurement of the circulation time in man are those in which a foreign substance is injected into a vein and the time of its arrival in the capillaries of the tongue is signalled by a sensation of taste. Winternitz, Deutsch, and Bruell[1] have used the interval between the intravenous injection of sodium dehydrocholate and the appearance of a bitter taste as a measure of the circulation time. Both they and Tarr, Oppenheimer, and Sager (personal communication) have obtained excellent results in the clinical application of the method.

We have found that soluble saccharin (sodium benzosulphinid) is admirably adapted to the estimation of the circulation time between the antecubital veins and the capillaries of the tongue. Soluble saccharine possesses the following advantages: 1. It stimulates the taste buds in very high dilution. 2. It is very soluble, so that only a small volume of solution is needed. This is important because the injection can be performed rapidly and the saccharin is contained in a small blood volume, with resultant sharp definition of both the time of injection and of arrival in the tongue. 3. It is apparently entirely harmless in the quantities used. In over 100 individuals no unpleasant reactions were encountered. Paravenous infiltration causes no necrosis. In several instances the circulation time was measured twice, and once even 3 times within a few min-

[4] Zimmerman, L. M., *Am. J. Med. Sci.*, 1929, **178**, 92.
[5] Ruedemann, A. D., *J. Am. Med. Assn.*, 1931, **97**, 1700.
[6] Benedict, W. L., *Arch. Ophth.*, 1933, **9**, 1.
[1] Winternitz, Deutsch, and Bruell, *Med. Klin.*, 1931, **27**, 986.