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Effect of Sodium Bromide on Thyroid Gland of the Guinea Pig.*

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It has been shown that iodine has a stimulating effect on the thyroid gland.[1, 2, 3, 4, 5, 6] It intensifies compensatory hypertrophy of the partly extirpated gland and it increases markedly the mitotic proliferation of the normal gland; it also increases somewhat the size of the acinus cells, softens to a moderate degree the colloid, and increases very much the number of phagocytes which invade the colloid. Considering the chemical similarity of bromine and iodine and their relationship in the periodic system of elements, it was of interest to determine whether bromine has a similar stimulating effect upon the thyroid.

Our experiments were carried out in accordance with methods previously used in our laboratory. Guinea pigs were injected intraperitoneally with NaBr solutions of various concentrations on consecutive days during a certain period of time, and the number of mitoses were counted. The size and character of the acinus cells and of the acini, and the consistency of the colloid and the presence or absence of phagocytes were observed.

A preliminary experiment was carried out to determine the range of effective doses. Five 200 gm. guinea pigs were injected daily intraperitoneally with .05, 0.1, 0.2, and 0.3 and 0.5 gm. NaBr in

* These investigations were in part carried out with the aid of a grant for research in science made to Washington University by the Rockefeller Foundation.

[1] Loeb, Leo, *J. Med. Res.*, 1920, **41**, 481.

[2] Loeb, Leo, *J. Med. Res.*, 1920, **42**, 77.

[3] Loeb, Leo, *Am. J. Path.*, 1926, **2**, 19.

[4] Loeb, Leo, *Endocrinol.*, 1929, **13**, 1.

[5] Gray, S., and Loeb, Leo, *Am. J. Path.*, 1928, **4**, 3.

[6] Rabinovitch, J., *Am. J. Path.*, 1928, **4**, No. 6; 1930, **6**, No. 1.

aqueous solution over a period of 10 days. The 2 animals receiving the largest doses, namely, 0.3 gm. and 0.5 gm. died on the third day. Thus the succeeding experiments were limited to doses below 0.3 gm. NaBr. The results are shown in Table I.

TABLE I.

Control Animals Weight	Mitoses	Injected Animals Weight	Dose NaBr	Mitoses
165	144	170	10 days 0.05 gm.	1570
165	195	225	10 days 0.1 gm.	5326
		165	10 days 0.2 gm.	0
Av.	169			Av. 2299

In the first series of experiments, guinea pigs weighing 150 gm. and 200 gm. were used and .05 gm. and 0.1 gm. doses of NaBr

TABLE IIa.

Control Animals Weight	Mitoses	Injected Animals Weight	Dose NaBr	Mitoses
140	140	175	8 days 0.05 gm.	254
135	85	155	8 days 0.1 gm.	504
125	82	165	8 days 0.1 gm.	1026
160	296	140	8 days 0.1 gm.	228
145	276	165	15 days 0.1 gm.	262
Av.	176			Av. 475

TABLE IIb.

Control Animals Weight	Mitoses	Injected Animals Weight	Dose NaBr	Mitoses
195	208	195	15 days 0.05 gm.	350
200	162	200	15 days 0.05 gm.	254
195	44	225	8 days 0.10 gm.	120
225	0	220	8 days 0.10 gm.	274
230	390	210	8 days 0.10 gm.	5430
		200	8 days 0.10 gm.	7632
		215	15 days 0.10 gm.	280
		215	15 days 0.10 gm.	2084
Av.	161			Av. 2055

TABLE IIc.

Control Animals. Weight	Mitoses
390	36
405 ♀	578
405 ♀	620
410	57
Av.	320

were injected for periods of 8 and 15 days. The results are shown in Table IIa and Table IIb.

At this time a group of guinea pigs weighing 400 gm. was added to the control series to determine whether mitotic activity may vary with the size of the animal. (Table IIc.) In this group the average number of mitoses is higher than those of the groups with lower weights. This may be due to the 2 females, which had 578 and 620 mitoses respectively. The remaining experiments were limited to male animals, since it was possible that cyclic changes in female guinea pigs might have some effect on thyroid activity.

The animals injected with NaBr showed increased activity in the thyroid gland, and wide variations in the number of mitoses are observed. However, the smallest number of mitoses in the injected animals is larger than the average number found in the controls.

In another series, animals weighing 150, 200, and 400 gm. were injected for 10 days with doses of NaBr varying between .025 and .2 gm. As recorded in Table III, the largest number of mitoses were found when .05 gm. doses were given to 150 gm. guinea pigs, .1 gm. doses to 200 gm. guinea pigs and .15 gm. doses to 400 gm. animals.

TABLE III.

Weight 150 gm.—10 days.		Weight 225 gm.—10 days.		Weight 400 gm.—10 days.	
Dose	Mitoses	Dose	Mitoses	Dose	Mitoses
.025	110	.025	84	.025	76
.5	496	.05	325	.05	125
.1	380	.1	912	.1	220
.15	240	.15	400	.15	340
.20	96	.20	150	.20	108
Av.	264	Av.	374	Av.	174

In a further series 200 gm. animals were injected with doses of .05 to .25 gm. NaBr for 6 and 8 days. The results are shown in Table IV.

TABLE IV.

Weight 200 gm.—6 days.		Weight 200 gm.—8 days.	
Dose	Mitoses	Dose	Mitoses
.05	398	.05	608
.1	188	.10	140
.15	346	.15	225
.20	230	.20	28
.25	100	.25	1264
Av.	252	Av.	453

TABLE V.

Control Animals Weight 180-210 gm.—10 days. Mitoses	Injected Animals—.1 gm. NaBr. Weight 180-210 gm.—10 days. Mitoses
105	452
56	288
88	176
116	312
68	406
24	524
84	128
92	
Av. 80	Av. 327

TABLE VI.

Control Animals Mitoses	Injected Animals—.05-.15 gm. NaBr. Mitoses
144	1570
195	5326
140	254
885	504
82	1026
296	228
76	262
208	350
162	254
44	120
0	274
390	5430
36	7632
578	280
620	2084
105	496
56	380
88	240
116	325
68	912
24	400
84	125
92	220
	340
Av. 158	398
23 animals.	188
	346
	608
	140
	225
	452
	288
	176
	312
	406
	524
	128
	Av. 897
	37 animals.

In the last series, guinea pigs weighing 200 gm. were injected .1 gm. NaBr over a period of 10 days. This dose and length of time of injection appear to be the optimal as indicated in the preceding experiments. The results recorded in Table V show that the average number of mitoses for the control group is 80, whereas that for the injected group is 327.

In Table VI, all the controls used in the various experiments are grouped together, and the animals injected with effective doses of NaBr ranging between 0.05 and 0.15 gm. form a second group. The average number of mitoses in the controls is 158, in the injected animals, 897. We determined the probability that these results are not due to a coincidence and found the probability to be about 60:1.†

Effect of NaBr on the size of the acinus cells and the character of the colloid. Histological examination in every case revealed a definite increase in size of the cells in the injected animals. The sizes were determined accurately by measuring with a micrometer scale and were found to be from 0.8 to 1.2 mu for the controls and from 1.3 to 2.2 mu for the injected animals.

The colloid in the injected animals was in general, soft, staining pale red with eosin, and containing numerous peripheral vacuoles. Lymphocytes and phagocytes are not seen. In this respect the glands differed from those of animals which had received injections of iodide, in which the number of phagocytes is considerable.

Swingle[7] studying the effect of various substances on the metamorphosis of anuran larvae observed that whereas diiodotyrosine induced a complete metamorphosis within a short time, dibromtyrosine was ineffective. In a second experiment, however, he found a slight effect with dibromtyrosine and he concluded, therefore, that bromine in this case was not entirely inert although it cannot take the place of iodine. After the completion of our experiments we found that Minowada[8] recently fed potassium bromide to pigeons and noted that the thyroid showed a state of high functional activity. However, his results are based on only a qualitative histological study.

Conclusion. We may, therefore, conclude on the basis of quantitative studies that bromine in the form of NaBr exerts a definite stimulating effect on the mammalian thyroid as manifested in the

† We are indebted to Professor Paul Rider for his advice in the determination of these figures.

[7] Swingle, W. W., *Biol. Bull., M. B. L.*, 1923, **45.**

[8] Minowada, M., *Acta Dermat.*, 1928, **2**, 385.

increase in mitotic figures, a slight but definite softening of colloid, and an increase in the size of the acinus cells. However, this effect is not as marked as that produced by iodine, inasmuch as with the latter the average number of mitoses is about 5 times greater than that in the animals treated with NaBr.

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Action of Theelin on the Domestic Fowl.

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Juhn and Gustavson[1] have demonstrated the effectiveness of extracts of human and pig placentae, and human pregnancy urine in altering to the female type the new-growing feathers of Brown Leghorn cocks and capons. These authors have also pointed out a positive oviduct response to the same extracts in the immature female.

The present paper reports some effects of the injection of the crystalline female hormone, theelin, into the ovariectomized Brown Leghorn fowl. The writer wishes to acknowledge his indebtedness to Dr. E. A. Doisy and the Department of Biochemistry of this university for helpful suggestions and for bio-assay of material, and to the Department of Pathology for the preparation of tissues for microscopic examination. Full credit and thanks are due also to Parke-Davis and Co. for their very generous supply of theelin. The birds used were pure-bred Brown Leghorn stock, ovariectomized at 3 months of age, and examined periodically thereafter for weight, plumage, comb, and other changes. Autopsy was done on all, with special gross and microscopic attention to gonads and accessory sex characters.

Recalling the work of Domm,[2] the female fowl after a successful ovariectomy assumes the male type of feathering, spurs, and head furnishings, the latter being contingent upon the development of a compensatory testis-like gonad on the right side. The following results present some of the effects of theelin when injected under these conditions:

[1] Juhn and Gustavson. *J. Exp. Zool.*, 1930, **56**, No. 1.

[2] Domm, L. V., *J. Exp. Zool.*, 1927, **48**, No. 1.