gen" responsible for the meningoencephalomyelitis is a phosphatide-like material present in the white matter of the central nervous system. Its properties serve to differentiate it from 4 of the 5 haptens thought to be present in brain.[7] "Neurokeratin"[10] has been eliminated by previous workers;[5] "protagon" and "sphingomyelin"[11] are included in the non-phosphatide fractions tested in the present experiments and found to be inactive; and the hapten thought to be present in gray matter[11,12] is obviously not necessary since it has now been found that white matter (optic nerve) contains the "antigen." Whether the "antigen" is the same as the "alcohol-soluble brain hapten"[11,12,13] must await further studies.

[10] Bailey, G. H., and Gardner, R. E., *Am. J. Hyg.*, 1942, **36**, 205.

[11] Schwab, E., *Z. f. Immunitätsforsch. u. exp. Therap.*, 1936, **87**, 426.

[12] Reichner H., and Witebsky, E., *Ibid.*, 1934, **81**, 410.

[13] Rudy, H., *Biochem. Z.*, 1933, **267**, 77.

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Thiouracil and Mammary Growth.*†

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There are a number of reports in the literature which would appear to indicate that the mouse and the rat may respond differently, as regards mammary development and responsiveness, during experimentally induced hypothyroidism.

Mixner and Turner[1] have reported an increased mammary responsiveness of ovariectomized female mice to estrogen and progesterone treatment when thyroxin was simultaneously administered, while a decreased responsiveness followed thyroidectomy. Mixner[2] later found that thiouracil administration had an effect similar to thyroidectomy in decreasing mammary responsiveness. Morris *et al.*, found considerable mammary atrophy in virgin female mice fed thiourea[3] and thiouracil[4]. Gardner[5] observed mammary growth in male mice fed desiccated thyroid, but the effect was dependent upon intact testes.

From these reports it would appear that, in the mouse, experimentally induced mild hyperthyroidism is conducive to enhanced mammary responsiveness, while the opposite is true of hypothyroidism.

In the rat, however, Leonard and Reece,[6] and Smithcors and Leonard[7] have found that thyroidectomy of both male and female rats caused an enhanced development of the mammary gland. Thyroidectomy also increased the effectiveness of administered estrogen or testosterone propionate in stimulating mammary alveolar development. Chamorro[8,9] has also reported that thyroid-

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[1] Mixner, J. P., and Turner, C. W., *Endocrinology*, 1942, **31**, 345.

[2] Mixner, J. P., *J. Dairy Science*, 1947, **30**, 578.

[3] Morris, H. P., Dubnik, C. S., and Dalton, A. J., *J. Nat. Cancer Inst.*, 1946, **7**, 159.

[4] Morris, H. P., Dubnik, C. S., and Dalton, A. J., Exhibit Abstract, Fourth Internat. Cancer Res. Congress, Sept. 2-7, 1947, St. Louis.

[5] Gardner, W. U., *Endocrinology*, 1942, **31**, 124.

[6] Leonard, S. L., and Reece, R. P., PROC. SOC. EXP. BIOL. AND MED., 1941, **28**, 65.

[7] Smitheors, J. F., and Leonard, S. L., *Endocrinology*, 1942, **31**, 454.

[8] Chamorro, A., *C. R. Soc. Biol.*, 1946, **140**, 499.

ectomy of rats caused mammary hypertrophy and augmented the mammary stimulating effect of pregneninolone. Smithcors[10] has found that thiouracil treatment of rats did not of itself produce mammary alveolar development, but enhanced the mammary alveolar response to administered estrogen.

Unlike the situation in the mouse, these reports indicate that in the rat experimentally induced hypothyroidism is conducive to enhanced mammary gland growth and responsiveness.

With regard to hyperthyroidism in the rat, Weichert, Boyd, and Cohen[11] reported enhanced mammary development, but the effect was one of induced pseudopregnancy, and hence dependent upon intact ovaries.

Certain recent observations on thiouracil administration at this laboratory appear to fit into the above pattern.

Twenty-one young male albino rats were castrated and divided into three groups. Group 1 (6 rats) served as a control. About 10 days later Group 2 (8 rats) and Group 3 (7 rats) were started on daily injections of 10 μg of diethylstilbestrol in oil. Group 3 had 0.1% thiouracil added to its feed. At the end of 21 days of this treatment all groups were sacrificed. Body weight, pituitary lactogen content and thyroid weight changes in these animals have been reported previously in connection with another experiment.[12]

The mammary glands of the control group showed small to medium sized duct systems with little or no alveolar development. Group 2 showed an enhanced state of mammary development, with additional alveolar development in most animals. Group 3 showed a striking advancement of mammary development over the control group, and a marked improvement over Group 2. Extensive alveolar development was present with good duct extension.

The mouse experiment involved 15 intact albino males. Five served as controls. Four were maintained for 6 weeks on a grain ration containing 1.23 mg of dimethyl ether of diethylstilbestrol per kilo of feed. This level of estrogen was known to promote good mammary duct extension in male mice. Six were maintained for 6 weeks on the same level of estrogen with 0.2% thiouracil added to the feed after the first week.

The estrogen treated animals showed good duct extension as compared to the controls, with some alveolar development in one animal. Unlike the results of the rat experiment, no difference in the response to estrogen could be detected in the estrogen and thiouracil treated mice.

The conditions of the rat and mouse experiments are unfortunately different in several respects such as dosage, duration, and mode of administration. However, taken together with previous reports, the present results are indicative of a difference in the effect of thiouracil upon mammary responsiveness in the rat and mouse.

With regard to the rat, there has been reported an effect of hyperthyroidism and hypothyroidism on vaginal sensitivity to estrogen. The effect appears to parallel that on mammary sensitivity to estrogen. Van Horn[13] found that in 20 of 24 castrated female rats in a hyperthyroid condition, approximately 3 rat units of theelin were necessary to produce estrus. Langham and Gustavson[14] found the vaginal rat unit of estrone to be 1.33 μg for castrate controls and 2.5 μg for castrates receiving thyroxin injections. Conversely thyroparathyroidectomized castrates required only 0.86 μg. Thiourea administered in the drinking water caused a marked immediate decrease in vaginal sensitivity to estrone followed by a gradual increase, the rats becoming as sensitive after 56 days as thyroparathyroidectomized castrate rats.

It is possible that the same underlying mechanism is responsible for the effect of

9 Chamorro, A., *C. R. Soc. Biol.*, 1946, **140**, 721.

10 Smithcors, J. F., PROC. SOC. EXP. BIOL. AND MED., 1945, **59**, 197.

11 Weichert, C. K., Boyd, R. W., and Cohen, R. S., *Anat. Rec.*, 1934, **61**, 21.

12 Meites, J., and Turner, C. W., PROC. SOC. EXP. BIOL. AND MED., 1947, **64**, 488.

13 Van Horn, W. M., *Endocrinology*, 1933, **17**, 152.

14 Langham, W., and Gustavson, R. G., *Fed. Proc.*, 1946, **5**, 143.

hypothyroidism on the observed variations in the vaginal and mammary sensitivity of rats to estrogen.

The seemingly anomalous situation of thiouracil enhancing mammary growth response in the rat may have an analogy in body growth also. Astwood[15] states that, although the prolonged administration of effective doses of thiouracil to rats causes an arrest of development and a retardation of growth, a small dose of thiouracil, given from the 21st day of life for a period of 9½ months, resulted in increased growth, including a gain in skeletal dimensions. The implication is that a mild degree of hypothyroidism is conducive to excessive growth in this species.

The authors are not familiar with any data indicating a similar relationship in the mouse.

Koger and Turner[16] have studied the effect of experimentally induced hyperthyroidism in 4 species, including the rat and mouse. In the mouse it was found that although excessive hyperthyroidism inhibited body growth, a mild degree of hyperthyroidism consistently accelerated the growth rate. In rats however, mild hyperthyroidism had no such desirable effect, with the possible exception of a few animals that showed limited acceleration of growth.

It would appear from such experiments that the rat is normally secreting a level of thyroxin close to the upper limit of tolerance, and may actually be benefitted in some respects by a slight reduction in the normal thyroxin secretion rate. If such is actually the case, this relationship would have wide implications in connection with the choice of experimental animals for certain types of investigation. It is known for instance that the normal rat is a poor animal for use in the assay of thyrotrophic hormone. Its thyroid gland is normally quite hyperplastic and relatively insensitive to further thyrotrophic stimulation.

That this relationship may not be true of all strains of rats is indicated by the work of Palmer *et al.*[17] These authors were able, by selection of the progeny of a single pair of rats, to produce two strains which differed appreciably in their efficiency of food utilization. This difference was accompanied by a difference in the basal metabolic rate and in the effect of administered thyroid on skeletal length and on efficiency of food utilization. This was interpreted by the authors as indicating a possible difference in the thyroid secretion rate of the two strains.

The inheritance of varying rates of thyroxin secretion may be responsible in part for the marked differences in the growth rate and body size of the Yale and Wistar strains of albino rats.[18]

Conclusion. It would appear that there exist differences in the reaction of the mouse and rat to experimentally induced hypothyroidism and hyperthyroidism, possibly dependent upon the relative thyroxin secretion rates of the two species.

[15] Astwood, E. B., *N. Y. Acad. Med., Harvey Lectures*, 1944-45, **40**, 195.

[16] Koger, M., and Turner, C. W., *Mo. Agr. Exp. Sta. Res. Bul.* 377, 1943.

[17] Palmer, L. S., Kennedy, C., Calverley, C. E., Lohn, C., and Weswig, P. H., *Minn. Agr. Exp. Sta. Tech. Bul.* 176, 1946.

[18] Harned, B. K., and Cole, V. V., *Endocrinology*, 1939, **25**, 689.