EFFECT OF ESTROGEN AND PROGESTERONE ON THYROID FUNCTION OF CATTLE

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SUMMARY

A preliminary study is presented concerning the possible role of the ovarian hormones (estrogen and progesterone) upon the rate of secretion of thyroid hormone during estrus and pregnancy. For this purpose, a technique was developed consisting of the measurement of thyroidal-131 release when recycling of I31 was prevented by a goitrogen (thiouracil) during a preliminary control period. During the subsequent period of ovarian hormone injection, the measurement of release rate is continued. If a change in release rate is noted, it is believed to indicate that a change in thyroxine secretion rate has been induced. The injection of 100 mg. per day of progesterone alone or in combination with 100 μg. of estradiol benzoate failed to alter the release rate of thyroidal I31 in groups of dairy cattle. While 1.15 mg. estradiol benzoate alone also failed, when 2.5 or 3.0 mg. were injected daily, the release rate was increased to a statistically significant extent. These observations are interpreted as indicating that the level of estrogen secreted in late pregnancy stimulates increased secretion of thyrotropin and thyroxine during early lactation.

One of the basic patterns of control of thyroid gland function resides in the action of the pituitary thyrotropin hormone upon the thyroid gland and the action of the thyroid hormone upon the pituitary. Thus, under constant conditions of environment (nutrition and temperature), the secretion of thyroxine would tend to be constant. Under these conditions, the variation in thyroxine secretion rate in animals might be ascribed to genetic differences. In a previous paper (12), a study was reported concerning genetic differences and seasonal changes (ambient temperature) upon thyroxine secretion rate of cattle under uniform nutritional conditions.

The present paper is concerned with the possible influence of the internal environment of the dairy cow during reproduction upon thyroxine secretion rate. This would include changes which might occur during estrous cycles, pregnancy, and lactation. Since the determination of thyroxine secretion rate requires a certain amount of time (about 2 wk. or more), short-time changes are difficult to measure. In beginning this study, it seemed of interest first to explore the influence of the two ovarian hormones separately and together, to note their effect upon thyroid function, before attempting to evaluate the more complicated normal physiological changes during estrus and pregnancy.

In experimental animals, many studies have been reported concerning the influence of estrogen upon thyroid function. In these studies, many indices of thyroid function have been employed, such as I131 uptake, thyroidal-I125 release rates, thyroid cytology, and hyperplasia. Estrogen has been reported to increase

Received for publication May 5, 1958.

1 Contribution of the Missouri Agricultural Experiment Station, Journal Series No. 1871. Approved by the Director.
2 Aided in part by a grant from the U. S. Atomic Energy Commission, Contract No. AT(11-1)-301.
thyroid activity, as shown by $^{131}$I uptake of the thyroid gland \((5, 7, 8, 9, 17)\), by the thiouracil-thyroxine secretion rate \((6)\), by increase in the PBI of blood \((4)\), and by increased hypertrophy of the thyroid gland \((3)\). It is of interest to note that Clifton and Meyer \((3)\) found that in rats estrogen depressed appetite and hypertrophy of the thyroid, but that force-fed, estrogen-treated rats showed thyroid hypertrophy. However, Noach \((9)\) found increased $^{131}$I uptake during estrogen administration when iodine intake was controlled. Under similar conditions, Soliman and Reineke \((15)\) found increased uptake during estrus in the rat. This finding had been previously demonstrated in the rodent by $^{131}$I uptake \((14, 16)\) under uncontrolled iodine intake.

Large doses of estrogen have been reported to have no effect on $^{131}$I uptake \((7, 10)\) in the rat and to inhibit the release of thyroidal $^{131}$I in the rabbit \((1)\).

Spaying has been found to produce no change in $^{131}$I uptake in the rat \((10)\) and to produce no change in release rate of thyroidal $^{131}$I in the rabbit \((2)\).

Progesterone \((7, 8)\) has been reported to increase $^{131}$I uptake in the rat, but when injected concurrently with estrogen \((14, 17)\) it has been shown to decrease uptake.

From the review of the literature, it is difficult to determine the role of the ovarian hormones, administered in physiological amounts, in the regulation of thyroid function during reproduction. Further, studies of this problem have not been conducted previously with domestic animals such as cattle.

**Indices of thyroid function.** Since $^{131}$I uptake by the thyroid gland appears to be subject to many influences, its value as an index of thyroid function appears to be limited. The release rate of thyroidal-$^{131}$I when recycling of iodine is prevented by the use of goitrogens appears to be a more useful measure of thyroid function \((11)\). It is not as satisfactory as thyroxine secretion rate determination, for reasons pointed out by Premachandra et al. \((12)\). However, by the use of the same animals, in which the rate of release of thyroidal-$^{131}$I is first determined (control period), followed immediately by an experimental period during which the hormone is administered, changes in the release rate may be considered to indicate altered thyroid function.

In using the thyroxine secretion rate technique, the control and experimental periods would require the elapse of about 1 mo. Since the ambient temperature of our cattle can not be controlled, temperature changes might influence the results during these longer time intervals. As a preliminary to such studies, it seemed of value to determine the possible influence of the ovarian hormones on the thyroidal-$^{131}$I release rate in cattle.

### EXPERIMENTAL PROCEDURE

Cows and calves in the experimental herd were injected intravenously with 200–300 μc. of carrier-free radiiodine (NaI$^{131}$). Daily measurements of thyroidal-$^{131}$I were made by the method described by Pipes et al. \((11)\). After maximum accumulation of $^{131}$I was observed in the thyroid, the release phase was measured for a number of days. The rate of decline thus observed served as a control period for the normal rate of release of thyroidal-$^{131}$I in the individual
animals. In most of the studies, thiouracil was administered in sufficient amounts to prevent the reutilization by the thyroid of I\(^{131}\) from metabolized thyroid hormone. Thiouracil was administered daily by gelatin capsule in 12- or 24-g. doses.

Estradiol benzoate and progesterone were dissolved in olive oil and injected subcutaneously during the test periods. The animals were allowed access to iodized salt blocks at all times.

Conventional corrections were made for background and for physical decay of the isotope. Results were expressed as per cent of injected dose.

Release rates of thyroidal I\(^{131}\) were calculated according to the methods previously described (11) with the term k\(^{-4}\) being employed for release rate constant per hour during thiouracil administration. For comparison, the daily percentage release rate is presented. These values indicate the percentage of the total I\(^{131}\) present in the thyroid glands which is released each 24 hr.

RESULTS

**Estrogen and progesterone.** During the first two-thirds of pregnancy, estrogen and progesterone are secreted to stimulate growth of the udder. While the levels of these two hormones normally secreted at this time are not known, Turner et al. (19) reported that the daily injection of 100 \(\mu\)g. estradiol benzoate and 100 mg. progesterone for 180 days was believed to stimulate satisfactory udder growth in heifers (13).

It was of interest, therefore, to determine the possible influence of these two hormones of pregnancy upon thyroid function, uncomplicated by fetal growth. Thiouracil was administered to five dairy heifers and two bull calves during a six-day control period, to determine the normal rate of release of thyroidal-I\(^{131}\). The ovarian hormones at the above levels were then injected daily for a period of eight days. If these hormones stimulated increased secretion of thyrotropin, it should be reflected by an increased rate of release of thyroidal-I\(^{131}\). It will be seen that no change was observed in the release rate during the injection of 100 \(\mu\)g. estradiol benzoate and 100 mg. progesterone (Table 1). Typical data on

<table>
<thead>
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<th>TABLE 1</th>
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<tr>
<td><strong>Effect of estrogen and progesterone on thyroidal-I(^{131}) release with concurrent administration of thiouracil</strong></td>
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<tr>
<td><strong>Experiment</strong>&lt;br&gt;(daily injection)</td>
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<tr>
<td>Progesterone, 100 mg.</td>
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<tr>
<td>Estrogen, 100 (\mu)g.</td>
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<tr>
<td>Estradiol benzoate 1.15 mg.</td>
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<td>Estradiol benzoate 2.5 mg.</td>
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<td>Estradiol benzoate 3 mg.</td>
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<td>Estradiol benzoate 6 mg.</td>
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<sup>a</sup> Each value in parentheses indicates the percentage of I\(^{131}\) present in the thyroid glands which is released each 24 hr. = k\(^{-4}\)×24×100.<br><sup>b</sup> Increase statistically significant (P < .01).
two heifers (No. 89 and 76) and one bull calf (H1) is presented (Figure 1). These data suggest that the ovarian hormones secreted during the udder growth phase of pregnancy do not stimulate increased thyroxine secretion.

**Progesterone.** To determine whether this level of progesterone alone would stimulate increased thyrotropin secretion, twin heifers were run during a control period of six days, then injected with progesterone (100 mg. daily) for seven days. Since the release rate of thyroidal-I\(^{131}\) was unchanged during the period of hormone injection, it was concluded that neither estrogen and progesterone nor progesterone alone at these levels influenced pituitary-thyroid relations (Figure 2).

**Estrogen.** In late pregnancy, the secretion of estrogen by the cow increases markedly. It is well known that estrogen, at this time, stimulates the increased proliferation of the acidophilic cells and secretion of the lactogenic hormone. For this reason, Turner et al. (19) administered 3 mg/day of estradiol benzoate to initiate lactation in heifers whose mammary glands had been grown previously with estrogen and progesterone. The question arose whether the estrogen level in late pregnancy might stimulate an increased secretion of thyrotropin and thyroxine and thus give the milk-secretion process an added boost.

In a series of experiments, increasing amounts of estrogen were given to
heifers and bull calves and the rates of release of thyroidal-I$^{131}$ observed after a preliminary control period. When 1.15 mg/day of estradiol benzoate was administered to seven heifers and two bull calves, no change in release rate was observed (Table 1). However, when the level of estrogen was increased to 2.5 mg daily, the release rate of I$^{131}$ was distinctly increased in two bull calves in comparison to the control period. At the 3.0-mg. level (which stimulates the initiation of milk secretion) two bull calves and five dairy heifers showed increases in thyroidal-I$^{131}$ release rates which were statistically significant when compared to their control periods (Table 1). Instead of the continued normal release rate, a rapid increase in release rate was observed (Figure 3).

The increased release rate of thyroidal-I$^{131}$ in itself indicates an increased daily rate of discharge of thyroxine into the blood and concurrently an increased rate of secretion of thyroxine. Since thyroid gland function is controlled by the thyrotropic hormone of the anterior pituitary, it is inferred that estrogen acts upon the pituitary to increase the rate of secretion of thyrotropin.

The role of increasing estrogen production in late pregnancy, in stimulating the increasing secretion of the lactogenetic hormone of the pituitary and the initiation of milk secretion at parturition, has been recognized for some time. The present observations indicate a second important function of estrogen at this time; namely, to stimulate increased secretion of thyrotropin and thyroxine, to increase the intensity of milk secretion, and to promote a rapid rise in milk secretion postpartum.

![Graph showing thyroidal-I$^{131}$ release rates.](image-url)
DISCUSSION

The endocrine interaction which stimulates the growth of the mammary glands of the udder of cattle during the first two-thirds of pregnancy, and later stimulates the initiation of milk secretion, is of great importance in understanding the fundamental causes of variation in the milk production of dairy cattle. Do the ovarian hormones (estrogen and progesterone) which play vital roles in stimulating mammary gland growth and the initiation of lactation interact with other endocrine glands to make possible the marked rise in milk secretion which occurs postpartum?

The data presented in this paper suggest that estrogen and progesterone in amounts and ratios which stimulate mammary gland growth have little influence upon thyrotropin secretion. However, the increasing level of estrogen secreted in late pregnancy not only stimulates an increased secretion of lactogenic hormone by the pituitary but also may stimulate the secretion of increased amounts of thyrotropin and correspondingly more thyroxine. Since it is well known that thyroxine stimulates more intense milk secretion, this effect could be expected to aid cows in reaching maximum levels of milk production.

Since estrogen secretion is discontinued at parturition, the stimulus to increased thyrotropin secretion would gradually decline. This might explain why the feeding of thyroprotein to dairy cattle is of less value during the rising segment and at the peak of production than when lactation begins to decline.
Feeding thyroprotein during normal declining lactation would thus maintain thyroxine levels of the blood, comparable to or above that initially stimulated by estrogen in late pregnancy.

Finally, it should be pointed out that estrogen apparently influences the secretion of pituitary growth hormone. This is the explanation of the favorable influence of diethylstilbestrol upon the growth of beef cattle. It has been shown by Struempler and Burroughs (18) that either diethylstilbestrol or growth hormone resulted in increased nitrogen retention in lambs. They concluded that diethylstilbestrol increases nitrogen retention in ruminants through the increased release of growth hormone in the animal’s body.

From these varied observations, it is suggested that the secretion of high levels of estrogen in late pregnancy stimulates the secretion of increased levels of three anterior pituitary hormones, lactogen, growth, and thyrotropin, all of which influence the intensity of milk secretion.

REFERENCES

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