The Hemodynamic and Metabolic Interrelationships in the Activity of Epinephrine, Norepinephrine and the Thyroid Hormones

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The hemodynamic and metabolic effects of a total sympathetic block and of the infusion of l-epinephrine or l-norepinephrine were studied in 27 euthyroid dogs and in 31 thyroid-fed dogs. The physiologic changes produced by increased concentrations of the thyroid hormones were abolished by preventing the reflex release of epinephrine and norepinephrine with a total sympathetic block. The inotropic, chronotropic and calorigenic effects of l-epinephrine and of l-norepinephrine were found to be increased by thyroid feeding. It is concluded that there is a dynamic interrelationship between the thyroid hormones and those of the adrenal medulla and sympathetic nerve endings. The hemodynamic and metabolic changes of thyrotoxicosis are not the result of the isolated activity of the thyroid hormones, but rather are due to the physiologic effects of epinephrine and norepinephrine, as augmented by the thyroid hormones. Studies indicate that l-norepinephrine is the predominant mediator of the changes produced by thyroid feeding.

Physiologists have long recognized that the thyroid hormones are fundamentally important in the regulation of the quantitative metabolic and hemodynamic response to epinephrine or norepinephrine. Clinical and laboratory investigators have reported an increase in all parameters of activity of epinephrine, norepinephrine or their combination, as adrenalin, in thyrotoxic man and in thyroid-fed or thyroxin-injected man and laboratory mammals. Conversely, the calorigenic, hemodynamic and metabolic effects of the known sympathoadrenal hormones have been shown to be diminished or absent in hypothyroid man and animals.

That there is a fundamental relationship between the activity of the thyroid hormones and those of the adrenal medulla and sympathetic nerve endings is further indicated by the clinical reports of the successful use of sympathetic block in both the prevention and treatment of thyrotoxic "crisis" or "storm." A total or near total sympathetic block, produced either by the subarachnoid injection of procaine or by the intravenous injection of hexamethonium, has been reported to be effective both in preventing or abolishing the physiologic manifestations of thyrotoxic crisis. The injection of the "sympatholytic" drug, phenoxybenzamine hydrochloride (Dibenzyline) has been reported to prevent an increase in the oxygen consumption, following the injection of thyroxine.

Barker, in a thorough review of the mechanism of action of the thyroid hormones, drew attention to the need for a technic which would...
quantitate the physiologic interrelationship between the thyroid and the sympathoadrenal hormones as follows: "Despite some conflicts, from the evidence thus far discussed emerges the currently prevalent concept that the normal thyroid gland functions to maintain the metabolic activity of most of the tissues of the body. Innervation, either somatic or visceral, is not essential to this effect, but there has been no procedure devised to determine a possible nerve borne reinforcing action."

The need for a technic, to separate the physiologic effects of the thyroid hormones from those of epinephrine and norepinephrine in the intact animal, is met by the use of a total sympathetic block. In the experiments reported below, a total epidural preganglionic sympathetic block was used to abolish the reflex release of epinephrine and norepinephrine in dogs in which increased concentrations of the thyroid hormones had been produced by thyroid feeding. In this manner, the physiologic effects of the thyroid hormones were determined in the intact animal in the absence of epinephrine and norepinephrine. Furthermore, the effect of increased concentrations of the thyroid hormones upon the physiologic effects of either L-epinephrine or L-norepinephrine was determined by the individual infusion of these substances into euthyroid and thyroid-fed animals in which the reflex release of these hormones was prevented by a total sympathetic block.

When the actions of the thyroid and sympathoadrenal hormones are thus dissected, the results, presented below, indicate that the physiologic changes, resulting from thyroid feeding, are not the result of an effect of the thyroid hormones per se, but are the result, rather, of the interaction of the thyroid hormones with those of the adrenal medulla and sympathetic nerve endings, L-epinephrine and L-norepinephrine.

**Method**

(1) **Animals.** Mongrel male dogs varying in weight from 10 to 23.4 Kg. were used.

(2) **Feedings.** Dogs were fed with a high protein, high vitamin diet prior to and during the thyroid feeding. The diet consisted of horsemeat, 3 to 4 pounds per day; cow's milk, one-half quart per day; mashed dog food,* one-half pound per day; and multivitamin capsules, supplying daily 10,000 units of vitamin A, 4 mg. thiamin, 90 mg. ascorbic acid, 1000 units of vitamin D₃, 4 mg. riboflavin, 40 mg. nicotinamide, 2 mg. calcium pantothenate, 1 mg. pyridoxine hydrochloride.

(3) **Thyroid Feeding.** Animals were fed a daily amount of thyroid powder (U.S.P.)† calculated on the basis of 0.8 Gm. per kilogram of body weight.

Animals were studied after: (a) 7 to 10 days of thyroid feeding; (b) 11 to 15 days of thyroid feeding and (c) 17 to 22 days of thyroid feeding. Animals, included in the study, were limited to those which had consumed the maximum of their daily feeding. All dogs were studied 18 hours after their last feeding.

(4) **Anesthesia.** All dogs were anesthetized with thiopental sodium‡ for surgical preparation for the physiologic observations described below. Following surgical preparation and prior to the control studies, the dogs were allowed to recover from the thiopental anesthesia to the extent that all superficial reflexes were present and the animal would react to cutaneous or ocular stimuli with a motor response.

(5) **Body Temperature.** The rectal temperature of all animals was determined with a mercury thermometer. Immediately after the dogs were anesthetized, their oxygen consumption was determined without attempted control of the body temperature. Prior to the control determinations, the dogs were allowed to recover from the thiopental anesthesia to the extent that all superficial reflexes were present and the animal would react to cutaneous or ocular stimuli with a motor response. Although the effect of a total sympathectic block tended to result in a reduction in the body temperature and the infusion of either epinephrine or norepinephrine, to increase the body temperature, this was controlled by warming or cooling as indicated.

(6) **Technic of Total Epidural Sympathetic Block.** Following laminectomy at the level of L-2 or L-3, four polyvinyl catheters were introduced into the epidural space. The tips of the catheters were introduced to varying levels, approximating D-1, D-2, D-9 and S-1, to insure uniform distribution of the injected procaine solution throughout the epidural space. The total epidural preganglionic sympathetically block was produced by the injection of a 0.45 per cent procaine hydrochloride§ solution into the epidural space. Twenty-five to 35 ml. of the

* Purina Laboratory Chow, Ralston Purina Company, St. Louis.
† Armour and Company, Chicago, Illinois.
‡ Pentothal Sodium, Abbott Laboratories, Chicago, Ill.
§ Procaine HCl, Abbott Laboratories, Chicago, Ill.
procaine solution were injected at 25 to 30 minute intervals in order to maintain the block.

(7) Criteria of the Completeness of a Total Epidural Sympathetic Block. In the dog whose efferent preganglionic sympathetic fibers are incompletely blocked, the injection of procaine solution will result in a pressor and cardioaccelerator response of 2 to 4 minutes duration. The primary criterion of an effective total preganglionic sympathetic block was the complete absence of a pressor or cardioaccelerator response immediately following the injection of the procaine solution into the epidural space. Hemodynamic and metabolic studies were not done until the block had been established and maintained for at least an hour.

(8) Oxygen Consumption and Ventilation of Dogs. The dogs were either intubated with a no. 35 Magill endotracheal tube with an inflatable cuff or a similar tube was inserted and firmly tied in the trachea via tracheotomy. The determinations of the oxygen consumption in the control state and during the infusion of either l-epinephrine or l-norepinephrine were done with the animals ventilating spontaneously through a standard Benedict-Roth spirometer. During the maintenance of a total sympathetic block, it was found essential to ventilate the dogs mechanically in order to maintain normal alveolar and blood tensions of carbon dioxide and oxygen. The system described elsewhere was used for the simultaneous intermittent positive pressure ventilation of the animal with an Emerson resuscitator and spirometric determination of the oxygen consumption.

The values of oxygen consumption, reported below, are the average of a five-minute observation period after a steady pressure-volume state was reached.

(9) Intracardiac and Extracardiac Pressures. Pulmonary arterial pressure and left atrial pressures were obtained via no. 10 polyethylene catheters placed directly through small vessels approached by thoracotomy. Right atrial pressures were measured through a no. 10 catheter inserted into the right atrium via the external jugular vein. Femoral arterial pressures were obtained through a no. 19 Cournand needle inserted percutaneously or through a no. 10 polyethylene catheter ligated into the femoral artery.

Mean pressures were obtained by the use of saline, Tycoe and Sanborn electromanometers. All pressures were recorded on a four-channel Sanborn oscillograph. Full range and condenser-integrated mean pressures were obtained.

Following thoracotomy for the insertion of catheters, the chest was closed, and an intrathoracic cannula was left in place for the purpose of measuring the intrathoracic pressure.

(10) Blood Volume. The blood volume was maintained in all dogs throughout each experiment by replacing blood withdrawn for sampling with an equal volume of dextran.

(11) Infusion of l-epinephrine or of l-norepinephrine. When so indicated, l-epinephrine hydrochloride or l-norepinephrine bitartrate was infused through a femoral venous cannula at a rate of 1 µg. of active base per kilogram of body weight per minute. In terms of the molecular weight of base, 1 µg. of l-norepinephrine is 8.2 per cent greater than 1 µg. of l-epinephrine.

(12) Piperoxan hydrochloride (Benzodioxane) was given, when indicated, in a dosage of 1 mg. per kilogram by injection into the femoral venous cannula.

Collection of Samples

Blood for mixed venous oxygen was drawn from the pulmonary arterial catheter. Blood was withdrawn from the femoral artery for the following: arterial oxygen content, pH, total carbon dioxide, hemoglobin, blood sugar, serum lactate and pyruvate, serum sodium, potassium, chloride and serum protein-bound iodine determinations. For determination of the oxygen content of arterial and mixed venous blood, 6 ml. was drawn into a 10 ml. syringe containing approximately 0.1 to 0.2 ml. of a 10 per cent heparin solution together with a small bead of mercury for thorough mixing of the blood on shaking. The blood was iced immediately, and the oxygen determinations usually were done within two hours of withdrawal. Blood for pH and carbon dioxide determinations was collected in oiled syringes, transferred under oil and iced. The pH determination was done within 15 to 60 minutes and the total carbon dioxide determination within two hours. Methods used in biochemical studies of blood are the same as presented elsewhere. Serum protein-bound iodine was done by the method of Barker.

Calculations

(a) The body surface area in square meters was obtained with Meeh's formula, using Rubner's constant for the dog as follows:

\[ \text{Surface Area/M}^2 = 1.12 \text{ (weight/Kg.)}^{467} \]

\[ \text{Rubner's constant for the dog is } 467. \]

\[ \text{Meeh's formula for body surface area is: } \]

\[ \text{Surface Area/M}^2 = 1.12 \times \text{weight (in kg.)} \]

\[ \text{Example: For a dog weighing 20 kg., the surface area would be: } \]

\[ \text{Surface Area/M}^2 = 1.12 \times 20 = 22.4 \text{ sq. m.} \]

\[ \text{Other examples: For a dog weighing 40 kg., the surface area would be: } \]

\[ \text{Surface Area/M}^2 = 1.12 \times 40 = 44.8 \text{ sq. m.} \]

\[ \text{For a dog weighing 60 kg., the surface area would be: } \]

\[ \text{Surface Area/M}^2 = 1.12 \times 60 = 67.2 \text{ sq. m.} \]

\[ \text{And for a dog weighing 80 kg., the surface area would be: } \]

\[ \text{Surface Area/M}^2 = 1.12 \times 80 = 89.6 \text{ sq. m.} \]

\[ \text{These calculations are based on the assumption that the dog's body is a simple geometrical figure, such as a cylinder or a sphere.} \]

\[ \text{In practice, the surface area is more accurately determined by using specialized formulas and equipment designed for this purpose.} \]

\[ \text{The values obtained through these calculations are approximate and should be used as a general guide.} \]

\[ \text{For more accurate results, specialized formulas and equipment should be used.} \]

\[ \text{The calculations provided here are for informational purposes only and should not be used as a substitute for medical advice.} \]

\[ \text{References:} \]

\[ \text{1 Flavolex, Wyeth Laboratories, Inc., Philadelphia, Pa.} \]

\[ \text{2 Suprarenin, Winthrop Stearns, Inc., New York, N. Y.} \]

\[ \text{3 Levophep bitartrate, Winthrop Stearns, Inc., New York, N. Y.} \]

\[ \text{* Benodaine, Merck and Company, Rahway, N. J.} \]
The oxygen consumption is expressed as milliliters per minute as corrected to standard temperature and pressure.

The oxygen consumption (ml./M.² body surface area) = \( \frac{\text{Oxygen consumption ml./min. (S.T.P.)}}{\text{Surface Area M}^2} \)

Cardiac index (liters/min./M.² body surface area) = \( \frac{\text{Oxygen consumption ml./M.² min.}}{\text{Arterio-venous oxygen diff. (vol. %) × 10}} \)

Index of total peripheral resistance (dynes/cm.⁻⁵/sec.) = \( \frac{FAm(mm.Hg) - RAm(mm.Hg)}{\text{Cardiac index (ml./sec.)}} \times 1332 \)

Index of pulmonary resistance (dynes/cm.⁻⁵/sec.) = \( \frac{PAm(mm.Hg) - LAm(mm.Hg)}{\text{Cardiac index (ml./sec.)}} \times 1332 \)

Left ventricular stroke work index (gram meters) \( \frac{FAm(cm.HO) - LAm(cm.HO) \times \text{Stroke volume index (ml./beat/M.² body surface area)}}{100} \)

Right ventricular stroke work index (gram meters) \( \frac{PAm(cm.HO) - RAm(cm.HO) \times \text{Stroke volume index (ml./beat/M.² body surface area)}}{100} \)

Stroke volume index = \( \frac{\text{Cardiac index (ml./min./M.² body surface area)}}{\text{Heart rate (min.)}} \)

Arterial carbon dioxide tensions were derived from the arterial serum pH and total carbon dioxide tensions using the nomogram of Singer and Hastings.⁴⁰

Procedure

Studies described above were done on 27 euthyroid dogs and on 31 thyroid-fed dogs. The duration of thyroid feeding was as follows: (a) 10 dogs were fed thyroid for 7 to 10 days; (b) 10 dogs were fed thyroid for 11 to 15 days; and (c) 11 dogs received thyroid for 18 to 22 days. All dogs, both euthyroid and thyroid-fed, were studied as follows: (1) under light thiopental sodium anesthesia prior to surgical stimulation, (2) after surgical preparation and prior to a total sympathetic block, (3) during a 1 to 4 hour period following the establishment of a total epidural preganglionic sympathetic block and (4) with the total sympathetic block maintained to prevent the reflex release of epinephrine or norepinephrine by the animal, studies were done during the infusion of either l-epinephrine or of l-norepinephrine individually in different animals.

During the above infusions, results, presented below, are from observations made 5, 30 and 60 minutes, following the start of the individual infusion; with the infusion continued, 1 mg. per kilogram of benzodioxane was injected. Its effects were studied 2 to 5 minutes following injection.

Results

Serum Protein Bound Iodine Concentrations.

The serum protein-bound iodine concentration of the 27 euthyroid dogs averaged 1.7 µg. per 100 ml. Following thyroid feeding, the average serum protein-bound iodine concentrations were as follows: 7 to 10 days, 16.6 µg. per 100 ml.; 11 to 15 days, 18.1 µg. per 100 ml. and 18 to 22 days, 16.9 µg. per 100 ml. There was no significant difference in the serum protein-bound iodine concentrations, whether the dogs were fed thyroid for approximately 1 or 3 weeks.

Hemodynamic Results

Heart Rate

Effect of Thyroid Feeding. There is a progressive rise in the heart rates following thyroid feeding (fig. 1). Surgical stimulation (tables 1 and 2)* caused a further small increase in the heart rates of all groups of dogs. The relatively fast heart rates, seen in the control state (fig. 1) in all groups of dogs, are due to three factors: surgical stimulation, the extremely light level of thiopental anesthesia in the animals during the control studies and the well-documented vagal inhibitory effect of even light thiopental anesthesia.

Effects of a Total Sympathetic Block. When the reflex release of epinephrine and norepinephrine was abolished by a total sympathetic block, the heart rates of the thyroid-fed animals declined to levels that were identical to those of the euthyroid dogs with a total sympathetic block (fig. 1).

Effects of l-Epinephrine and of l-Norepinephrine Infusion. The infusion of either l-epinephrine or of l-norepinephrine into the thyroid-fed dogs resulted in increases in the average heart rates that were significantly greater than those observed in similarly infused

* At the request of the editor, tables 1 and 2 are being omitted. These will be furnished on request.
Fig. 1. Effect of thyroid feeding, total sympathetic block and the infusion of l-epinephrine or l-norepinephrine on the heart rate per minute in euthyroid and thyroid-fed dogs. All figures include the mean and the standard error of the mean.

euthyroid dogs (fig. 1). However, inasmuch as the mean femoral arterial pressures during the infusion of l-epinephrine and of l-norepinephrine were lower in the thyroid fed dogs than in the euthyroid dogs, it became essential to compare the average heart rates of the dogs at comparable arterial pressure levels to rule out reflex baroreceptor inhibition as an important factor influencing the heart rates. For this purpose Benzodioxane was used. It has been shown that Benzodioxane, in doses of 1 mg. per kilogram, intravenously, inhibits the systemic vasoconstrictor effects, but does not inhibit the chronotropic effects of epinephrine. When the mean femoral arterial pressures of both the euthyroid and thyroid fed dogs were reduced to the same levels, following the injection of Benzodioxane (fig. 3) during the infusion of epinephrine, the average heart rate of the thyroid-fed dogs remained greater than that of the euthyroid dogs. The same principle held true in the case of l-norepinephrine infusion (fig. 4). Thus, it can be concluded that the feeding of thyroid results in an increase in the positive chronotropic effects of both l-epinephrine and l-norepinephrine.

Cardiac Index

Thyroid Feeding. Thyroid feeding produced significant increases in the cardiac indices of all groups of thyroid fed animals (fig. 2, tables 1 and 2).* The greatest average increase occurred in the dogs fed thyroid for 11 to 15 days.

Total Sympathetic Block. Following a total sympathetic block, the average cardiac indices of the thyroid-fed dogs decreased to values that were not significantly different from those observed in the euthyroid dogs with a total sympathetic block (fig. 2).

Infusion of l-Epinephrine and l-Norepinephrine. During the infusion of either l-epinephrine or l-norepinephrine in all groups of thyroid-fed dogs (fig. 2), there was a greater rise in the average cardiac indices than was observed in similarly infused euthyroid dogs. In order to determine whether the positive inotropic effects of epinephrine and norepinephrine were increased by thyroid hormones, it was necessary to quantitate, as well as possible, all factors that may vary the total blood flow per minute. In the presence of a constant blood volume, freely available for ventricular filling, the important determinants of minute blood flow are: (1) the contractile force of the ventricles, (2) the heart rate and (3) the resistance which the peripheral or pulmonary vascular bed offers to the effective emptying of blood from the left and right ventricles respectively. The following relationship, then, exists in determining the cardiac index:

Cardiac Index

\[
\frac{\text{Force of Ventricular Contraction)(Rate)}}{\text{Pulmonary or Peripheral Resistance}}
\]

* See footnote p. 4.
To shed further light on the individual factors responsible for the greater cardiac indices of the thyroid-fed dogs during epinephrine or norepinephrine infusion, 1 mg. per kilogram of benzodioxane was injected intravenously in both euthyroid and thyroid-fed dogs during the infusion of either epinephrine or norepinephrine. In this dosage, sympatholytic drugs, similar to benzodioxane, have been shown to reduce or abolish the peripheral vasoconstrictor component of activity of l-norepinephrine, and in the case of l-epinephrine both to abolish the peripheral vasoconstrictor component of activity and to result in an active vasodilation. Benzodioxane does not alter the quantitative inotropic or chronotropic effects of either l-epinephrine or l-norepinephrine.

As shown in figure 3, the injection of 1 mg. per kilogram of benzodioxane, during epinephrine infusion in the euthyroid dogs, resulted in a fall in the average mean arterial pressure from 169 mm. Hg to 64 mm. Hg, this fall being the result of an intense peripheral vasodilation. Consequent to this drop in peripheral resistance, there was an increase in the cardiac index of the euthyroid dogs from 4.21 to 6.23 liters per minute. The injection of 1 mg. per kilogram of benzodioxane into the thyroid-fed dogs during the infusion of epinephrine, while the mean femoral arterial pressure fell to the same levels observed in euthyroid dogs, resulted in an increase in the average cardiac index from 7.80 to 10.23 liters per minute. This illustrates that with the inotropic effect of epinephrine remaining constant, and, therefore, with the effective ventricular contractile force remaining constant, the cardiac index (the total minute volume of blood flow) increases as a result of a decrease in resistance to effective left ventricular emptying.

Much more important, this experiment may be used to demonstrate that thyroid feeding caused an increase in the positive inotropic effect of l-epinephrine. Evidence for this is the fact that the average cardiac index of the thyroid-fed dogs during epinephrine infusion alone (7.80 liters per square meter per minute) is greater than that of the euthyroid dogs in which the peripheral resistance has been lowered by the injection of Benzodioxane during the infusion of l-epinephrine (6.23 liters per square meter per minute).

The increases in the average cardiac indices, observed to occur in both euthyroid and thyroid-fed dogs following the injection of Benzodioxane during the infusion of epinephrine, were
greater than can be accounted for by an increase in the heart rates alone. The increase in cardiac index was proportional to the increase in stroke volume output (tables 1 and 2).* Figure 4 shows that similar, though not as great, increases in the average cardiac indices occurred following the injection of benzodioxane during the infusion of l-norepinephrine.

In summary, the infusion of either l-epinephrine or of l-norepinephrine into thyroid-fed dogs resulted in increases of the average cardiac indices that were significantly greater than those observed in the euthyroid animals. Three factors have been shown to play an important role in the increased cardiac indices of the thyroid-fed animals during the infusion of the catechol amines, as contrasted to similarly treated euthyroid animals: (1) an increase in the inotropic effects of epinephrine and norepinephrine by the increased concentrations of the thyroid hormones, (2) an increased heart rate, due to an increase in the chronotropic effects of epinephrine and norepinephrine by the thyroid hormones and (3) a decrease in the resistance to left ventricular emptying in the thyroid-fed animals, as contrasted to the euthyroid animals during the infusion of either epinephrine or of norepinephrine.

Right and Left Ventricular Stroke Work Indices and the Mean Right and Left Atrial Pressures

To examine the effects of drugs, hormones or pathologic events upon the energetics of the ventricles, it is necessary to examine these indirectly by measuring the capacity of the ventricles for doing work. To study the effective work of the ventricles, it has been emphasized that it is necessary to quantitate the mechanical work done by the individual ventricle in relationship to its filling pressure. Starling's law of the heart has been recently clarified and confirmed to apply in the dog and in man. It has been demonstrated that both l-epinephrine and l-norepinephrine, by virtue of their positive inotropic effects, are capable of increasing the energy of ventricular contraction per unit of ventricular filling pressure.

Results demonstrated in figures 5 to 8 were obtained in investigating the direct effects of the thyroid hormones per se on the energetics of the ventricles, as contrasted to the effects of the thyroid hormones in augmenting the inotropic effects of epinephrine and norepinephrine.

Effects of Thyroid Feeding. There was a significant increase in the left ventricular stroke work relative to the average left atrial mean pressure in the thyroid-fed dogs (figs. 5 and 6).

There was a progressive rise in the right ventricular stroke work of the thyroid-fed dogs.

* See footnote p. 4.
animals, compared with that of the euthyroid animals. Relative to the right atrial mean pressure, this rise was not significant in the dogs fed thyroid for one week, but was highly significant in the dogs fed thyroid for a two to three-week period (figs. 7 and 8).

**Effects of a Total Sympathetic Block.** Figures 5 and 6 demonstrate that, following a total sympathetic block, the left ventricular stroke work of the euthyroid and thyroid-fed dogs decreases to levels that are not significantly different. During the maintenance of a total sympathetic block, the average left atrial mean pressures of all groups of animals rose above the levels observed in the control state. There was no significant difference in the average left atrial mean pressures observed in the euthyroid dogs and the thyroid-fed dogs with a total sympathetic block.

Figure 7 and 8 demonstrate that there was no significant difference in the average right ventricular stroke works and average right atrial mean pressures of euthyroid dogs and one- and two-week thyroid-fed dogs during a total sympathetic block. Although within the range of values observed in euthyroid-blocked dogs, the average right ventricular stroke work of the 3-week thyroid-fed animals was a little higher than that of the euthyroid dogs per unit of right atrial mean pressure.

When the right and left ventricular stroke work and right and left atrial mean pressures of all thyroid-fed dogs are compared with those of all euthyroid dogs during the maintenance of a total sympathetic block (tables 1 and 2)*, no significant difference existed between these two groups of animals.

**During total sympathetic block, the close correlation between the mean right and left ventricular stroke work and the average right and left atrial mean pressure of the euthyroid and thyroid-fed dogs, despite marked differences in the circulating thyroid hormone concentrations in the two groups, indicates that the thyroid hormones, in the absence of circulating epinephrine and norepinephrine, have no direct effect upon the function of the ventricles.**

**Effects of l-Epinephrine or of l-Norepinephrine Infusion.** During the infusion of either l-epinephrine or of l-norepinephrine at rates of 1 μg. per kilogram per minute, there were equivalent increases in the average left ventricular stroke work of euthyroid and thyroid-fed dogs (fig. 5). In the thyroid-fed dogs, however, there was a greater reduction than in the euthyroid dogs in the average left atrial mean pressure, during epinephrine and norepinephrine infusion (fig. 6). The increase in the left ventricular stroke work of the thyroid-fed dogs per unit of left atrial mean pressure was significantly greater than that observed in the euthyroid group of animals.

The right ventricular stroke work of the thyroid-fed dogs, during the infusion of either epinephrine or norepinephrine, increased more

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* See footnote p. 4.
than did that of the euthyroid dogs (fig. 7). Simultaneously, there was a greater decrease in the average right atrial mean pressure in the thyroid-fed animals during the infusions than was observed in the euthyroid animals (fig. 8). Thus, the effective right ventricular stroke work per unit of filling pressure, during the infusion of epinephrine or norepinephrine, was significantly greater in the thyroid-fed dogs than in the euthyroid dogs.

Effect of Benzodioxane Injection. Following the injection of Benzodioxane (1 mg. per kilogram, intravenously) during the infusion of either l-epinephrine or of l-norepinephrine in euthyroid and in thyroid-fed animals, there was a decrease in both the average left ventricular stroke works and in the average left atrial mean pressures (figs. 9 and 10). In general, there was an increase in the right ventricular stroke works, together with a fall in the average right atrial mean pressures. It is seen that both the right and left ventricular stroke works in the thyroid-fed dogs remain consistently higher per unit of filling pressure, following benzodioxane injection, than in the euthyroid animals. This is in keeping with the analysis of changes in the cardiac indices, presented above. The consistently higher ventricular stroke works of the thyroid-fed animals as compared with that of the euthyroid dogs, following Benzodioxane injection during the infusion of either l-epinephrine and l-norepinephrine, is a further indication that an increase in the thyroid hormone concentrations will increase the positive inotropic effects of both l-epinephrine and l-norepinephrine.

Average Mean Femoral Arterial Pressures

There was no significant difference in the mean femoral arterial pressures of the euthyroid and thyroid-fed dogs in the control state (tables 1 and 2).*

Following a total epidural sympathetic block, the mean femoral arterial pressures of both the euthyroid and thyroid-fed dogs decreased. The pressures of the thyroid-fed animals, during the period of a sympathetic block, were 10 to 15 mm. Hg lower than these of the euthyroid dogs. Despite this difference, the average mean femoral arterial pressures of the thyroid-fed dogs fell well within the range of values observed in individual euthyroid animals with a total sympathetic block (tables 1 and 2).*

During the infusion of l-epinephrine or of l-norepinephrine, the average mean femoral

* See footnote p. 4.
arterial pressures, as well as the calculated total peripheral resistance (tables 1 and 2)* of the thyroid-fed animals, were significantly lower than in the euthyroid dogs. Because of the changes in other variables, namely the heart rate, cardiac index and total peripheral resistance, the extent of rise of the average mean femoral arterial pressures alone did not serve as an index of potentiation of the physiologic activity of epinephrine and norepinephrine by the thyroid hormones.

**Arteriovenous Oxygen Difference**

There was no significant difference in the arteriovenous oxygen difference of the euthyroid and thyroid-fed dogs in the control state, following a total sympathetic block, or during the infusion of either l-epinephrine or of l-norepinephrine (fig. 11).

**Metabolic Results**

**Oxygen Consumption**

*Effect of Thyroid Feeding.* The average oxygen consumption of the animals under light thiopental sodium anesthesia prior to thyroid feeding was 130.9 ml. per M.² per minute (table 2).* Under identical circumstances, following thyroid feeding and prior to surgical preparation of the animals, increases in the average oxygen consumption of 50 ml., 54 ml. and 58 ml. per square meter per minute had occurred in the dogs fed thyroid for 1, 2 and 3 weeks, respectively. The difference in the average oxygen consumption of the thyroid-fed dogs, before and after surgical stimulation, was not statistically significant at the p < .05 level.

*Effect of Total Sympathetic Block.* Following a total sympathetic block, the average oxygen consumption (ml. per square meter per minute) of the thyroid-fed animals decreased to levels that were within the range of values observed in individual euthyroid dogs with a total sympathetic block (fig. 12). However, the average oxygen consumption of the thyroid-fed dogs remained higher statistically (at the p < .05 level) than the average of the euthyroid dogs with a total sympathetic block.

In view of the significantly higher oxygen consumption in the thyroid-fed animals during a total sympathetic block, figure 13 was prepared to show variations in the average oxygen consumption of the dogs in ml. per minute as well as in ml. per square meter per minute. During thyroid feeding, the dogs lost an average of 1.7 Kg. body weight. In contrast to the euthyroid group of animals, in which subcutaneous fat constituted an appreciable proportion of their body weight, the thyroid-fed group of dogs showed little or no subcutaneous fat. The surface area (M.²) of the dog was calculated from the dog's weight directly, using Meeh's formula with Rubner's constant. Since fat has a relatively low oxygen consumption, as

* See footnote p. 4.
contrasted to lean body mass, a discrepancy can be expected in the comparison of the oxygen consumption on a body weight basis in dogs where the amount of fat per total weight is different. Figure 13 shows that, prior to thyroid feeding, the average oxygen consumption in ml. per square meter per minute of the dogs was 130.9, while the average oxygen consumption in ml. per minute was 93.3. During the period of a total sympathetic block following thyroid feeding the oxygen consumption in ml. per square meter per minute was 136.5 cc., whereas the oxygen consumption in ml. per minute was 90 cc. Thus, although the actual average oxygen consumption in ml. per minute was lower, following rather than prior to thyroid feeding and during a total sympathetic block, the oxygen consumption in ml. per square meter per minute is higher than the same prefeeding control.

When the discrepancy in the oxygen consumption in ml. per square meter per minute, resulting from differences in the total body fat of euthyroid and of thyroid-fed animals, is taken into consideration, little or no significant difference could be seen in the oxygen consumption of euthyroid and thyroid-fed dogs during the maintenance of a total sympathetic block.

Effect of l-Epinephrine or of l-Norepinephrine Infusion. In euthyroid dogs, the calorigenic effects of l-epinephrine and of l-norepinephrine were quantitatively identical. When l-epinephrine or l-norepinephrine was infused intravenously into thyroid-fed animals, there was potentiation of their calorigenic effects which resulted in a significantly greater increase in the pulmonary oxygen uptake of the thyroid-fed animals, as contrasted with the euthyroid animals (fig. 12). As in the case of epinephrine and norepinephrine infusion in euthyroid dogs, the greater average increase in the oxygen consumption, produced by norepinephrine, can be accounted for in terms of molecular weight. Since the molecular weight of l-epinephrine is 8 per cent greater than that of norepinephrine, the infusion of these substances in equal metric weights should result in l-norepinephrine having approximately 8 per cent greater activity than l-epinephrine. This was the case.

Effect of Benzodioxane Injection during the

Infusion of l-Epinephrine or l-Norepinephrine. In contrast to the profound effects of benzodioxane on blood flow per minute, as reported above, it was found (tables 1 and 2)* that it has little significant effect upon the calorigenic activity of either l-epinephrine or l-norepinephrine during their infusion.

Lactate, Pyruvate and Glucose Concentrations

Thyroid Feeding. There was no change in the serum lactate, pyruvate or blood sugar concentrations of the thyroid-fed dogs, when their postfeeding levels, determined under light Thiopental sodium anesthesia, are compared with their prefeeding levels determined under similar circumstances. Following surgical stimulation in control determinations (fig. 14, tables 1 and 2),* the serum levels of lactate and pyruvate and blood sugar levels of the thyroid-fed dogs showed a small but significant increase as contrasted to the euthyroid dogs.

Effect of Total Sympathetic Block. There was

* See footnote p. 4.
no significant change in the serum lactate and pyruvate concentrations following a total sympathetic block in any of the groups of dogs. The average serum lactate and pyruvate concentrations increased slightly in the euthyroid dogs and in the dogs thyroid-fed for one- and three-weeks and decreased slightly below control values in the two-week thyroid-fed dogs (fig. 14). There was, however, a decrease in the blood sugar concentrations of all groups of dogs below their control values following a total epidural sympathetic block (tables 1 and 2).* There was no significant difference in the blood sugar determinations of all groups of dogs, following a total sympathetic block.

Infusion of l-Epinephrine and l-Norepinephrine

The infusion of l-epinephrine resulted in significant increases in the serum lactate and pyruvate levels in all groups of dogs, the increases being greater in the thyroid-fed dogs than in the euthyroid dogs. The infusion of l-epinephrine produced a significant increase in blood sugar in both euthyroid and thyroid-fed animals (fig. 14).

In contrast to the effects of l-epinephrine infusion upon the serum levels of lactate and pyruvate and the blood levels of sugar, the infusion of l-norepinephrine did not result in significant rises in the blood or serum concentrations of any of these metabolites. Rather, the infusion of l-norepinephrine resulted, in all groups of animals, in an average fall of serum concentrations of lactate, pyruvate and of the blood sugar concentration (fig. 14, tables 1 and 2)*. The serum pyruvate concentrations during norepinephrine infusion were significantly lower than prior to infusion. The decrease in the serum lactate and blood sugar concentrations were not statistically significant at the p < .05 level.

**DISCUSSION**

The technic of a total sympathetic block, either by the subarachnoid injection of a local anesthetic agent or by the use of intravenous ganglionic blocking agents (hexamethonium), has been demonstrated by clinicians to be capable of either preventing or abolishing the physiologic changes associated with thyrotoxic crisis or "storm." Physiologists, interested in the mechanisms of action of the thyroid hormones, have failed to utilize similar technics in order to quantitate the role played by variations in epinephrine and norepinephrine activity in the physiologic effects observed in hyperthyroid man and laboratory animals. Isolated organ and tissue preparations have been used primarily. The slow rate of oxidation of the catechol amines in isolated organ or tissue preparations from hyperthyroid animals can be expected to result in a persistence in the activity of epinephrine and norepinephrine in such preparations for varying periods of time, following removal. The use of isolated organ or tissue preparations, therefore, does not necessarily separate the activity of the thyroid hormones from that of epinephrine and norepinephrine, as has been previously believed. Thus, the technic of a total sympathetic block, new to the laboratory investigation of the mode of action of the thyroid hormones though not new to the clinical treatment of thyrotoxicosis, has been used to analyze both the separate and combined effects of the thyroid hormones and of the sympathoadrenal hormones.

The occurrence of thyrotoxicosis in man, and the injection of l-thyroxine or the feeding of whole thyroid in both man and laboratory animals, has been shown to increase both the rate of metabolism of the body as a whole and

* See footnote p. 4.
the dynamic activity of the heart, in particular. The literature on hemodynamic and metabolic effects of hyperthyroidism in man and laboratory animals has been excellently reviewed by Raab,49 Means,50 Andrus51 and Rasmussen.52 The hemodynamic and metabolic changes, observed in the control state in our animals following thyroid feeding, are in agreement with the changes referred to or reported by the above authors.

The data presented above, together with a review of the literature, serve to emphasize two important points: (1) the hemodynamic and metabolic response to reflexly released, injected or infused epinephrine and norepinephrine may be increased by increased concentrations of the thyroid hormones and decreased or abolished in the hypothyroid state and (2) a total sympathetic block, in preventing the reflex release of epinephrine and norepinephrine, has diminished or abolished the metabolic and hemodynamic changes resulting from thyrotoxicosis, thyroxin injection or thyroid feeding in man and laboratory mammals.

In regard to the first point, the inotropic,2 chronotropic,1-8, 11, 12, 20, 21 calorigenic1, 17, 18, 22, 24 and pressor2, 5, 7 effects of adrenalin or of its components, epinephrine and norepinephrine, have been found to be increased in hyperthyroid man and animals. The glycogenolytic effects of adrenalin or of l-epinephrine19, 28 are similarly increased by thyroid feeding or thyroxin injection. The data presented have demonstrated that the calorigenic effects of both epinephrine and of norepinephrine (fig. 12) are identical in euthyroid animals and equally increased in thyroid-fed animals. The chronotropic effects of both epinephrine and norepinephrine have been found to be increased in all groups of our thyroid-fed dogs (figs. 1, 3, 4). That there is an increase in the positive inotropic effects of both l-epinephrine and of l-norepinephrine in our dogs, as a result of thyroid feeding, is substantiated by the following:

(a) There was a significant increase in the effective right and left ventricular stroke work of the thyroid-fed dogs during the infusion of epinephrine and norepinephrine over the values observed in euthyroid dogs at similar rates of infusion (figs. 5-8). It has been made clear in the work of Sarnoff, Berglund and Case44-48 that the functional capacity of ventricular heart muscle is best reflected in the relationship of right and left atrial mean pressures to the stroke works of the right and left ventricles, respectively. These workers have demonstrated that both epinephrine and norepinephrine, by virtue of their positive inotropic effects, increase the force of ventricular contraction and thus increase the right and left ventricular stroke work per unit of individual filling pressure.44, 46 It has also been demonstrated that the positive inotropic effects of l-epinephrine and of l-norepinephrine in dog and in man are quantitatively identical.43 In our series of euthyroid dogs, epinephrine and norepinephrine infusion produced equivalent increases in right and left ventricular stroke work per unit of right and left atrial mean pressure, respectively. In the thyroid-fed dogs, the infusion of both epinephrine and norepinephrine resulted in significantly greater increases in both right and left ventricular stroke work and significantly greater reductions in both right and left atrial mean pressures, than observed in the euthyroid dogs. (b) Benzodioxane was used to reduce and make the peripheral resistance comparable during the infusion of epinephrine and norepinephrine in both euthyroid and thyroid-fed dogs. It has been pointed out that, at fairly comparable resistances, the cardiac indices (figs. 3 and 4) and indices of right and left ventricular stroke work (figs. 9 and 10) of the thyroid-fed dogs remain well above those observed in the euthyroid dogs.

The increases in the cardiac indices and the decrease in the average mean femoral arterial pressures are uniformly greater following the injection of benzodioxane during epinephrine infusion, than during norepinephrine infusion. These changes are in agreement with the work of Johnson, Green and Lanier42 who demonstrated that similar adrenergic blocking agents merely decreased or abolished the vasoconstrictor component of activity of l-norepinephrine, whereas they both blocked the vasoconstrictor component of activity of l-epinephrine and produced an active vasodilation.
Dose response curves have been constructed from the infusion of either l-epinephrine or l-norepinephrine in euthyroid dogs. Rates of infusion were as follows: 0.25, 0.50, 1.0, 2.0, 4.0, 8.0, 16.0, and 32.0 μg. per kilogram per minute. These dose-response curves indicated that a near maximum physiologic response to both epinephrine and norepinephrine was obtained at an infusion rate of 1 μg. per kilogram per minute. The peak physiologic response occurred at 2 to 4 μg. per kilogram per minute. At infusion rates greater than 4 μg. per kilogram per minute, a progressive decrease in all parameters of physiologic activity of l-epinephrine and l-norepinephrine, was observed. The physiologic activity of l-epinephrine and of l-norepinephrine in thyroid-fed dogs was consistently greater at all dose levels than in the euthyroid dogs, the peak response occurring at the same dosages as in the euthyroid dogs. The infusion of 1 microgram per kilogram per minute of l-epinephrine and of l-norepinephrine produced greater physiologic responses than were observed in euthyroid dogs at much higher rates of infusion. On the basis of these observations, clear potentiation of the physiologic activity of epinephrine and norepinephrine by the thyroid hormones is evident.

The calorigenic effects of epinephrine and of norepinephrine have here been shown to be equivalent in euthyroid dogs and equally increased by thyroid feeding. There is, however, a fundamental difference in their effects upon liver and muscle glycogenolysis, as reflected in part by changes in the serum concentrations of lactate and pyruvate and blood sugar (fig. 14, tables 1 and 2). Whereas l-epinephrine uniformly produced a significant rise in the serum concentrations of lactate, pyruvate and sugar, a consistent fall in the average serum concentrations of these metabolites resulted from the infusion of l-norepinephrine. It is thus clear, in view of the normal or near normal blood and serum concentrations of lactate, pyruvate and sugar observed in the thyroid-fed animals in the control state, that norepinephrine is probably the predominant mediator of the physiologic effects of thyrotoxicosis, as far as the activity of the sympathetic nervous system is concerned. If epinephrine were a predominant mediator, higher levels of lactate, pyruvate or sugar than were observed would be expected in the control state.

Von Euler,52 in his classic studies, has identified norepinephrine as the primary substance contained in and released from the sympathetic nerve endings as the predominant mediator of the activity of the sympathetic nervous system. It is, thus, not surprising that norepinephrine should appear from our control observations as the sympathetic substance most nearly reproducing in every way the physiologic effects of thyrotoxicosis.

In regard to the second point, the total sympathetic block, by preventing the reflex release of epinephrine and norepinephrine, effectively abolished the physiologic changes that occur as a result of thyroid feeding. Following a total epidural preganglionic sympathetic block, there was a decrease in the oxygen consumption, heart rate, cardiac index and right and left ventricular stroke works of the thyroid-fed dogs to values observed in euthyroid dogs with a total sympathetic block. There was a similarly observed elevation of the right and left mean atrial pressures to comparable levels in both the euthyroid and the thyroid-fed dogs. When one uses the individual filling pressures and the stroke works of the right and left ventricles as indices of ventricular contractility, it is seen that the thyroid hormones per se have no observable effect upon the dynamics of ventricular contraction in the absence of epi- nephrine or norepinephrine. This fact is in sharp contrast to the increase ventricular contractility in the same animals during the infusion of either l-epinephrine or of l-norepi- nephrine.

It is also to be noted that the arteriovenous oxygen differences of the thyroid-fed dogs with a total sympathetic block are not significantly different from the average arteriovenous oxygen differences of the euthyroid animals. There are also no differences in the serum metabolite or electrolyte concentrations of the euthyroid or thyrotoxic dogs with a total sympathetic block.

The complete similarity of the hemodynamics

* See footnote p. 4.
and metabolism of the euthyroid and thyroid-fed dogs with a total sympathetic block does not only indicate the absence of a quantitatively significant direct effect of the thyroid hormones on these parameters, but also establishes a physiologic rationale for the use of a total sympathetic block in the treatment or prevention of thyrotoxic crisis and storm. Crile, Maddox, Coller and Pedersen, Rea, Bartels and co-workers and Knight have reported that the production of a total sympathetic block by the use of high spinal anesthesia is effective in reducing to normal or near normal values the accelerated heart rate and elevated rectal temperature of hyperthyroid individuals during a thyrotoxic crisis. Crile and Knight similarly reported the use of high spinal anesthesia to prevent the occurrence of tachycardia, hypertension and hyperthermia in thyrotoxic individuals during surgery.

Although no data has been presented in this paper to bear directly upon the problem, it is important to mention that a review of the work of others indicates that the adrenal cortical steroids are essential to the integrity of the end-organ effects, resulting from the combined activity of the thyroid hormones and of L-epinephrine and of L-norepinephrine. The evidence that a dynamic interrelationship exists in the activity of the thyroid hormones, L-epinephrine and L-norepinephrine, and the adrenal cortical steroids comes from the following facts:

(1) Adrenal cortical hypertrophy and hyperplasia occur in thyroid-fed or thyroxine-injected laboratory animals, similar adrenal cortical changes have been observed in the hyperthyroid human, although their occurrence is not uniformly seen. (2) Adrenal cortical atrophy occurs in hypothyroid animals. (3) Adrenalectomy in the hyperthyroid animal results in a decrease in the oxygen consumption of the animal, which may be restored by the administration of adrenal cortical extract alone. (4) Thyroid feeding or thyroxine injection in the adrenalectomized dog or in the Addisonian human results in an increase in the amounts of adrenal cortical steroids necessary to maintain life. (5) Survival time in untreated adrenalectomized animals is greatly shortened by previous thyroxine injection.

(6) Exhaustion atrophy and vacuolization of the adrenal cortex occurs in humans who died, primarily from thyrotoxic crisis. A later paper will deal with these observations.

Variations Between Results Obtained Utilizing a Total Sympathetic Block and Results Obtained Using Denervated or Isolated Organs or Tissues

The following types of preparations have produced results which have led to the conclusion that the thyroid hormones per se directly influence heart rate, ventricular contractility and tissue oxygen consumption. They are presented to show the possible errors which may result from their use in attempting to isolate the activity of the thyroid hormones from that of epinephrine and of norepinephrine.

(1) The Denervated Heart. The denervated hearts in situ or the denervated transplanted heart of thyroid-fed or thyroxine-injected dogs continue to beat at an accelerated rate. This fact has been accepted as evidence that the increased heart rate was due not to sympathetic activity, but to the direct effects of the thyroid hormones. As Cannon and Sawyer and Brown have shown, the heart is perfused by adrenalin released from the adrenal medulla and from the liver, spleen and other organs, following sympathetic stimulation. Not only is the denervated heart not isolated from the activity of epinephrine and norepinephrine, but this preparation was used by Cannon in a classic technic to determine, by observational increases in the rate of the denervated heart, the quantitative release of adrenalin from the adrenal medulla and sympathetic nerve endings of cats in varying physiological states.

(2) Bilateral Adrenalectomy. The persistence of an elevated heart and metabolic rate in adrenalectomized thyroxine-injected animals, maintained with adrenal cortical extract, has been presented as proof that the role of thyroxine in producing these effects is primary in nature. This is not valid since this preparation does not alter the concentrations of norepinephrine and epinephrine released from sympathetic nerve endings throughout the body.

(3) The Isolated Heart-Lung Preparation and the Isolated Tissue Slice. The heart-lung prepa-
Activity of Epinephrine, Norepinephrine and Thyroid Hormones

Rations taken from thyroxine-injected animals were found to beat, immediately after removal and preparation, at a rate faster than those removed from euthyroid animals. This difference in heart rate, immediately after removal, was advanced as evidence of the direct effects of thyroxine upon the heart. However, in the work of Priestley and associates, protocols show that during a four-hour period, following removal of the hearts, there was a progressive fall in the heart rate so that, at the end of four hours, there was little difference in the heart rate of preparations taken from thyroxine-injected and euthyroid animals. The defects in this type of preparation in terms of isolating the activity of epinephrine and norepinephrine from that of the thyroid hormones are several: (a) heart muscle, as shown by Raab, avidly takes up and retains epinephrine and norepinephrine and (b) it has been demonstrated that thyroxine will specifically inhibit the oxidation of epinephrine and norepinephrine. Thyroxine, theoretically by virtue of substitution at the alpha carbon atom on its side chain, can inhibit the activity of amine oxidase and thereby decrease the rate of destruction of epinephrine and norepinephrine by oxidation and deamination. The demonstration of a significant decrease in the amine oxidase concentration in the liver and blood vessels of thyroxine-injected animals by Spinks and Burn and Spinks lends further support to these observations. Furthermore, it has been shown that thyroxine can inhibit the oxidation of epinephrine and norepinephrine to adenochrome and noradrenochrome by a cytochrome-indophenol-oxidase system. Thus, in the heart-lung preparation from a thyroid-fed or thyroxine-injected animal, effective concentrations of epinephrine and norepinephrine may be expected to persist for an appreciable period of time.

In reference to the use of isolated atriums or isolated tissue slices, the persistence of an increased rate of contraction or of an elevated qO2 cannot be taken as an index of the isolated activity of the thyroid hormones. Hökfelt has demonstrated that heart muscle slices, removed from the euthyroid animal and kept at room temperatures for 12 hours, show no appreciable change in the concentrations of epinephrine or of norepinephrine. In the case of other tissues, normal epinephrine and norepinephrine concentrations in the tissue slice persist for as long as 24 hours at room temperature. In contracting perfused heart muscle, a more rapid decline in the concentration of epinephrine and norepinephrine can be expected.

Hökfelt and Goodall have further demonstrated an increase in the norepinephrine concentration in the heart muscle of thyroxine injected rats and sheep. It is thus evident that greater concentrations of the catechol amines may persist and remain active for a longer period of time in tissues isolated from thyrotoxic animals than from euthyroid animals.

In summary, the above technics, purportedly indicating a direct action of the thyroid hormones, do not necessarily, for the reasons outlined, separate the activity of the thyroid hormones from those of epinephrine and of norepinephrine. The technic of a total sympathetic block in the intact thyroid-fed animal is better able to abolish effectively the activity of epinephrine and norepinephrine, both by preventing their reflex release and by leaving intact normal routes for the oxidation or excretion of the catechol-amines, keeping in mind that the destruction of epinephrine and norepinephrine may be significantly retarded in the thyroid-fed animal.

**Summary**

1. Thirty-one dogs were made hyperthyroid by the feeding of 0.8 Gm. U.S.P. thyroid per kilogram of body weight per day for periods varying from 1 to 3 weeks. Twenty-seven euthyroid dogs were studied as controls. The serum protein-bound iodine concentrations of the euthyroid dogs averaged 1.7 μg per 100 cc. Following thyroid feeding, the following serum protein bound iodine concentrations were observed: 7 to 10 days, 16.6 per 100 cc.; 11 to 15 days, 18.1 per 100 cc.; and 18 to 22 days, 16.9 μg. per 100 cc.

2. Thyroid feeding produced the classic hemodynamic and calorigenic effects of hyper-
thyroidism, including significant increases in the heart rate, oxygen consumption, cardiac index and effective ventricular stroke works.

(3) To differentiate between the effects of l-epinephrine and l-norepinephrine and those of the thyroid hormones, the reflex release of epinephrine was abolished in both euthyroid dogs and thyroid-fed dogs by the use of a total epidural preganglionic sympathetic block. The total sympathetic block was produced by the epidural injection of a 0.45 per cent procaine hydrochloride solution.

(4) The metabolic and hemodynamic effects of thyrotoxicosis could be abolished by preventing the reflex release of epinephrine and norepinephrine with a total sympathetic block. Studies done during a 1 to 4 period of total sympathetic block demonstrated that there was no significant difference in the oxygen consumption, cardiac indices, heart rates, average right or left atrial mean pressures, ventricular stroke works and arteriovenous oxygen differences of the thyroid fed dogs as contrasted to the euthyroid group of dogs.

(5) All parameters of activity of l-epinephrine and l-norepinephrine were found to be increased by increased concentrations of the thyroid hormones. The infusion, either of l-epinephrine or l-norepinephrine into thyroid-fed dogs with a total sympathetic block, resulted in a rise in the oxygen consumption, heart rate, cardiac index and ventricular stroke works per unit of filling pressure, significantly greater than that seen during infusion in a comparable series of euthyroid dogs.

(6) Whereas the infusion of l-epinephrine or l-norepinephrine in euthyroid or thyroid-fed animals resulted in equivalent inotropic, chronotropic or calorigenic effects, there was a fundamental difference in the glycogenolytic effects of l-epinephrine and of l-norepinephrine, as reflected in the blood and serum concentrations of lactate, pyruvate and sugar. Whereas the infusion of l-epinephrine consistently resulted in a rise in the serum lactate, pyruvate and blood sugar, the infusion of l-norepinephrine, despite its equal calorigenic effect, produced a fall in the blood and serum concentrations of lactate, pyruvate and sugar.

(7) The normal values of serum lactate, pyruvate and of blood sugar observed in the thyroid-fed animals in the control state suggest that l-norepinephrine is the predominant mediator of the physiologic effects of thyrotoxicosis, as far as the activity of the sympathetic nervous system is concerned.

(8) It is concluded that there is a dynamic interrelationship between the thyroid hormones and l-epinephrine and l-norepinephrine. The physiologic effects of thyrotoxicosis are not the result of the isolated action of the thyroid hormones per se but are due to the physiologic effects of l-epinephrine and of l-norepinephrine, as augmented by the thyroid hormones.

(9) Consideration of the work of others and unreported data from our laboratory indicate that optimal concentrations of the adrenal cortical steroids are essential in order that the dynamic activity of the hormones of the thyroid and sympathetic nervous system become manifest.

Acknowledgment

The authors wish to express their appreciation for the advice and counsel of Dr. Chester A. White, Dr. Claude A. Villee and Dr. John Stanbury. We are indebted to Mrs. Frances Ashodian and Miss Vivian Mays of the Protein-Bound Iodine Laboratory at the Massachusetts General Hospital, and to Mrs. Anne Hurley and Miss Anna Murphy for their assistance in this work.

Summario in Interlingua

Le effectos hemodynamic e metabolic de un bloco sympathetic total e del infusion de l-epinephrina o l-norepinephrina eseva studiate in 27 canes euthyroid e in 31 canes a alimentation thyroide. Le alterationes physiologic producute per le augmentate concentrationes del hormones thyroide eseva abolite per prevenir le discarga reflexe de epinephrina e norepinephrina per medio de un bloco sympathetic total. Il eseva constataque le effectos inotropic, chronotropic, e calorigene de l-epinephrina e l-norepinephrina eseva accentuate per le alimentation thyroide. Nos conclude que il existe un relation dynamic inter le hormones thyroide e inter le hormones del medulla adrenal e le terminationes nerveose sympathetic. Le alterationes hemodynamic e metabolic de thyrotoxi-
cosis non resulta del activitate isolate de hormones thyroide; illos es plus tosto causate per le effectos physiologic de epinephrina e norepinephrina, augmentate per le hormones thyroide. Nostre studios indica que l-norepinephrina es le mediator predominante in le alterationes effectuate per le alimentation de thyroide.

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The Hemodynamic and Metabolic Interrelationships in the Activity of Epinephrine, Norepinephrine and the Thyroid Hormones

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*Circulation*. 1956;13:1-20
doi: 10.1161/01.CIR.13.1.1

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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