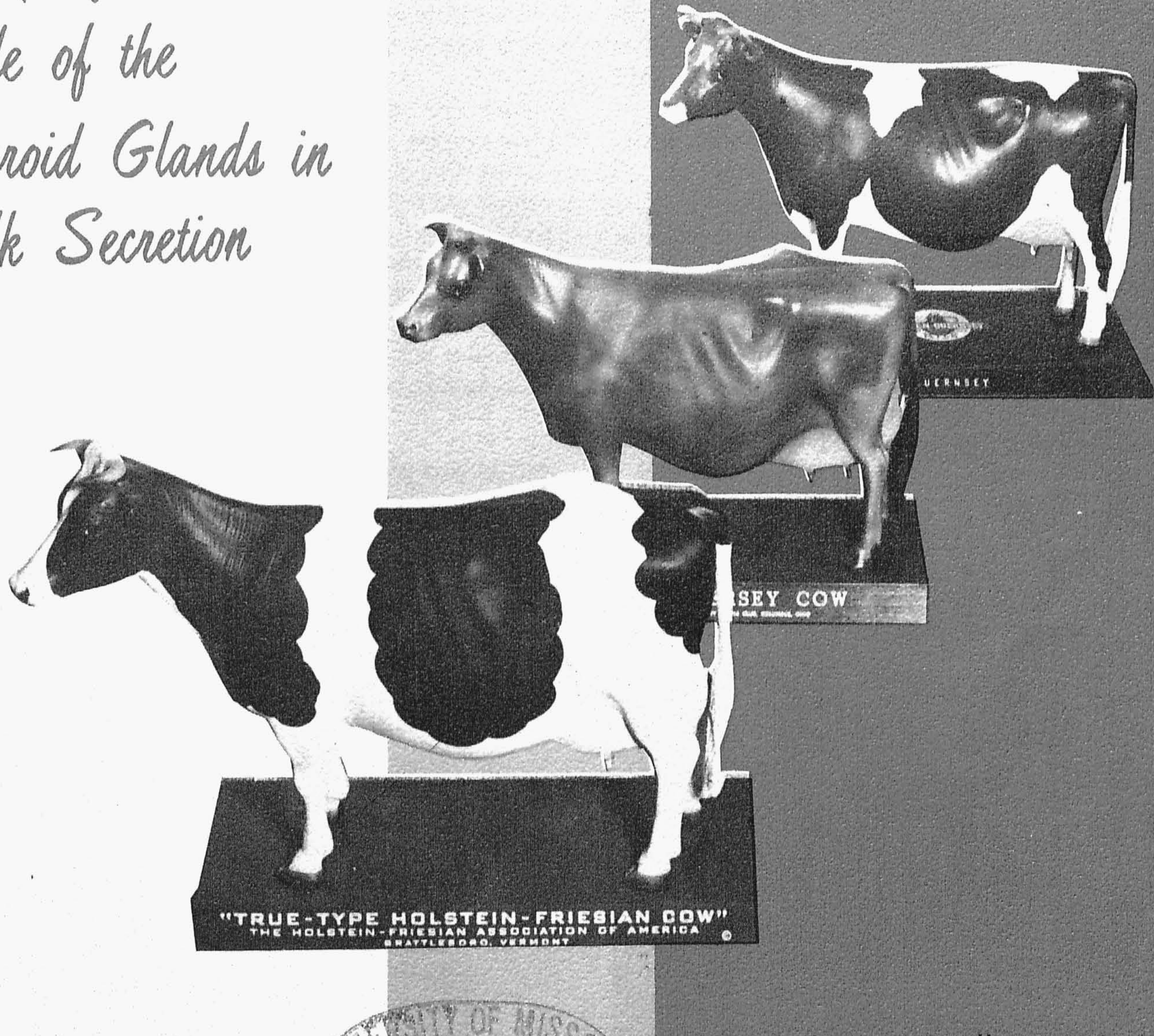
WHAT CAUSES HIGH PRODUCTION?

Story of the Role of the Thyroid Glands in Milk Secretion



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WHAT CAUSES HIGH MILK PRODUCTION?

Story of the Role of the Thyroid Glands in Milk Secretion

C. W. TURNER
Professor Emeritus of Dairy Husbandry

The first bulletin of this series[1] suggested that the inherited capacity of a cow for high milk and fat production was largely dependent upon *the inherited ability to secrete optimum amounts of a number of hormones which influence her productivity.*

For high production it is necessary that the cow have a large udder. The story of the role the endocrine glands play in udder growth is presented in Missouri Agricultural Experiment Station Bulletin 793. The stimulus of the milk secreting cells of the udder is under control of the lactogenic hormone. It must be secreted continuously but discharged periodically (at each milking period) for the cells to continue to secrete milk. The story of the role of the lactogenic hormone in milk secretion is told in Experiment Station Bulletin 836.

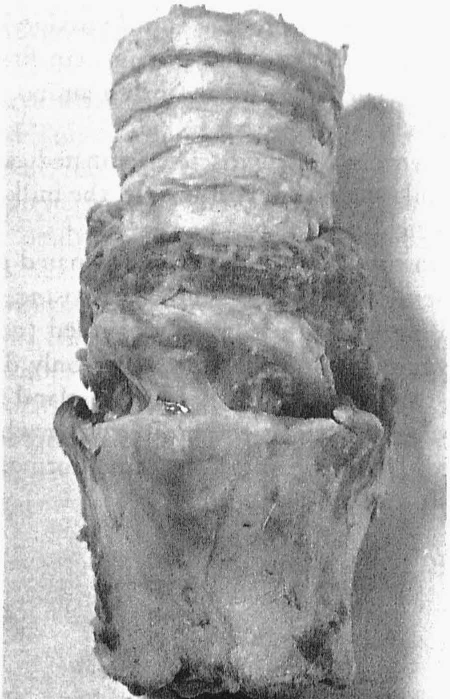
While the lactogenic hormone is necessary for the cells of the udder to secrete milk, a number of other hormones influence the rate at which milk is secreted. Those secreted by the thyroid gland are very important. This bulletin will be devoted to the story of the role of the thyroid hormones in influencing the milk yield. It will also explain how the thyroid hormones influence body growth and other important body processes.

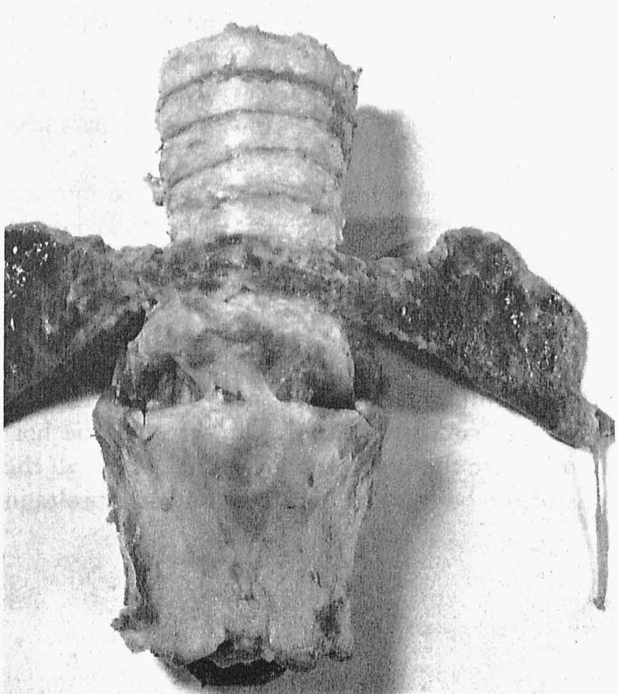
THE THYROID GLAND

The thyroid gland is an *endocrine gland.* This means that the hormones it secretes are discharged directly into the blood stream and circulated to all parts of the body. The thyroid gland of cattle is composed of two lobes connected by a band of tissue called the isthmus. It wraps around the wind-pipe in the neck (Fig. 1).

[1] University of Missouri Station Bulletin 793, *What Causes High Milk Production,* C. W. Turner, 1963.

Fig. 1—(a) A dissection of the thyroid gland of the dairy cow showing how it wraps around the wind-pipe in the neck. (b) The two lobes of the thyroid gland have been dissected free of the wind-pipe. Note that the two lobes of the thyroid are connected by a band of similar tissue called the isthmus.





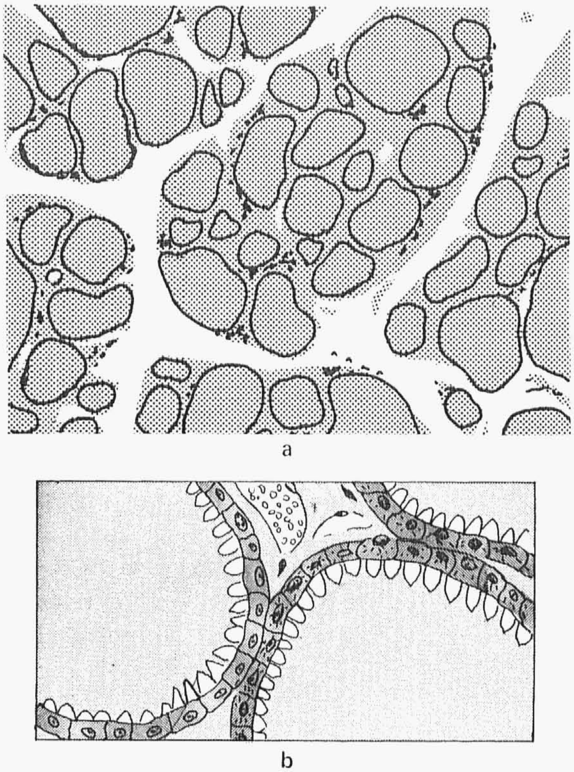


Fig. 2—(a) A cross section of the thyroid gland. Many follicles are shown filled with thyroglobulin, also called colloid. The thyroid epithelial cells which secrete thyroglobulin into the lumen of the follicle line the follicles. (b) An enlargement of a section of the gland.

In a cross-section of the thyroid gland (Fig. 2) a large number of follicles can be seen with cells lining the inner face of each follicle. These cells secrete a protein material called *thyroglobulin,* which is discharged into and is stored in the cavity or lumen of each follicle. This material is called *colloid* and contains the hormones of the thyroid gland.

In the secretion of the colloid, the thyroid gland picks up iodine from the blood and the iodine becomes attached to tyrosine (an amino acid) of the thyroglobulin molecule. The thyroglobulin remains in the thyroid gland. It does not normally pass into the blood.

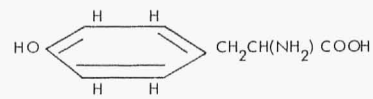
For the thyroid hormones to be released into the blood, the thyroglobulin is digested and broken down into its constituent amino acids, just as food protein is digested in the intestinal tract before being absorbed into the blood.

The two thyroid hormones are thyroxine and triiodothyronine. These hormones leave the thyroid gland and circulate in the blood stream. The hormones leave the blood and are picked up by all the cells of the body where they play important roles in the normal functioning of the cells of the entire body.

SYNTHESIS OF THYROID HORMONES

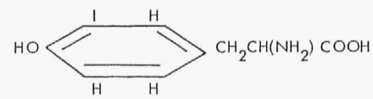
The thyroid cells secrete a protein called thyroglobulin. This protein contains the usual amino acids characteristic of the globulins, but one amino acid is of special importance—tyrosine.

TYROSINE

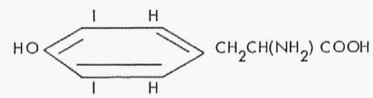


Tyrosine has the capacity of picking up iodine from the blood to form mono- and di-iodotyrosine.

MONOIODOTYROSINE

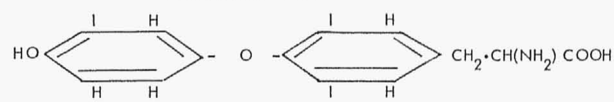


DIIODOTYROSINE



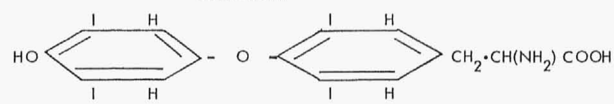
Then monoiodotyrosine and diiodotyrosine are oxidatively coupled with the loss of one alanine side chain to form triiodothyronine.

TRIIODOTHYRONINE



The final step in the biosynthesis of thyroxine is the coupling of two molecules of diiodotyrosine.

THYROXINE



These changes occur in the thyroglobulin in the lumen of the thyroid follicle.

For the triiodothyronine and thyroxine in thyroglobulin to enter the blood, the protein first has to be digested. Then the two iodinated amino acids are able to reach the blood.

The synthesis of thyroactive iodinated casein follows a similar pathway. Fortunately, the milk protein, casein, is rich in tyrosine.

When solutions of casein are iodinated the tyrosine present is converted to diiodotyrosine. The diiodotyrosine is then oxidatively coupled (combined with oxygen) to form thyroxine. The only difference between thyroglobulin of the thyroid gland and that of thyroactive casein is the protein with which it is associated. Upon digestion, the same hormone—thyroxine—is released in both cases.

Since thyroxine is an amino acid, it may be fed either as desiccated thyroid tissue or as synthetic thyroprotein. Following digestion the hormone is absorbed by the blood and is of value as a substitute for the thyroxine coming from the thyroid gland.

EFFECTIVENESS OF THYROID PREPARATIONS

Wiberg *et al.* (1962) reported that the thyroid glands of cattle and sheep contained one part of triiodothyronine to three parts of thyroxine. It may be assumed that the two hormones are secreted into the blood in the same ratio.

The question arises as to the effectiveness of these two hormones. Premachandra *et al.* (1961) used thyroxine and triiodothyronine to inhibit the secretion of pituitary thyrotropin and thus the discharge of thyroidal I-131 in dairy cattle. They found that the mean ratio in 22 cows was 1:2.14, indicating that triiodothyronine (L-T_3) was slightly over twice as effective as thyroxine (L-T_4).

It has been recognized for many years that the thyroid hormones are iodinated amino acids and upon the digestion of thyroglobulin or of thyroprotein these amino acids are absorbed into the blood just as other amino acids are absorbed.

In recent years, studies have been conducted to compare the efficiency of oral and intravenous or subcutaneous administration of thyroid hormones in dairy cattle. Mixner and Lennon (1960) reported that in two groups of lactating cows the efficiency of oral absorption of thyroprotein was 12.3 and 13.9 percent, compared to intravenous administration. Comparable data on L-T_4 indicated an efficiency of 11.6 percent.

Premachandra *et al.* (1960) used the thyroxine secretion rate technique in cattle. Thyroprotein containing 1.0 percent L-T_4 was found to be 10 percent as effective when given orally as when injected. Bauman and Turner (1965) used 10 non-lactating cows to compare the oral effectiveness of L-T_3, L-T_4, and thyroprotein. In this study, L-T_4 was 9.4 percent as effective orally and L-T_3 was 21.4 percent as effective orally as was injected L-T_4; thyroprotein was 9.9 percent as effective orally as by injection. The study with L-T_3 confirms the earlier study indicating that L-T_3 is about twice as active as L-T_4 either by injection or orally.

The oral effectiveness of thyroid hormones is much higher in single stomached animals. Bauman and Turner (1966) reported that L-T_4 was 37.9 percent and thyroprotein, 36.2 percent as effective when given orally to rats as when injected subcutaneously. Srivastava and Turner (1967) reported that male and female fowls showed about 60 percent effectiveness of thyroprotein orally, compared with injection.

The low oral effectiveness of thyroxine and thyroprotein in ruminant animals has not been explained. The fact that only about 10 percent of the thyroxine content of thyroprotein or of thyroxine in the free form is biologically active in cattle indicates the relationship between the thyroxine secretion rate of cattle determined by subcutaneous injections and the equivalent amount of thyroprotein required. Since thyroprotein contains 1 percent thyroxine, each gram would contain 10.0 mg of thyroxine. Of this, 10 percent or 1 mg would be effective. When cows are fed 10 g of thyroprotein per day per 1000 pounds body weight, they would absorb 10 mg of thyroxine.

GENERAL FUNCTIONS OF THE THYROID HORMONES

Metabolic Rate.

The cells of the body use the energy in the blood (sugar and fat) to carry on their normal functions. In this process oxygen (O_2) is utilized, heat is produced, and carbon dioxide (CO_2) is eliminated through the lungs. The speed with which O_2 is used by the cells and with which CO_2 is produced is called the *basal metabolic rate* (BMR). In animals whose thyroid glands have been removed, the basal metabolic rate of the cells is reduced. Then when the thyroid hormones are administered in graded levels, the metabolic rate of the cells is increased gradually, the cells become more active, and more heat is produced by the body.

In normal animals, the rate of secretion of the thyroid hormones regulates, in part, the metabolic rate.[2] If the thyroid hormone secretion rates are low, the metabolic rate is low and the cells of the body function at a low level.

The thyroid hormones have been compared to the draft in a furnace. When the draft is opened, the fire burns more rapidly and more heat is produced. When more thyroid hormone is available, the body cells consume more energy (sugar) and function at a higher level. Thus in the fall and winter as the

[2] The adrenal cortical hormones (glucocorticoids) also stimulate the basal metabolic rate.

environmental temperature decreases, the secretion of the thyroid hormones increases to maintain normal body temperature.

While more energy is used by animals secreting higher levels of the thyroid hormones and the body maintenance requirement is increased, the beneficial effects upon the activity of the body cells far outweighs the increased energy requirements.

Relation of Thyroid Hormones to Growth Rate

If the thyroid glands are removed from young animals, the growth of the animal slows down and soon stops (Fig. 3). If thyroid hormone is not administered, the animals remain small throughout their life.[3] The reproductive process is slowed down and may stop completely. Hair and horn growth is greatly reduced. While the animals consume less feed because they have a low metabolic rate, *they are of little value as they do not grow normally* (Fig. 4).

If thyroidectomized animals (animals with their thyroid removed) are administered graded amounts of the thyroid hormone, then their growth is resumed, feed consumption is increased, and they become productive animals again. Similarly, in animals with low normal thyroid hormone secretion rates, their growth rate is slow and it takes longer for them to reach maturity. *They are less efficient animals.* When cows have an optimal thyroid hormone secretion rate, they grow more rapidly and eat more feed but the feed required to make a pound of gain is less because they reach a marketable weight or a reproductive state earlier. Maintenance feeding is required for fewer days.

That cattle may secrete less than optimal levels of thyroid hormone has been shown in several experiments. Dryendahl (1949) reported that the feeding of thyroprotein to growing cattle resulted in an increase in weight and in both body height and length. Body fat was reduced.

In an experiment with identical-twin heifers, Hancock *et al.* (1955) administered thyroxine to six pregnant animals for a period of six months. Three of the six twins showed marked increases in height at withers in comparison with their control mates. While body weight gains were less in experimental twins than in the control twins after the cessation of injections, the treated heifers had gained at a more rapid rate during injection so that at calving time the weight difference was negligible.

Why Thyroid Hormones Influence Growth

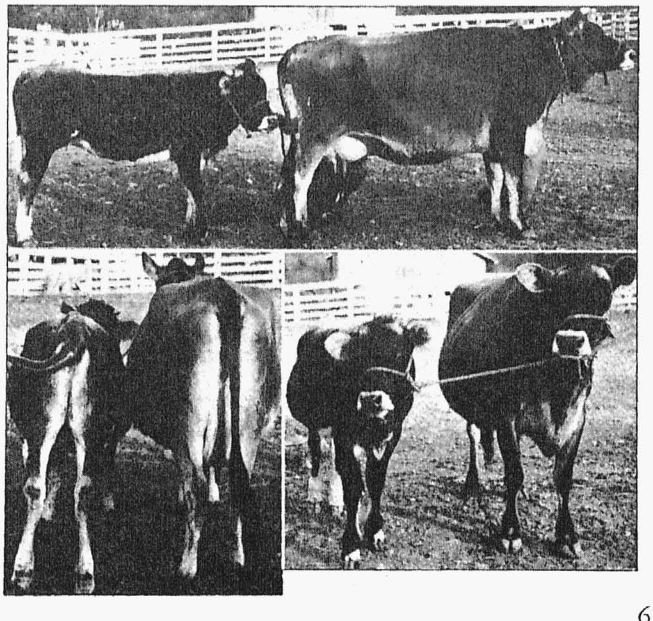
The growth hormone secreted by the anterior pituitary regulates body and skeletal growth. When the pituitary is removed from young animals, growth ceases due to the absence of growth hormone. Growth also declines markedly when animals have their thyroids removed. The cause of the decline in growth may be due to the depressing effect of a lack of thyroxine upon the secretion of growth hormone. In other words, the rate of secretion of growth hormone may be regulated by the thyroxine level. When throxine secretion is low or absent, the secretion of growth hormone is depressed.

Low levels of circulating growth hormone not only limit the growth rate of cattle but also depress milk secretion by depressing milk protein synthesis.

[3] Brody and Frankenbach (1942) compared a Jersey calf thyroidectomized at 54 days of age with a normal calf. The growth rate began to decline after a month. Between 8 and 18 months the weight gains were 100 lbs. compared to 250 lbs. for the control. Practically no weight gain was made between 18 and 40 months, whereas the control increased from 700 to over 1000 lbs. The skin was dry and scaly, hair short, horns failed to grow. Metabolic rate 40 percent below normal, heart rate reduced. Completely undeveloped sexually.

When this heifer was fed thyroprotein, her metabolic rate increased to normal, body growth began, hair and horn growth occurred, and sexual cycles and udder growth were observed.

Fig. 3—Comparison of a Jersey heifer thyroidectomized when 54 days of age with a normal heifer when both were 40 months of age. Note retardation of growth and development. Her skin was dry and scaly, hair short, lacked horn growth and never showed signs of heat. (Figure 1 of Mo. Res. Bul. No. 349)



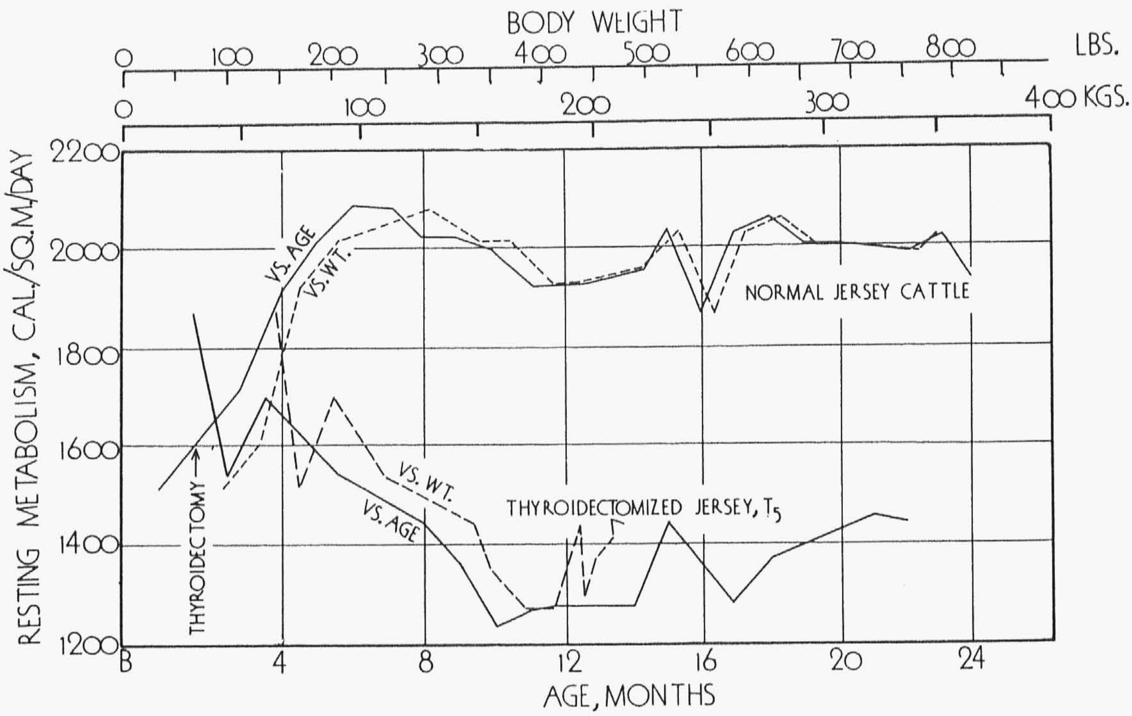


Fig. 4—Comparison of growth of a thyroidectomized and a normal Jersey heifer. Note that growth ceased at about 20 months of age in the thyroidectomized animal. (Fig. 2 - Mo. Res. Bul. No. 349)

Recently, researchers have demonstrated the thyroid hormones have a direct effect upon the incorporation of amino acids into protein in the cells of the body. This action would also favorably influence body growth and milk protein synthesis.

Relation to Reproduction

Low levels of thyroid hormone secretion have an unfavorable effect upon the reproductive organs of both males and females. Ovarian cycles may decrease or stop entirely and the various hormones secreted may be reduced. In some species, such as cattle, the ovarian cycles have been observed to occur without showing an estrus period (heat); i.e., the cows do not accept the bull (Spielman, *et al.,* 1945). This condition has been called a "silent heat period." It is due to insufficient production of estrogen and progesterone, which stimulate receptivity of the cow.

Similarly, in bulls it has been reported that semen production (sperm) continues but the bulls lack the normal sex urge (libido) and will not mate with the cow (Petersen *et al.,* 1941). Thus, under normal herd management, such animals would be considered non-breeders. Many dairy cattle with presumed low thyroid hormone secretion rates show these same deficiencies and show improvement of libido when thyroid hormones are administered.

Reineke (1946) reported the feeding of thyroprotein to 14 bulls (average age 8 years) which had poor breeding records. Of this number, 10 showed improvement in vigor and libido. Definite evidence of improvement in the conception record was observed in four cases.

Some cows with borderline thyroid deficiency may have calves which are weak or dead at birth.

Relation to Feed Consumption

Body growth and milk production are dependent upon the nutrients absorbed from the digestive tract. If the appetite is poor, the amount of nutrients absorbed from the digestive tract will be low and milk production will suffer.

It has been shown in many experiments that animals secreting larger amounts of the thyroid hormones have a better appetite. In such animals the rate of passage of food through the digestive tract is speeded up. Absorption of nutrients from the tract is also improved. This is due to the increased activity of the cells lining the digestive tract and to the increased secretion of the digestive enzymes.

Part of the nutrients absorbed by cows being stimulated by optimal levels of the thyroid hormones is utilized by the increased metabolic rate of the cells of the body. However, the rest of the feed is utilized for more rapid growth and for increased milk production.

That the thyroid hormones increase feed consumption has been shown by the injection of thyroxine or by the feeding of thyroprotein. To take advantage of the increased appetite of such animals, it is important to provide more feed of high energy content. If the appetite is stimulated and the metabolic rate is increased and more feed is not provided, the cow will use stored body nutrients first, then body tissues. The animals will lose body weight and milk production.

Evidence that the thyroid hormones influence appetite is shown also by the seasonal variation in appetite. During cold winter months, when thyroxine secretion is at a peak, the appetite is keen and milk production is maintained at a high level. In hot summer months, thyroxine secretion declines to about one-third of the winter level; appetites decline and milk and fat production is greatly reduced.

If the thyroxine level of the blood is maintained by feeding thyroprotein during summer months, the appetite can be maintained and the usual summer slump in milk production can be avoided, provided high energy feed also is supplied. If the full potential of cows with high normal thyroid hormone secretion rates and good appetites is to be realized, they must be fed up to their full appetite to get maximum milk production.

Relation to Heart Rate

If the thyroid glands of animals are removed, the heart rate declines in association with the decreased metabolic rate and reduced feed intake. Less nutrients are required by the body and the rate of blood flow is reduced. As increasing levels of thyroxine are administered, the metabolic rate of the cells increases, the appetite is increased, and more nutrients are required by the cells (Sykes *et al.,* 1947-1948).

As the heart rate increases the volume of blood flowing to the various parts of the body increases. The increased flow of blood is of special importance to the secretion of milk.

It has been shown that 300 to 400 pounds of blood must flow through the cow's udder to enable the glands to secrete one pound of milk. In a 24 hour period, cows producing 50 pounds of milk per day require a blood flow of 15,000 to 20,000 pounds; those producing 75 pounds of milk require a blood flow of 22,500 to 30,000 pounds; and those producing 100 pounds of milk require a blood flow of 30,000 to 40,000 pounds.

Obviously highly productive cows must have a higher heart pumping rate to move this large amount of blood through the udder. Cows with optimal secretion of the thyroid hormones have heart rates above the average and cows administered thyroid hormones show moderate increases in heart rate.

Relation to Udder Growth

The growth of the udder of cattle occurs during pregnancy and early lactation. The ovarian hormones, estrogen and progesterone, stimulate the growth of the lobule-alveolar system during pregnancy. Little is known about the role of the thyroid hormone in udder growth, but we do know that in thyroidectomized cows little udder growth occurs.

In rats, however, it has been shown that thyroxine stimulates about 25 percent more gland growth in normal pregnant animals and even in those with ovaries removed if they receive the ovarian hormones (Moon and Turner, 1960; Griffith and Turner, 1961). If dairy cattle respond similarly, normal cows with higher thyroxine secretion rates would have larger udders than those with low thyroid secretion rates.

If cows were fed thyroprotein during pregnancy, the hormone would tend to stimulate increased udder growth. Result of this increase in milk secreting cells should be reflected following the next calving period in increased milk yield.

In addition to the udder growth which occurs during pregnancy in rate, growth of the mammary glands occurs during early lactation. Recent research with dairy cattle indicates that the same may be true in them (Hindery and Turner, 1968).

This growth is due to the release of pituitary hormones induced by the milking or nursing stimuli. Undoubtedly, thyroxine plays a role in this growth due to the release of thyrotropic hormone. In cows fed thyroprotein, the optimal level of thyroxine in the blood should stimulate increased "lactational" growth of the udder. Thus, in addition to stimulating increased milk secretion in cells in the udder, thyroxine should stimulate growth of additional milk secreting cells in early lactation.

Effect on Milk Production

When Graham (1934a) reported that the milk yield of lactating dairy cows declined markedly when their thyroids were removed and that feeding of dried thyroid glands stimulated milk secretion in such animals, a new field of endocrine research was revealed. He then fed dried thyroid glands to normal cows in declining lactation and caused them to increase in milk yield. That the stimulating factor in the thyroid gland was thyroxine was shown by Graham (1934b) when he induced an increase in milk secretion by injecting cows with synthetic thyroxine.

A number of subsequent experiments using thyroxine and desiccated thyroid tissue confirmed the effectiveness of this hormone in stimulating increased milk and fat production in many dairy cows during declining lactation (Blaxter, *et al.*, 1949).

The daily feeding of 2 oz. of desiccated thyroid gland tissue for a period of eight weeks produced an average increase of 18.2 percent in milk yield of a group of dairy cows (Herman *et al.*, 1938). But this product cost too much to be used as a practical stimulant to milk yield.

Research to find a cheaper source of thyroxine was initiated at the Missouri Station. The success of this work will be described later.

Effect on Milk Composition

The best summary of the literature on the effect of feeding thyroprotein or the injection of thyroxine on milk composition has been presented by Blaxter *et al.* (1949). The most marked effect has been on the increase in fat percentage of the milk. This effect might have been predicted on the basis of the early studies indicating a seasonal variation in percentage of fat (Turner, 1924). It was shown that the percentage of fat gradually increased in the fall and winter, reaching a maximum during December, then gradually declined until August. These changes parallel the changes in seasonal thyroxine secretion (Fig. 5).

Under most conditions milk fat increases with a decline in milk yield. The effect of thyroprotein is the opposite: Milk yield increase is associated with an increase in percentage of fat. The percentage increase in fat yield however, is greater than the increase in milk yield.

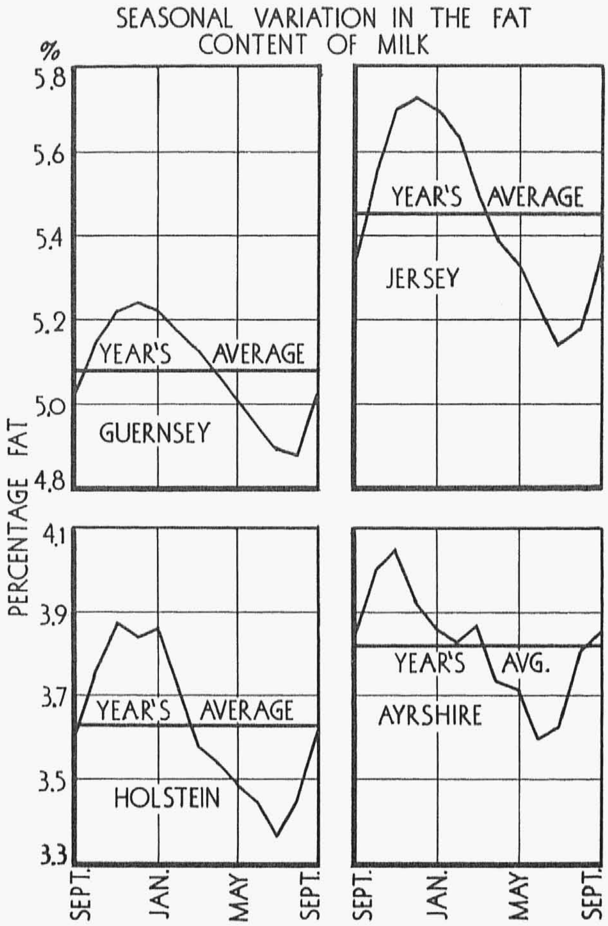


Fig. 5—Seasonal variation in the fat content of milk. It has been known for many years that the percentage of fat in milk gradually declines in the spring and summer. It was suggested that these changes were due to the seasonal change in environmental temperature. In our studies it was shown that thyroxine secretion rate also varied seasonally, increasing in the fall and winter and declining in the spring and summer. When thyroprotein is fed and the level of thyroxine in circulation is raised, fat secretion is stimulated just as it would be by a low environmental temperature.

Reece (1947) reported that in long term thyroprotein-feeding there was no indication of a decline in the response in fat percentage.

The solids-not-fat content of milk increases during thyroprotein-feeding. This is due primarily to a 5 to 10 percent increase in lactose. Thus the total lactose yield is considerably increased. It is interesting to note that several studies of solids-not-fat (S.N.F.) indicate that the lowest S.N.F. occurs in the summer and the highest in the winter, as in the case of fat.

The effect of thyroprotein feeding on the protein content of milk is still controversial. Some investigators have observed a decline in milk protein, others have observed no change. Since recent research has shown thyroxine stimulates increased protein synthesis in body cells, there appears no reason for milk protein synthesis to be depressed. If it occurs it may be due to the increased yield of milk stimulated and the inability of the mammary glands to increase milk protein synthesis at the increased rate.

Vitamins of Milk

The experiments which have been reported indicate that the feeding of thyroprotein does not influence the carotene content of milk. Some studies have indicated that there is no change in the vitamin A content but others have suggested that a decline occurs. It should be pointed out that the increase in milk fat secretion stimulated by thyroprotein would require increased amounts of vitamin A to maintain a constant level in the fat.

Research indicates the vitamin C content of milk is decreased by thyroprotein, whereas the injection of thyroxine is without effect. It has been suggested that the iodine in thyroprotein causes the decrease.

A steady increase in vitamin C has been observed in Holstein and Guernsey cows from November to February, followed by a drop to May, but other investigators have observed no seasonal variation.

Feeding thyroprotein to cows results in an increase in the niacin content of milk. The effect on the pantothenic acid content has not been reported. Some investigators have reported that thyroprotein slightly reduced the riboflavin content of milk but others have observed no effect.

All of the research on the effect of thyroprotein feeding on milk composition leads to the conclusion that the milk is a perfectly safe and nutritionally adequate food for human nutrition. Associated with the increase in milk yield are increases in fat and lactose contents. The vitamin content is little affected with the exception of vitamin C, which may be decreased. Since milk is not considered an important source of vitamin C, the possible fall in vitamin C is not considered of great importance in human nutrition.

THYROXINE IN MILK

Since thyroid hormones circulate in the blood, the question arises as to the presence of these hormones in the milk secreted by dairy cattle. Early studies of this problem were inconclusive. When thyroprotein was developed and fed to increase the level of circulating hormone, it became of importance to determine whether the mammary glands were permeable to thyroxine and if the higher levels of the hormone in the blood would increase the thyroxine content of milk.

In a series of experiments, it was shown conclusively that the feeding of thyroprotein to dairy cattle did not increase the thyroxine content of milk. In fact, it appeared that thyroxine in the blood did not pass through the cells of the udder into milk. In other words, the mammary glands are not permeable to the thyroid hormones.

IODINE IN MILK

In contrast to the lack of thyroxine in milk, inorganic iodine has been recognized as one of the most permeable of the inorganic constituents of the blood. As the iodine content of the diet of cattle increases, there is an increase in the iodine content of milk. The amount transferred from the blood to the milk varies greatly in various species. In the dairy goat, from 25 to 50 percent of the iodine administered is incorporated in the milk. By the use of radioactive iodine (I-131) it is possible to measure the rate of transfer very accurately. Lengemann and Swanson (1957) reported that about 6 percent of orally-administered I-131 was secreted into the milk during seven days by dairy cattle.

In a later study by Premachandra and Turner (1961) with dairy cattle, following the injection of I-131, 5.8 percent appeared in the milk in 24 hours and 8.2 percent during a five-day period. When these same cows were injected with thyroxine 50 percent above their secretion rate, milk yield was increased 22 percent, but the iodine in the milk during the first 24 hours was reduced to 2.9 percent of the injected dose, a reduction of 50 percent. During five days it was reduced to 4.8 percent, a reduction of 41 percent. These data indicate that less I-131 is secreted in the milk of cows during mild hyperthyroidism. In the event that nuclear fall-out should occur in the future, it is reassuring to know that the milk of the dairy cow would contain relatively little I-131 and that milk from cows of higher thyroxine secretion rates would tend to have lower I-131 content.

Binnerts (1956) has made an extensive study of the iodine content of milk produced by cows in the

Netherlands. It is reported that the average iodine content varies between 3 and 7 ug per 100 ml of milk. During the first few days of lactation the iodine concentration seems to be high (colostrum). In the course of lactation the iodine content of the milk rose with declining milk yield. A drastic decline in milk iodine occurred when cows were put out to pasture in the spring and a reverse occurred in the autumn.

Lengemann *et al.* (1957) noted a rise in concentration of I-131 in milk from a low value during January to a high in May. Binnerts (1964), however, is of the belief that not all of the seasonal (temperature) change in iodine content of milk is due to temperature and increased thyroxine secretion in the winter. It does not explain the drastic decline in milk iodine when cows are turned on pasture.

THYROPROTEIN (THYROACTIVE IODINATED CASEIN)

Years of research culminated in the synthesis of thyroprotein, a product quite similar to that produced by the thyroid gland. In the thyroid gland of the cow, iodine is picked up combined with a blood protein called globulin. This is in turn converted to thyroglobulin, which contains the thyroid hormones.

It was discovered that the milk protein, casein, could be iodinated by mixing iodine with a solution of casein. By a further process the iodinated casein was changed so that thyroxine was formed. Thus the synthesis of thyroxine by the thyroid gland via thyroglobulin was duplicated by the synthesis of thyroactive iodinated casein in the laboratory. The only difference between these two products is the protein—globulin and casein. The hormone in both cases is thyroxine.

However, the best product of the thyroid gland contains only one-third as much hormone as does thyroprotein. In the manufacture of thyroprotein, the thyroxine content is standardized at 1 percent, so that a product of known potency is always used.

Thyroprotein, or *protamone,* as it is known commercially, has been used both experimentally and commercially in dairy cattle for many years to increase the milk and fat production.

CONTROL OF THE THYROID GLAND

Under ideal environmental conditions of feed and temperature, each animal inherits the ability to secrete a certain level of the thyroid hormones. This level varies greatly in individual animals. Some cows have received an inheritance for only low levels of secretion, many cows are intermediate (average) and some secrete high levels of the hormone. To breed dairy cows which secrete optimal amounts of the thyroid hormones should be the objective of dairy cattle breeders, for only such animals will grow rapidly, have good reproductive performance, have large udders, and secrete large amounts of milk.

During the past few years much progress has been made in understanding the mechanisms controlling the secretion of the thyroid gland.

The Pituitary and Hypothalamus

The *pituitary gland* is located at the base of the brain and is connected to the brain by a structure called the stalk. It is divided into two important parts, the *anterior* and the *posterior* lobes.

The posterior lobe secretes two hormones called oxytocin and vasopressin. Oxytocin, or the milk "letdown" hormone, is an important aid in the removal of milk at milking time. Its role in milk production will be described in a later bulletin.

The anterior lobe secretes a number of important hormones, including: (1) The gonadotropins, follicle stimulating hormones (FSH), and luteinizing hormones (LH) which act upon the ovaries and testes to regulate the reproductive process; (2) the lactogenic hormone which stimulates milk secretion; (3) adrenal corticotropic hormone (ACTH) which stimulates the secretion of hormones by the adrenal cortex; (4) the growth hormone which stimulates growth of the skeleton and muscles (general body growth); and (5) the thyrotropic hormone (TSH).

The anterior lobe of the pituitary is free of nerve fibers. Therefore, nervous stimuli cannot reach the anterior lobe directly. However, it is known that various nervous stimuli do affect the hormones secreted. The way the nerves transmit their stimuli to the anterior lobe has been discovered recently.

The Relation of the Hypothalamus to the Anterior Pituitary. It has been known for many years that the anterior pituitary secreted a hormone called the thyroid stimulating hormone (thyrotropin or TSH). This hormone acts upon the thyroid gland to stimulate the secretion of the thyroid hormones. In its absence, the thyroid gland secretes only minute amounts of hormone.

Regulation of secretion rate of the thyroid-stimulating hormone (TSH) was thought to be located in the anterior pituitary, but since the anterior pituitary was not connected to the nervous system, it was not possible to explain how nervous impulses could influence TSH secretion.

Recently, it has been shown that an area of the hypothalamus secretes a hormone or factor called the *TSH-releasing factor,* which flows down the portal blood vessels from the brain to the anterior lobe. The lobe in turn stimulates the secretion and release of TSH into the blood for action upon the thyroid gland.

Since the hypothalamus is connected with the central nervous system, neural stimuli such as heat and cold can influence the TSH-releasing factor and in turn the rate of thyroid hormone secretion.

Relation of Pituitary TSH Secretion and Thyroxine Secretion

Under ideal environmental conditions (temperature and nutrition), the daily secretion of thyroxine by each dairy cow is quite uniform and a constant level of thyroxine is maintained in the blood. This constancy in the level of thyroxine is maintained by an interesting mechanism called the "feed-back" mechanism. This feedback functions between the rate of secretion of TSH by the pituitary and the secretion of thyroxine by the thyroid gland to maintain the balance. Each dairy cow inherits a certain fixed relationship between these two hormones. As the pituitary secretes TSH into the blood, the secretion of thyroxine is stimulated. When the level of thyroxine exceeds the normal for that animal, the thyroxine acts upon the pituitary to depress the secretion of TSH, which in turn depresses thyroxine secretion slightly, and causes it to return to the normal for that cow.

When cows are subjected to an increasingly cold environment in the fall and winter or to increasing heat in the spring and summer, this normal "feed-back" mechanism becomes altered. Increased levels of blood thyroxine are secreted before TSH secretion is blocked during cold weather. Smaller levels of thyroxine block TSH secretion during hot weather. By this mechanism thyroxine secretion is increased above normal cold weather and decreased below normal during hot weather.

Recent research in our laboratory suggests that the hypothalamus which can receive neural stimuli concerning temperature variation, is responsible for altering the "feed-back" mechanism.

DETERMINING THYROID HORMONE SECRETION RATE (TSR)

The "feed-back" mechanism which controls the normal thyroid hormone secretion rate also provides a method by which the secretion rate may be determined.

If graded amounts of thyroxine are injected into a cow, the level of thyroxine in the blood is increased. The above-normal level of thyroxine acts upon the pituitary and reduces the secretion of TSH. As the blood level of TSH is reduced, the secretion of thyroxine is reduced. When the amount of thyroxine injected equals the normal thyroxine secretion rate, TSH secretion is entirely stopped. The absence of TSH in the blood stops the secretion of thyroxine by the thyroid gland and the cow becomes entirely dependent upon the injected thyroxine (Fig. 6).

Thus, the administration of thyroxine does not supplement the cow's own secretion; it blocks it.

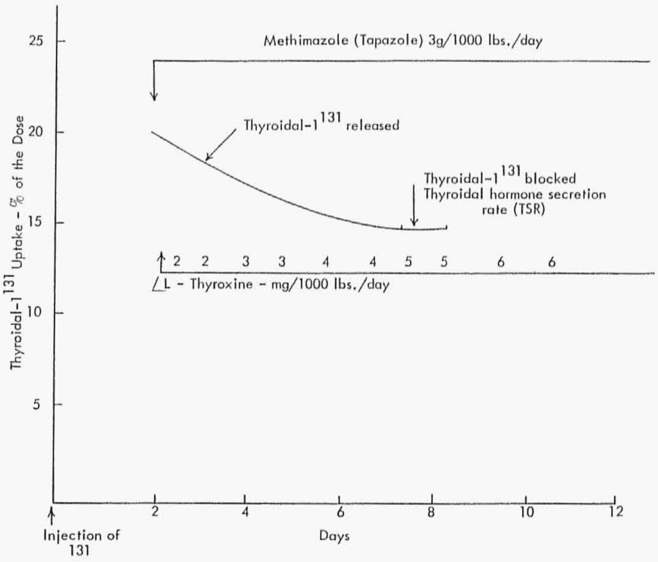


Fig. 6—Estimating thyroid hormone secretion rate (TSR). Iodine-131 is injected into the cow. In the example 20 percent of the dose was picked up by the thyroid gland by the second day. After this time, the thyroidal-I-131 begins to be released into the blood and the amount of I-131 left in the thyroid gland begins to decline. Methimazole is given daily to block the reutilization (uptake) of I-131 from the thyroxine which is metabolized with the release of free I-131. Thyroxine is then injected daily for two days at a level below the estimated secretion rate. After two injections, the level of thyroxine is increased until an amount is reached which blocks the release of thyroidal-I-131. This blockage of release is due to the injection of thyroxine which blocks the secretion of the thyroid stimulating hormone (TSH) which in turn stops thyroxine secretion. The level of thyroxine which blocks thyroidal I-131 release is considered the thyroid hormone secretion rate (TSR).

To increase the circulating thyroxine, it is necessary to inject or feed thyroxine in excess of the cow's own secretion rate.

The action of thyroxine in blocking TSH secretion and, in turn, thyroxine secretion has been employed as a method of determining thyroid hormone secretion rate (Premachandra *et al.*, 1960). Thyroxine contains iodine. If radioactive iodine (I-131) is injected into a cow it is picked up by the thyroid gland and within several days the thyroxine secreted contains I-131. The total radioactivity in the thyroid gland can be measured by instruments. As the thyroxine I-131 is secreted into the blood, the amount of I-131 left in the thyroid gland declines gradually until it has all been secreted. If the radioactivity left in the thyroid gland is measured every other day, the rate of discharge can be determined.

However, if thyroxine is injected each day into a cow in increasing dosages, it gradually blocks the secretion of TSH, which in turn decreases the rate of discharge of thyroxine I-131. When the amount of thyroxine injected just equals the cow's own thyroxine secretion rate, TSH secretion is stopped and no more thyroxine I-131 is discharged from the thyroid gland. The cow's thyroxine secretion rate is defined as the minimum amount of injected thyroxine which blocks its discharge from the thyroid glands, as measured by the amount left in the thyroid gland.

Thyroxine secretion rates (TSR) of many dairy cattle have been determined by this method.

VARIATION IN THYROXINE SECRETION RATE (TSR)

During the winter months (October to April) a total of 106 thyroxine secretion rates were determined in Jersey, Guernsey, Holstein, and Brown Swiss cows in Missouri. The average TSR per 1000 pounds body weight was 5.4 mg of thyroxine per day. The greatest frequency in TSR was 5 to 6 mg per day (Fig. 7). Thus, individual cows vary widely in their inherited TSR under low environmental temperature.

At Columbia, Mo., the Weather Bureau reports the mean seasonal variation in temperature as follows: January-February, 30°F.; March-April, 49°F; May-June, 71°F; July-August, 76°F; September-October, 67°F; and November-December, 38°F. The mean temperature of the six winter months would be 39°F; whereas, the six summer months would average 71°F; a difference of 32°F.

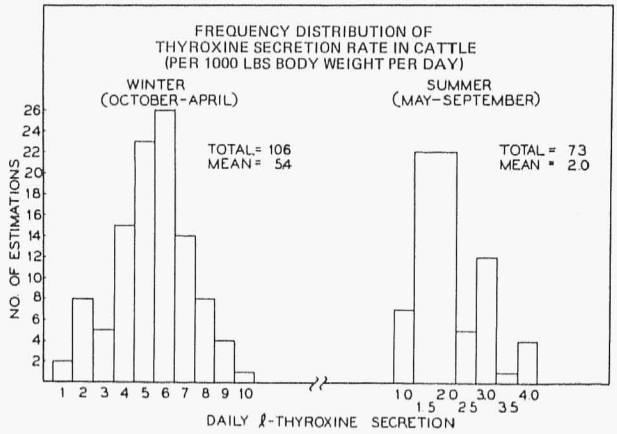


Fig. 7—A study showing the frequency distribution of thyroid hormone secretion rate in dairy cattle during the winter (Oct.-April) and summer (May-Sept.) in Missouri. During the winter months, the animals showed a range from 1 to 10 mg/1000 lbs. body weight. The greatest number secreted from 4 to 7 mg. with an average of 5.4 mg/1000 lbs. During the summer months the secretion rate declined to 30 to 40% of the winter rate. The average secretion rate was only 2.0 mg/1000 lbs. body weight.

The feeding of thyroprotein at the winter level in Missouri would begin in October as the mean temperature begins to decline. The summer level would be fed beginning in June when higher summer temperatures begin. In other parts of the United States, one would be guided by the local temperature variation.

Effect of Summer Temperature on TSR

The TSR for 73 of the same cows was also determined during the summer months (May to September). The average TSR of these cows was 2.0 mg per 1000 pounds per day. The greatest frequency was 1.5 and 2.0 mg and the total range was 1.0 to 4.0 mg. While the decline in TSR during the summer was more marked for some cows than others, these cows secreted only 30 to 40 percent as much thyroxine in the summer as in the winter (Fig. 8).

The decline in secretion rate in the spring occurs more rapidly than the increase in the fall. This has been shown to be true in experimental animals. When they are shifted from cold to warm temperatures, the TSR declines very rapidly. When they are shifted from room temperature to a cold environment, the TSR may continue to increase for many months. The TSR would be expected to gradually increase so long as the temperature in the winter remained low, but to begin to decrease as warmer weather approached.

As the thyroxine secretion rate is related to appetite and milk yield, it is clear why the milk yield and fat percentage decline in the spring and summer. It also explains why dairy cattle in the northern United States produce more milk on the average than those in the southern states, where higher summer temperatures prevail.

PROBLEMS IN THE FEEDING OF THYROPROTEIN

When thyroprotein is fed to dairy cows in declining milk yield, a marked average increase in milk and fat yield occurs. Some cows increase only slightly, other cows show a very marked increase. On the average, an increase of 20 to 30 percent has been observed.

In the early studies, the amount of thyroprotein to feed daily was determined by trial and error. When excessive amounts were fed, the milk yield was increased but the cows were not able to eat sufficient feed, and excessive body weight losses were observed.

As a result of extensive research at the Missouri Agricultural Experiment Station, many of the problems of the proper application of thyroprotein to dairy cattle have been solved.

Level of Thyroprotein Feeding—Winter

Once the normal range in thyroxine secretion in dairy cattle (from 1 to 10 mg. per 1000 pounds body weight per day) had been determined, it was possible to estimate the amount of thyroprotein to be fed daily to equal the animal's secretion rate.

Results of a number of studies (Premachandra *et al.,* 1960; Bauman, 1965) showed that the feeding of 1 gm of thyroprotein equaled 1 mg in thyroxine secretion rate. In other words, if a cow secreted 5 mg thyroxine per day per 1000 pounds body weight, daily feeding of 5 g of thyroprotein would be required to equal her thyroxine secretion rate. This level of feeding thyroprotein would block the secretion of thyroxine by the cow, but would have no beneficial effect upon her milk production. In order to stimulate an increase in milk yield, it is necessary to feed thyroprotein in excess of the cow's thyroxine secretion rate.

Two experiments were conducted with lactating cows to determine the level of thyroxine in excess of the secretion rate which would stimulate the greatest yield of milk. In the first experiment (Premachandra and Turner, 1962), nine lactating cows were injected with thyroxine daily at a level 50 percent above their individual winter secretion rates during the spring and summer. All of the cows reached their peak production within four weeks. The mean increase in milk yield was 27.6 percent, with a range from 12.1 to 67.9 percent.

In a second experiment, two groups of cows were first injected with thyroxine 25 percent above their secretion rate (Hindrey and Turner, 1965). Six mature cows in advanced lactation and producing an average daily yield of 46.9 pounds in the third week increased to 56.1 pounds of milk, an average increase of 27.0 percent with an individual range from 8.5 to 81.2 percent. Twelve other heifers had been induced to lactate experimentally by the injection of the estrogenic hormone. Five heifers only 18 months of age increased 31 percent in milk yield with a range from 8.7 to 62.9 percent. The seven other heifers ranged from two to four years of age. They increased 34 percent in milk yield with a range from 11.6 to 62.0 percent.

After seven weeks on 25 percent above their thyroxine secretion, the thyroxine was increased to 50 percent above normal.

Of the six normal cows, three showed a further slight increase in milk yield and three did not. Three of the five 18-months-old heifers showed further increases in production and four of the six two- to four-year-old heifers showed further increases. It would appear that thyroxine at a level 25 percent above the secretion rate stimulates marked increases in milk yield. However, about half of the cows would have responded still better if 50 percent above the secretion rate had been injected.

The maximum thyroxine secretion of dairy cattle observed in our studies has been 10 mg per 1000 pounds body weight in a very few cows. It is desirable to feed thyroprotein at a level about 50 percent above their secretion rate. *The recommended feeding level of thyroprotein during the winter months is of 10 g per 1000 pounds body weight.* This level would equal the highest secretion rate and would provide a 50 percent or greater increase above the secretion rate of animals secreting up to about 7 mg per day per 1000 pounds body weight. As noted by the frequency distribution (Fig. 7), only a few cows exceed this level.

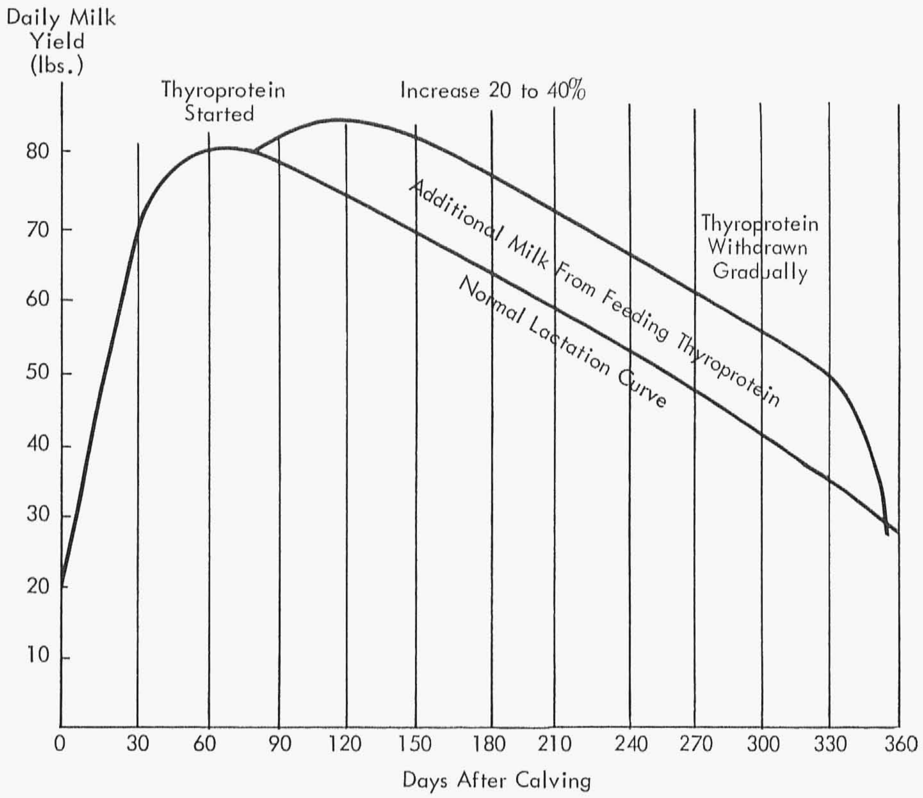


Fig. 8—Lactation response to feeding of thyroprotein. Milk yield may increase 20 to 40 percent, then decline parallel to the normal lactation curve. When thyroprotein is withdrawn gradually, the milk yield will decline to the level of the normal lactation.

Level of Thyroprotein Feeding—Summer

During the summer months, the thyroxine secretion rate declines in dairy cattle. At this time cows have an increased problem in the dissipation of body heat. The thyroxine secretion rate declines so that heat production will be reduced.

If thyroprotein feeding is continued at the winter level, excessive heat may be produced and body temperature may increase above normal.

In areas of high summer temperature associated with low humidity, cows are able to dissipate excessive heat much better than in areas where high humidity and temperature prevail.

Further, in areas where high day temperature is followed by cool nights, cows are able to tolerate the higher heat produced by thyroprotein feeding.

To maintain normal milk production and increased fat secretion during the summer months, thyroprotein should be fed. It is recommended that the level of feeding be reduced from 10 g per day per 1000 pounds body weight to 7.5 g per day. Since climatic conditions during the summer may vary widely in different parts of the United States, it is best to reduce the level as indicated. However, experience may indicate that in certain regions (northern states), the level recommended for the winter months may be fed safely during the summer.

When to Feed Thyroprotein

(a) During declining lactation. Dairy cattle normally increase in milk yield to a peak 30 to 60 days or more after calving, then gradually decline until dried off.

All of the early research in thyroprotein feeding was concerning with the declining phase of lactation. Milk and fat production could be increased during this phase by varying amounts, investigators found. A few cows showed little or no response. The majority of cows increased in milk yield from 20 to 40 percent; a few showed increases of 60 to 80 percent. In large groups of cows, average increases of 20 to 30 percent in milk yield could be expected (Fig. 8).

The course of the variation in response of individual cows to thyroprotein fairly clearly was related to thyroid hormone secretion rate or to other hormones limiting their milk yield.

If a cow is secreting optimal amounts of thyroid hormone, the feeding of thyroprotein will be ineffective in stimulating increased yields of milk. It is possible, also, that individual cows might be deficient in thyroid hormone but still be incapable of increased milk production because of a deficiency of some other hormone. The number of cows which show no response is quite limited.

As the inherited deficiency in thyroid hormone secretion increases, the feeding of optimal amounts of thyroprotein produces a blood level of thyroxine adequate for the stimulation of the greatest amount of milk and fat of which the cow is capable, and the total yield will increase proportionally. In many cows, the increase will amount to 20 to 40 percent above the previous yield.

If an individual cow increases 40 percent in milk yield, this indicates she is capable of secreting 40 percent more milk but has been limited by the inheritance of a thyroid hormone secretion rate 40 percent below her capacity to secrete milk (Fig. 9).

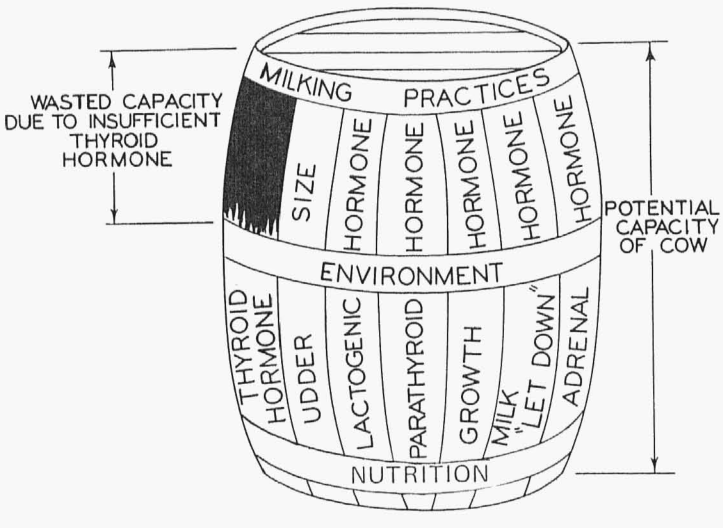


Fig. 9—The potential capacity of a dairy cow for high milk and fat production is dependent upon good nutrition with adequate protein and a high energy diet. Favorable environment and good milking practices influence this. However, fundamentally, it is dependent upon the optimum inheritance for the secretion of a number of hormones which stimulate milk production. When one of these hormones is deficient, such as thyroxine, the cow is incapable of reaching her potential capacity. By supplying optimal amounts of thyroxine, this deficiency is corrected. When a cow shows a large increase in milk yield after being supplied with thyroxine it indicates she secretes sufficient amounts of other important hormones but did not inherit ability to secrete enough thyroxine.

Thus, the response of individual cows to the feeding of thyroprotein is a valuable index of their inherited hormone secretion capacity. It does not measure secretion rate but indicates the extent of a cow's deficiency.

A few cows may increase in milk yield as much as 60 to 80 percent. Such increases not only indicate a deficiency in thyroid hormone secretion, but, more important, indicate that such cows have received an inheritance for high secretion of a number of other hormones favorable to large milk and fat production. This high potential is being masked or neutralized by a deficient thyroid hormone secretion.

Such cows have received an inheritance and potential transmitting ability for high production. Marked increases in milk yield should be expected of the progeny of such cows if they are mated with bulls with the capacity to transmit high capacity to secrete thyroxine.

In summary, the response of cows to the feeding of thyroprotein provides an excellent index of their inherited capacity for milk production. If cows show little response, it indicates that their thyroid hormone secretion rate is adequate. If they are naturally high producing cows, this indicates that other hormone secretion rates are also high. Such cows are valuable brood cows.

If low producing cows show no response to thyroprotein, their secretion rate apparently is adequate for their low yield. They are probably cows with one or more other hormone deficiencies. They should be culled.

Cows which show marked responses and high yield after thyroprotein administration are likely secreting less than optimal amounts of thyroxine but have received an inheritance for the secretion of large amounts of other hormones necessary for high milk production. The high potential milk secreting capacity of such cows can be realized by the feeding of thyroprotein. Even more important is the identification of such cows for their capacity to transmit high production to their progeny, especially if mated with dairy bulls of high thyroxine secretion rate.

When thyroprotein feeding is started after cows begin to decline in milk yield, they may continue to increase for two to four weeks before they reach the new peak of production. After the peak is reached, decline should be expected at about the same rate of persistency that would normally occur. However, this decline is based on the increased level attained, so that the net percentage increase in yield will be continued during the remaining period of lactation.

(b) At the beginning of lactation. When thyroprotein is fed starting at parturition, it is not possible to measure its effectiveness since all cows increase in milk yield for 30 to 60 days or more. There is experimental evidence indicating that when thyroprotein is fed at this time, however, the secretion of milk is stimulated, so that higher levels of maximum production will be attained.

Tucker and Reece (1961) reported on a short-time experiment with two groups of cows at the peak of production. The control group was fed three additional pounds of a high-energy grain ration during a 14-day period; the experimental group was fed this and thyroprotein in addition. The control cows showed an increase of 1.1 percent in milk yield; the cows which received thyroprotein showed an average increase of 9.9 percent (range 3.4 to 18.4 percent). Seven cows in this group attained a maximum response within seven days and three cows reached a new maximum within 14 days. Tucker and Reece concluded that the results suggested that thyroid hormone secretion rate may be a limiting factor in milk secretion at the peak of lactation.

In extensive trials at the Iowa Station, Johnson and Catron (1957) fed thyroprotein to sows for three days before farrowing and during the first week of lactation. The nursing pigs gained 27 percent more than the controls, indicating increased colostrum and milk secretion and one-third to one-half more pigs per litter were weaned. In further trials, sows were fed thyroprotein for two, three and five weeks. In all experiments, the experimental groups exceeded the control groups in pounds gained per pig.

The experiments with swine indicate that thyroprotein stimulates increased secretion of milk following farrowing during the period of two to three weeks when sows normally reach the peak of lactation.

Undoubtedly, all lactating animals, including dairy cattle, will show an increased lactation response to thyroprotein when its feeding is initiated at calving time.

Although it is not possible to measure the favorable effect of the hormone at the beginning of lactation, the total effect on a 10 month or yearly lactation may be measured. This is a truer measure of the benefit of thyroprotein. In this case it is necessary to determine the total lactational milk and fat production of a cow without thyroprotein and compare it with the total yield of the same cow under the stimulus of thyroprotein.

The percentage increase in milk and fat production of cows fed thyroprotein as compared to their previous production indicates the extent of the deficiency in thyroid hormone secretion. This observation can be used in the selection of dairy cattle for high production on the same basis as suggested for the increase in milk production caused by feeding thyroprotein during declining production.

Withdrawal of Thyroprotein

When thyroprotein is fed at a level above the cow's thyroxine secretion rate, the cow's thyroid glands stop secreting thyroxine. This is due to the action of thyroxine on the animal's hypothalamus and pituitary gland. Thyrotropic hormone is no longer secreted. If the feeding of thyroprotein is stopped suddenly, the amount of thyroxine in the blood is quickly reduced and the cow reacts just as if she had been thyroidectomized. Her milk and fat secretion may decline 30 to 40 percent or more.

Following this decline, milk production will increase, but not to the level prior to the feeding of thyroprotein. The cause of the reduction is the time required for the pituitary to return to the normal secretion of thyroprotein and, in turn, thyroxine secretion.

The time required for the dairy cow to return to normal secretion of thyrotropin and thyroxine may be measured by the injection of I-131 at intervals after the withdrawal of thyroxine. In such a study (Premachandra and Turner, 1962), it was shown that thyroidal I-131 uptake commenced 12 days after withdrawal and had returned to normal at the end of three weeks.

On the basis of this study, it was suggested that if thyroxine (or thyroprotein) was withdrawn gradually, blood thyroxine would be reduced more slowly, while at the same time the thyroid gland would begin to function gradually. In this experiment (Bauman *et al.,* 1965) a group of 18 cows and heifers was receiving thyroxine at a level of 50 percent above their secretion rate. At the beginning of the experiment, thyroxine was reduced one-half, from 150 to 75 percent of their secretion rate for one week. Next, thyroxine was again reduced one-half, to 37.5 percent of the secretion rate for two weeks. At the end three weeks, thyroxine was completely withdrawn.

In a group of six 5-year-olds, none of the cows began to pick up I-131 during the period of withdrawal. After complete withdrawal, one cow collected 5 percent of the injected iodine on the first day, a second collected 5 percent on the fourth day, two cows collected 8 percent and 3 percent on the seventh day, and two cows collected 11 percent and 8 percent on the tenth day.

Of the 12 heifers, four collected 5 percent or more during the two-week period they were on 37.5 percent of their secretion rate. After withdrawal, two heifers collected 5 percent or more on the first day, two on the fourth day, and three on the tenth day.

In the light of these observations, it is suggested that the 37.5 percent withdrawal period be extended to three weeks rather than two, so that normal secretion of the thyroid hormone will be re-established before complete withdrawal.

SUGGESTIONS FOR PRACTICAL USE OF THYROPROTEIN.

When thyroprotein was first introduced for commercial feeding to dairy cows, our knowledge concerning the best application was limited. Much progress has been made during the intervening years as a result of research and practical trials in its use.

Standardization of Product

When thyroprotein was first manufactured, it varied somewhat in thyroxine content, resulting in variations in its effectiveness. As chemical methods of determining the thyroxine content were developed, the production was standardized to contain 1 percent thyroxine; thus each gram of thyroprotein contains 10 mg of pure thyroxine.

Level to Feed

In early research on the feeding of thyroprotein to dairy cattle, it was suggested that it be fed at a level of 15 g per 1000 pounds body weight per day. On the basis of later research, it is now recommended that it be fed at a level of 10 g per 1000 pounds body weight during the winter months. While the higher level (15 g) was not harmful to the cows, and a few cows may even benefit from this amount, the reduction to 10 g saves one-third the cost of the hormone and is sufficient for most cows.

Base Feeding Level on Body Weight

It will be noted that the recommended level of feeding thyroprotein per day is based upon 1000 pounds body weight. The reason for the use of body weight rather than the stage of lactation or milk yield is due to the need of maintaining a constant optimal level of thyroxine in the blood.

Lactating dairy cattle have about 5 percent of body weight of circulating blood plasma. Thus, a 1000-pound cow has about 50 pounds of plasma in which the thyroxine circulates. If the cow weighs only 800 pounds, she will have only 40 pounds of plasma; whereas, a 1200- or 1400-pound cow will have 60 or 70 pounds of plasma.

If 10 g of thyroprotein per day is fed to an 800-pound cow, the thyroxine is diluted in 40 pounds of plasma, thus increasing the level above the optimum; whereas, if fed to a 1200- or 1400-pound cow, the circulating thyroxine would be below the optimal level due to the greater amount of circulating blood plasma.

In herds of cows weighing between 900 and 1100 pounds, feeding at the 10 g level of thyroprotein is recommended. For herds or groups of cows weighing 1200 to 1400 pounds, 12 to 14 g per head per day should be fed, and larger cows should receive proportionally more.

Since the grain mixture consumed by dairy cows varies with milk yield and stage of lactation, it is not possible to put the thyroprotein in the total grain mixture.

In herd practice, it is suggested that the thyroprotein, in the proper amount, be added to the grain mixture as a top dressing. Or, it can be mixed in part of the grain mixture so that all of the cows will receive a certain amount, then additional grain mixture without thyroprotein can be fed up to the appetite of the cow.

Feed Once or Twice per Day

When thyroprotein is fed, it is digested in the small intestine and thyroxine is gradually absorbed into the blood. Investigators have observed the peak increase in the blood in about 20 hours (Pipes, *et al.,* 1962). From this observation, it seems reasonable to conclude that thyroprotein could be fed either once or twice per day, at the convenience of the feeder.

This belief is further confirmed by the relatively slow rate at which thyroxine leaves the circulating blood. When some hormones are injected into the blood, they are quickly picked up by the cells of the body (15 or 20 minutes). In the case of thyroxine, it appears to leave the blood of the cow very slowly. Two and one-half days were required for one-half of the thyroxine to leave the blood in one study (Pipes, *et al.,* 1959). This means that of the amount of thyroxine in the blood at any time, only 28 percent of it leaves the blood each day.

When thyroprotein feeding is begun, and the thyroxine level of the blood is increased, it takes a number of days before the new higher level of blood thyroxine is reached. It has been observed that milk yield rises gradually when thyroprotein feeding is begun and the new peak of production may not be reached for as long as three or four weeks. This slow increase may be due in part to the time required for the thyroxine level to reach the new higher peak. To hasten the time required for the milk yield to reach the new peak, it has been suggested that the level of thyroprotein feeding be doubled for the first three to five days, thus increasing the blood thyroxine level more rapidly.

High Energy Ration Required

In the early experiments on the feeding of thyroprotein, it was observed that many cows lost excessive amounts of body weight. This may have been due in part to the use of 15 g per 1000 pounds per day. However, it was discovered that the principal cause was the limitation in the nutrient intake and the feeding of rations containing limited energy.

When cows were receiving thyroprotein and increasing 5 to 10 pounds per day or more in milk yield and fat percentage was increasing, the cows were unable to continue the production from the feed available and had to use body reserves. Thus, an excessive decline occurred in body weight.

The feeding of thyroprotein increases the appetite, thus aiding in furnishing the increased nutrients required for the secretion of more milk. There is no need of limiting the feed intake. Cows fed thyroprotein will not get fat when fed all they will eat.

To increase the energy content of the ration, it is important to limit bulky feeds in the grain ration. Rations should be formulated to contain the greatest amount of carbohydrates (energy) possible. When high energy rations are fed up to the appetite of the cows, losses of body weight should be no greater than in normal cows.

Feeding Thyroprotein to High Producing Cows

To cows producing 60 to 70 pounds of milk per day, the feeding of thyroprotein has usually resulted in a marked increase in milk production and the maintenance of normal body condition. However, in cows producing from 80 to over 100 pounds of milk daily, the response in milk yield may be so great that the cows cannot consume sufficient nutrients to support the stimulus for the increased production. As a result, they may lose body condition.

Cows of this type should be gradually withdrawn from the thyroprotein and not fed more hormone until they have declined to about 60 or 70 pounds per day.

It is possible that a few cows producing 60 to 70 pounds of milk per day cannot consume sufficient additional nutrients to sustain the increased milk yield of which they are capable. If they lose condition, it is advisable to withdraw thyroprotein gradually until they have declined in milk yield equal to the increase in milk yield stimulated.

Observations of this type are of interest in that they indicate that cows inherit differences in capacity to consume feed. It is highly desirable to select cows with high capacity for feed intake. Cows of very high normal milk yield which respond to thyroprotein by increased yield and yet are able to maintain body condition would prove that they have the capacity for high feed intake.

Feeding Thyroprotein to Beef Cows

Because the yield of beef cows is comparatively low, breeders of purebred beef cattle frequently use dairy animals as nurse cows to increase the rate of gain of calves. While accurate records are not available on the feeding of thyroprotein to lactating beef cattle, it is probable that some would respond with increased milk production.

In an extensive study of the thyroid hormone secretion rate in beef cattle, Pipes *et al.* (1963) observed a range from 1 to 7 mg per 1000 pounds body weight per day with a mean secretion of 2.7 mg (Fig. 10). Thus, the average beef animal secretes only one-half as much thyroxine per day as a dairy cow.

On this basis, it is suggested, tentatively, that lactating beef cows be fed 5 g of thyroprotein per day to stimulate increased milk production. While several other hormones are involved in the low milk production of beef cattle, a low thyroxine secretion rate apparently plays an important role and replacement therapy with thyroprotein would increase milk yield considerably.

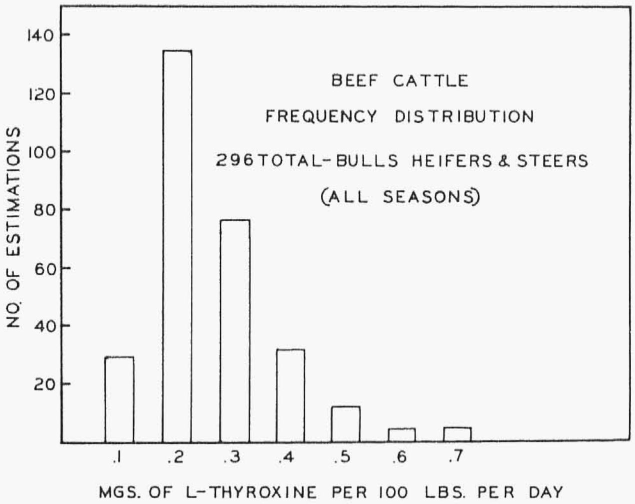


Fig. 10—A study showing the frequency distribution of thyroid hormone secretion rate in beef cattle. The secretion rate varies from a low of 0.1 mg L-thyroxine per 100 pounds body weight (1 mg/1000 lbs.) to 0.7 mg. (7 mg/1000 lbs.) for the highest. The greatest number of beef animals showed secretion rates varying from 2 to 4 mg per 1000 pounds body weight.

RULES USED IN TESTING DAIRY CATTLE

When thyroprotein first became available for commercial dairymen, fear was expressed by the various purebred cattle registry associations that it would be fed to cows on official test and thus increase their milk and fat production above their inherited level. As a result of this fear, the feeding of thyroprotein to purebred cows on official test was prohibited. Later, the same rule was applied to records made under Dairy Herd Improvement Association (DHIA) testing.

It is clear that thyroprotein should not be fed to dairy cattle to influence the records of cows on test without the knowledge of the tester. However, in the light of our present knowledge, this leaves out much hormone information that could be of great value to dairymen in the selection of breeding animals.

It is suggested that the rules be altered to permit the feeding of thyroprotein or other hormones under supervision and that the record of its use be indicated. Records of cows on test with and without thyroprotein could thus be compared and the status of the inheritance of the cows for thyroid hormone secretion could be estimated. How these comparisons of the productivity of dairy cattle with and without thyroprotein may be used in the selection of dairy cattle was described earlier.

Until the rules are changed, a dairyman who wishes to use thyroprotein can keep owner-sampler records and can continue on the record program.

Summary

Dairy cattle of similar external conformation and body weight vary greatly in their capacity to secrete large quantities of milk and fat. To explain this variation, it is suggested that dairy cows vary in the inheritance of genes which cause them to secrete the hormones that stimulate udder growth, milk secretion, and milk removal at milking time.

Some cows may be low producers due to a limited secretion of one hormone and when it is supplied by injection or feeding it will cause a great increase in the cows' milk yield. Other cows may secrete low levels of a number of hormones and fail to respond to the administration of a single hormone due to the deficiency of others.

In the first bulletin of this series, seven major endocrine causes of differences in milk yield were described. In the second bulletin, the role of the hormones in stimulating udder growth was described. The third bulletin explained the role of the lactogenic hormone in milk secretion. This bulletin describes the important role of hormones of the thyroid gland in body growth, reproduction, and lactation. Cows vary greatly in their secretion of thyroid hormones. Replacement therapy supplying thyroid hormones through feed or injection will stimulate increases in milk and fat production in cows that secrete less than optimal amounts of the hormones.

Research to determine a cheap synthetic hormone has been very successful. It was found that the milk protein, casein, could be iodinated to produce three times as much thyroxine as is present in thyroglobulin secreted by the thyroid gland.

This product, called thyroprotein (thyroactive iodinated casein) has been studied extensively as a substitute for the injection of thyroxine or the feeding of thyroid tissue.

In large groups of cows, the feeding of thyroprotein has increased milk production from 20 to 30 percent. The thyroprotein feeding does not increase production in individual cows that secrete optimal amounts of thyroid hormones. The greater production comes from the ones that do not secrete enough thyroid hormones naturally. Increases in milk yield of cows short on the hormones varied from 5 to 10 percent to as much as 60 to 80 percent.

It is believed that the cows showing the largest responses have inherited a deficiency in thyroid hormone secretion but a high secretion rate for other hormones required for high milk yield. When thyroprotein is supplied to such animals, their true production potential is demonstrated.

The thyroprotein feeding or injection increases the percentage of fat as well as total milk. Thus the increase in fat production is greater than that of milk yield.

The milk sugar (lactose) content of the milk also may be increased slightly. Vitamin content of milk is not altered significantly with the possible exception of vitamin C. The seasonal variation in milk yield and composition is believed to be due to the percentage of fat as well as total milk. Thus, the hormone secretion during the winter months and high temperatures causing a decreased role during the summer.

As a result of recent research, the suggested level of thyroprotein feeding has been reduced one-third. The feeding of as much of a high energy ration as it takes to satisfy the appetite of the cow is recommended to prevent loss of body weight (condition). In very high producing cows, the feeding of thyroprotein may increase milk yield above their capacity to consume high energy feed. In such cases it is necessary to withdraw thyroprotein until their milk yield has declined somewhat.

The most significant discovery concerning thyroid physiology is the great importance of the thyroid hormones concerning the stimulus of milk secretion. It is clear that dairy cattle which respond to the feeding of thyroprotein have inherited thyroid hormone secretion rates that are less than optimal for high production.

From the point of view of breeding cows for high production, the selection of cows and bulls with a high inherited level of thyroxine secretion is imperative. The method developed for measuring the thyroid hormone secretion rate can be used at experiment stations but is not adaptable for dairy cattle breeders. The feeding of thyroprotein is an alternative. It is suggested that the records of individual cows' responses to thyroprotein be analyzed as follows:

1. *If a cow with low to average production fails to respond to thyroprotein, her thyroxine secretion may be adequate but, if so, she has one or more other hormone deficiencies. She should be culled.*

2. *Failure of high producing cows to respond to thyroprotein indicates that their secretion rates for thyroxine and other hormones are adequate. They should be kept for breeding purposes.*

3. *If cows with average production show a marked response to thyroprotein, they apparently have inherited a markedly deficient thyroxine secretion rate but adequate secretion rates of other hormones. If the increased milk yield stimulated by thyroprotein is satisfactory, these cows can be kept for breeding purposes. If mated to a bull having the ability to transmit high thyroxine secretion, their progeny should be better producers.*

4. *If high producing cows show a marked response to thyroprotein feeding, it indicates that such cows have received an inheritance of genes for secretion of many of the hormones needed for high milk yield but lack the ability to secrete optimal levels of thyroxine. Such cows would normally be kept for breeding purposes. But knowledge they should be mated to bulls of high transmitting ability for thyroxine secretion. The progeny of such matings can be outstanding.*

5. *To determine the transmitting ability of sires for thyroxine secretion rate, a breeder could determine the thyroprotein response of a group of his daughters. If they show little response to thyroprotein, this suggests that the sire is transmitting an adequate thyroid hormone secretion rate. If their mean response to thyroprotein feeding is great, less than optimal thyroxine secretion is being transmitted.*

Until more cows are bred with high normal thyroid hormone secretion rate, commercial dairymen can completely replace the thyroid deficiency by feeding thyroprotein.

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