

Goiterogenic Action of Iodide and the Etiology of Goiters in Chicks from Thyroprotein-fed Hens. (17397)

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It has been shown recently that the feeding of synthetic thyroprotein (STP) to hens increases the time required to hatch their eggs and results in the presence of goiters in the chicks hatched from these eggs.^{1,2} These chicks are apparently hypothyroid as shown by their lowered oxygen consumption rate.³ These results are contradictory because STP fed directly to adults and growing stock^{4,5} results in an elevated metabolic rate and in thyroid involution. Injection of STP into fertile eggs also results in thyroid involution.⁶ In the present communication, a mechanism involved in this paradox is established. It had been postulated that maternal thyroxine deposited in the egg regulates the thyroid function of the embryonic chick. Thus the goiters in chicks from STP-fed dams were believed due to reduced maternal thyroid activity with attending failure of the thyroidal substance in STP to be deposited within the egg. This hypothesis proved untenable, however, when the feeding of desiccated thyroid to hens failed to alter incubation time of their eggs or thyroid size of their chicks.⁷

A new hypothesis based on the relatively high inorganic iodide content of STP was developed following the report by Wolff and Chaikoff that the administration of large amounts of inorganic iodide inhibited thyroxine synthesis in the thyroid gland of the nor-

mal rat.⁸ In these experiments thyroid inhibition was of short duration and it is not surprising that thyroid enlargement did not occur. However, it might be expected that prolonged inhibition of the thyroid by any agent would result in a compensatory enlargement. As a result of our efforts to test this thesis, it has been demonstrated that inorganic iodide can act as a goiterogenic agent.⁹ When large amounts of inorganic iodide were injected into the white of fertile eggs on the 16th day of incubation, the chicks exhibited marked thyroid enlargement at the time of hatch. Moreover, these goiterous chicks exhibited typical hypothyroid symptoms: delayed hatching and delayed closure of the umbilicus.

To establish inorganic iodide as the cause of goiters in chicks from STP-fed dams, it was necessary to demonstrate that the inorganic iodide content of the hen's diet could affect the thyroid size of her chicks. This might be expected since the iodide content of the hen's diet determines to a large extent the iodine content of her eggs.¹⁰ In the commercial manufacture of STP, casein is incubated with elemental iodine and the resulting product contains 1.5-2.0% inorganic iodine as iodide as well as 3.0% crystalline thyroxine.¹¹ Hence, it seems logical that this inorganic iodide in STP might increase the iodide content of the egg sufficiently to inhibit thyroxine synthesis in the embryonic chick thyroid and produce a compensatory thyroid enlargement.

Experimental. To test this hypothesis, groups of 12 hens were fed a conventional diet

¹ Wheeler, R. S., and Hoffmann, E., *Endocrinology*, 1948, **42**, 326.

² Wheeler, R. S., and Hoffmann, E., *Endocrinology*, 1948, **43**, 430.

³ McCartney, M. G., and Shaffner, C., *Poultry Sci.*, 1949, **28**, 223.

⁴ Wheeler, R. S., Hoffmann, E., and Graham, C. L., *Poultry Sci.*, 1948, **27**, 102.

⁵ Wheeler, R. S., and Hoffmann, E., *Poultry Sci.*, 1948, **27**, 509.

⁶ Booker, E. E., and Sturkie, P. D., *Poultry Sci.*, 1949, **28**, 147.

⁷ Brooke, J. F., and Wheeler, R. S., unpublished data.

⁸ Wolff, J., and Chaikoff, I. L., *Endocrinology*, 1948, **42**, 468.

⁹ Wheeler, R. S., and Hoffmann, E., *Endocrinology*, 1949, **45**, 208.

¹⁰ Wilder, O. H. M., Bethke, R. M., and Record, P. R., *J. Nutrition*, 1933, **6**, 407.

¹¹ Graham, W. R., Jr., personal communication. Cerophyl Laboratories, Kansas City, Missouri.

TABLE I.
Thyroid Weight of Adult Hens Fed Diets Containing Large Amounts of Inorganic Iodide, and
Thyroid Weight of Their Progeny on Day of Hatch.

Diet of hens	Amt thyroxine added to diet, (mg/lb)	Amt inorganic I, added to diet, (mg/lb)	Mean thyroid wt* of chicks, (mg $\pm$ S.E.)	Mean thyroid wt† of hens, (mg $\pm$ S.E.)
Control	—	—	3.0 0.06	98 16.9
.04% STP‡	6	4	7.2 0.22	22 0.7
.001% KI	—	4	7.0 0.15	149 45.9
.002% "	—	8	8.1 0.12	162 16.9
.005% "	—	16	8.5 0.33	143 43.9
.009% "	—	32	8.4 0.32	352 30.0
.018% "	—	64	12.6 1.18	330 63.9

* Avg of thyroids from 10 day-old chicks.

† Avg of paired thyroids from 7 hens except in groups fed 32 and 64 mg I per lb of feed, which included 6 and 5 paired thyroids, respectively.

‡ STP, trade name Protamone, furnished by Cerophyl Laboratories, Kansas City, Mo.

supplemented with varying amounts of iodide (as KI), or STP. It is necessary to emphasize the excessive nature of the iodide levels. To meet the recommendation of the National Research Council, practical poultry diets should contain 0.5 mg iodine per pound. The diets employed in the present study contained 8 to 128 times this amount. The results are presented in Table I. It will be observed that the feeding of KI induced thyroid enlargement in the adult hens, confirming the goiterogenic action of excessive amounts of inorganic iodide which had been previously demonstrated in the chick embryo. As expected, STP caused thyroid involution in the adults, indicating that the thyroxine intake was sufficient to inhibit thyrotropin secretion.

The offspring of KI-fed hens also showed marked thyroid enlargement. It is of particular interest that hens fed approximately the same amount of iodide as was supplied by STP, produced chicks with thyroid enlargement comparable to that in the offspring of the STP-fed hens. Apparently the thyroid enlargement found in chicks from STP-fed hens is associated with the iodide rather than with the thyroxine in STP. This would explain why the feeding of desiccated thyroid,⁷ or STP^{1,2} to hens, or the injection of crystalline thyroxine into hens,³ fails to decrease thyroid size in their chicks. Apparently any thyroxine naturally deposited in the egg is metabolized or inactivated by the time the chick

thyroid becomes functional (about the 14th day of incubation) and, therefore, fails to modify thyroid size. It should be noted, however, that if STP⁶ or thyroxine^{3,6} is injected directly into eggs during the first week of incubation, chick thyroid size at time of hatch is significantly reduced.

The hypothyroid symptoms of offspring of hens fed inorganic iodide are essentially the same as those in chicks from eggs injected with thiourea,¹² or KI⁹; in chicks from dams fed STP;¹² and in squabs from iodine-deficient dams.¹³ The delay in hatching caused by feeding iodide to hens may explain the findings of Wilgus, *et al.*¹⁴ that hatchability was unfavorably affected by amounts of iodine in the hen's diet in excess of 23 mg/lb. In the present study no decrease in hatchability was noted if the eggs were left in the incubator an extra day to allow for the delayed-hatching effect of the iodide supplement.

Further evidence of the like effects of feeding KI and STP to the hens on the thyroid glands of newly hatched chicks has been obtained from histological sections. (Fig. 1.) The thyroid glands of chicks whose dams were

¹² Grossowicz, N., *PROC. SOC. EXP. BIOL. AND MED.*, 1946, **63**, 151.

¹³ Hollander, W. F., and Riddle, O., *Poultry Sci.*, 1946, **25**, 20.

¹⁴ Wilgus, H. S., Gassner, F. X., Patton, A. R., and Harshfield, G. S., *Poultry Sci.*, 1948, **27**, 686, (abstract).

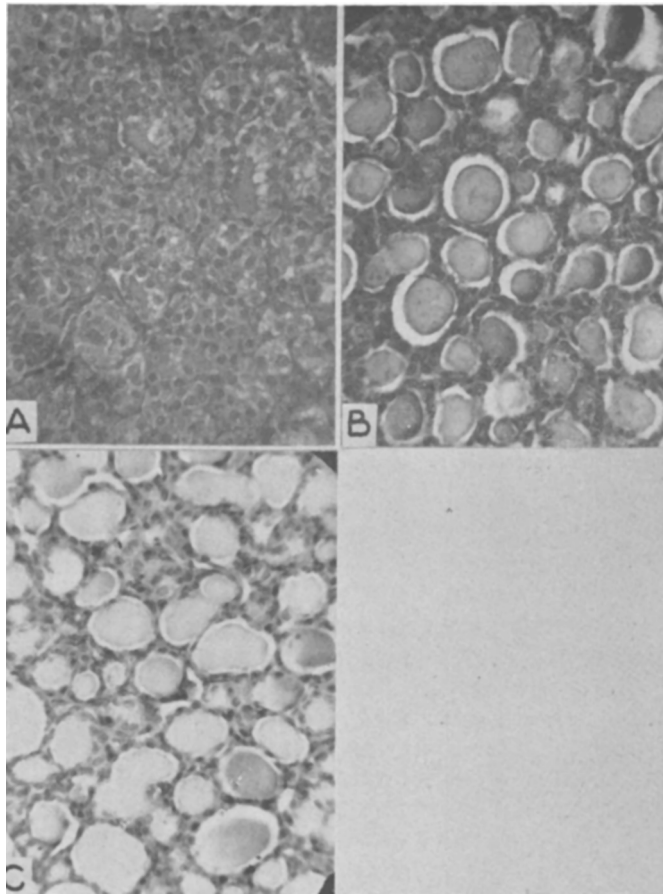


FIG. 1.

Histological sections of the thyroid gland of day-old chicks 225 X. A. Normal chick thyroid. B. Thyroid of chick from STP-fed hen. C. Thyroid of chick from KI-fed hen.

fed either KI or STP are indistinguishable; the many follicles are distended with colloid and the epithelial cells are flattened. In the normal gland very few follicles are seen and the epithelial cells are cuboidal.

Histological sections of the thyroid glands of hens fed KI are of interest because of marked colloid storage. (Fig. 2.) In most cases the follicles were so large that it was not possible to photograph a sufficient area to convey the true picture. It would appear that the generally accepted concept of Marine¹⁵ that colloid goiter is the result of involution of a previously hyperplastic gland, cannot explain the tremendous enlargement

observed in the present study after only one month of treatment. In 3 cases where hens received the 2 highest dosages of KI, goiters with colloid nodules and cystic degeneration were observed. A line drawing of one of these glands is presented in Fig. 3. Apparently the follicles become confluent and form large colloid vesicles surrounded by a pseudo encapsulation. There was no evidence of neoplasia. However, the trabeculae forming the boundaries of the vesicles contained some thyroid tissue which appears to be normal and some thyroid tissue showing only slightly increased colloid storage. The weights of these glands were not included in the data because of their extreme deviation from the mean. The largest gland was 50 x 35 mm and the

¹⁵ Marine, D., *Medicine*, 1924, **3**, 453.

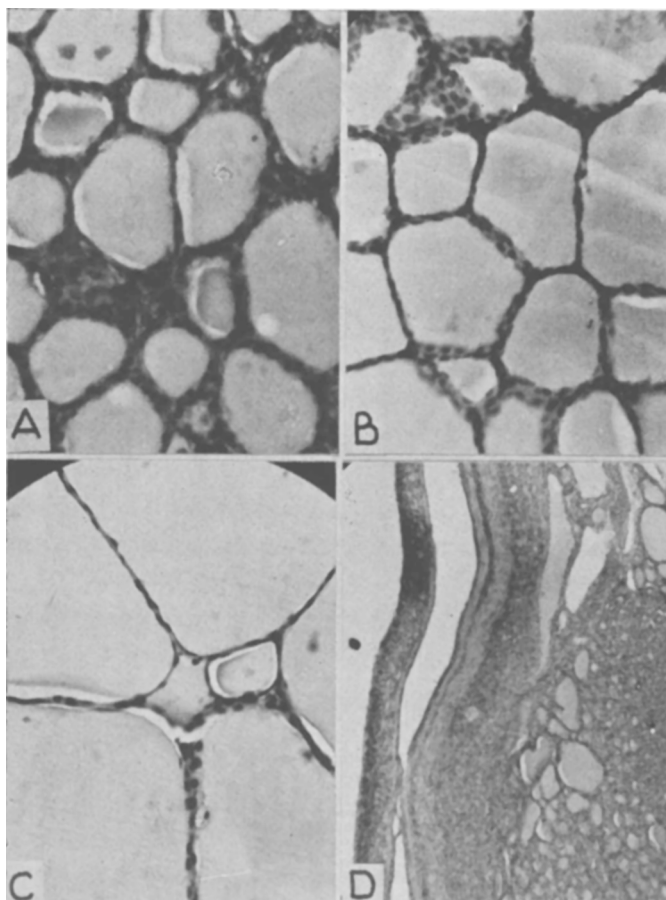


FIG. 2.

Histological sections of the thyroid gland of laying hens. A. Thyroid of normal hen. B. Thyroid of STP-fed hen. C. Thyroid of KI-fed hen. D. Low power field of the "normal" thyroid tissue and pseudo-encapsulation found in the nodular, colloid goiter observed in three out of fourteen hens when the higher dosages of KI were fed. Note the transitional tissue progressing from right to left. The condensed tissue to the extreme left forms the border of a large colloid nodule or cyst. A, B, C, 225 X; D, 75 X.

smallest was 35 x 30 mm in the longest and shortest dimension as compared to 7 x 3 mm in size for glands of normal birds. Some of the nodules (cysts) observed in these goiters were as large as 10 mm in diameter.

Discussion. It is difficult to integrate the present finding of a goiterogenic effect of iodide in the normal animal with the iodine-thyroid literature. Morton, Chaikoff and Rosenfeld showed¹⁶ that thyroxine synthesis by thyroid slices *in vitro* was inhibited by the presence of an excess of iodide ions. In later work, Wolff and Chaikoff⁸ obtained an inhi-

bition of thyroxine synthesis *in vivo* which could be prolonged by nephrectomy. They suggest that the effect of large doses of inorganic iodide on a hyperactive gland (Graves' disease) is to reduce thyroxine secretion and thus ameliorate the symptoms of hyperthyroidism.¹⁷ One might guess from this work that continued suppression of the thyroxine secretion of the normal gland would lead to

¹⁶ Morton, M. E., Chaikoff, I. L., and Rosenfeld, S., *J. Biol. Chem.*, 1944, **154**, 381.

¹⁷ Wolff, J., and Chaikoff, I. L., *J. Biol. Chem.*, 1948, **172**, 855.

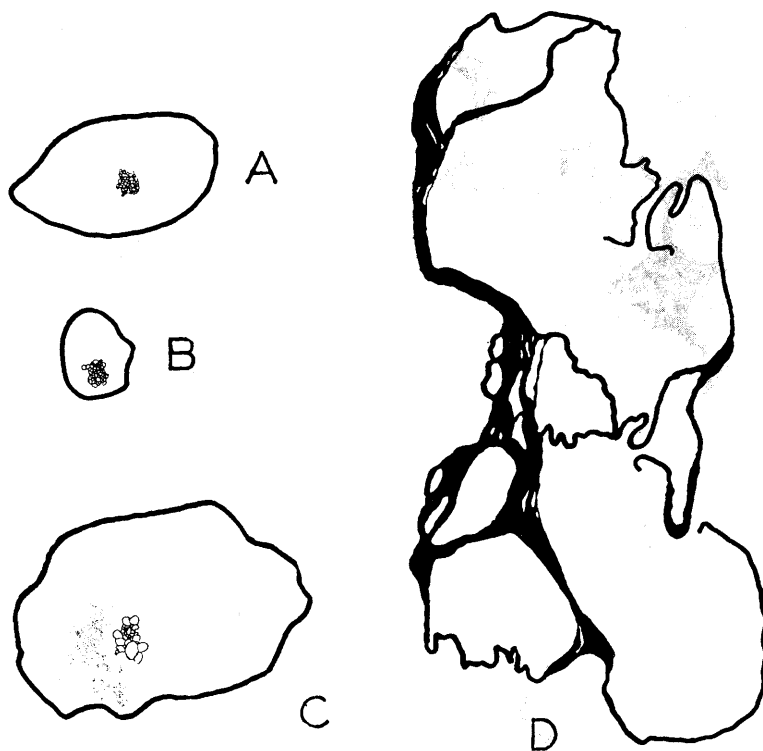


FIG. 3.

Line drawing of median frontal sections of thyroid from: A. Normal hen. B. STP-fed hen. C. KI-fed hen. D. KI-fed hen showing nodular colloid goiter with cystic degeneration. Note the relative follicle size in A, B, C. All figures 4.3 X.

subsequent enlargement of the thyroid via increased thyrotropin from the pituitary.

In the absence of histological evidence this might explain the thyroid enlargement resulting from administration of large doses of iodide. But Rawson *et al.*¹⁸ have differentiated between the antithyroid action of iodide and thiouracil on a hyperplastic gland. Whereas thiouracil produces a columnar epithelium in a gland devoid of colloid, iodide produces an involution of epithelial cells and the storage of colloid. These effects of iodide have been recently confirmed for normal animals by Lesser, Winzler and Michaelson,¹⁹ who also noted that rats fed KI but exposed to cold had more normal appearing glands than

treated rats held at room temperature. Thus, in this instance, increased thyrotropin partly reduced the colloid storing effect of iodide. In the light of these findings, it is doubtful if an increase in thyrotropin secretion can adequately explain the goiterogenic effects of iodide, but no alternative hypothesis can be proposed at this time.

Summary. The goiterogenic action of increased iodide intake is demonstrated both in the normal fowl, following continuous treatment, as well as in the developing chick embryo. The goiters in chicks presumably result from large amounts of inorganic iodide deposited in the egg by the hen and are comparable in weight and histology to those observed in chicks from dams fed synthetic thyroprotein. It is suggested that the goiters observed in chicks from dams fed synthetic thyroprotein are caused by the iodide present in thyroprotein.

¹⁸ Rawson, R. W., Moore, F. D., Peacock, W., Means, J. H., Cope, O., and Riddell, C. B., *J. Clin. Invest.*, 1945, **24**, 869.

¹⁹ Lesser A. J., Winzler, R. J., and Michaelson, J. B., *PROC. SOC. EXP. BIOL. AND MED.*, 1949, **70**, 571.