

THE METABOLIC EFFECTS OF THE ACETIC AND PROPIONIC
ACID ANALOGS OF THYROXINE AND TRIIDO-
THYRONINE *

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(Submitted for publication September 21, 1959; accepted November 19, 1959)

Within the last six years the identification of several new substances with thyroid hormone-like activity has led to a re-evaluation of the physiological role of thyroxine and of its analogs and derivatives. Since its isolation in 1915 (1) thyroxine was considered the most biologically potent of all simple thyroactive materials until the discovery by Gross and Pitt-Rivers (2) and by Roche, Lissitzky and Michel (3) that 3,5,3'-triiodo-L-thyronine (trit) was four to five times more effective in both animals and man.

The acetic acid analogs of thyroxine and trit have been actively investigated since 1953 (4). Thibault and Pitt-Rivers (5-7) described a unique action of these compounds in that they produced an increased oxygen consumption *in vitro* without previous injection into animals. The maximum effects were reached in 15 minutes and disappeared after 90 minutes. A single injection of these drugs into thyroidectomized rats increased oxygen consumption within two hours. Although these studies have not been confirmed (8, 9), they resulted in the postulate that this might be the form of the thyroid hormone utilized at the tissue level. This suggestion became even more attractive when these substances were isolated from tissues and homogenates (10-17).

Other studies in man have suggested a dissociation of responses to those drugs (18-25). In patients with hypothyroidism, (19, 21) it was noted that on small doses of the acetic acid analogs the serum cholesterol level fell, the nitrogen and

phosphorus balances became negative, and the patients were clinically improved without any significant change in basal metabolic rate. Other studies in euthyroid subjects have demonstrated a lowering of the serum cholesterol level, which was usually temporary, with no effect on the basal metabolic rate, following the administration of small amounts of these acetic acid analogs (18, 20-22, 24-27). These findings suggested that there might be more than one thyroid hormone, that the acetic acid derivatives were primarily effective in cholesterol metabolism, or that a change in the basal metabolic rate was not an obligatory accompaniment of thyroid hormone activity. Other workers, (9, 26-29) have been unable to find a unique dissociation of responses to these compounds in patients with myxedema, although one study (29) has demonstrated a dose-related dissociation of responses to all thyroactive substances investigated.

The present studies were designed to evaluate further, both in animals and in man, the metabolic actions of 3,5,3'-triiodothyroacetic acid (triac), 3,5,3',5'-tetraiodothyroacetic acid (tetrac), 3,5,3'-triiodothyropropionic acid (triprop), and 3,5,3',5'-tetraiodothyropropionic acid (tetprop). The effects of these compounds were compared qualitatively and quantitatively with those of L-thyroxine and trit.

MATERIALS AND METHODS

Animal studies. Thyroidectomized rats were used as sensitive test animals on which to determine the comparative metabolic effects of L-thyroxine, trit, and their respective acetic acid and propionic acid analogs.¹ Four

¹ The authors are grateful to the following for the compounds used in these studies: a) Dr. H. A. Fevold of Travenol Division of Baxter Laboratories for L-thyroxine; b) Smith, Kline and French Laboratories for 3,5,3'-triiodo-L-thyronine; c) Dr. Rosalind Pitt-Rivers

* These studies were supported in part by the Warner-Lambert Research Institute, Wyeth Laboratories, the Eli Lilly Company and the Upjohn Company.

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**EFFECTS ON TISSUE OXYGEN CONSUMPTION OF THYROACTIVE MATERIALS
ADDED TO INCUBATION MEDIUM IN VITRO**

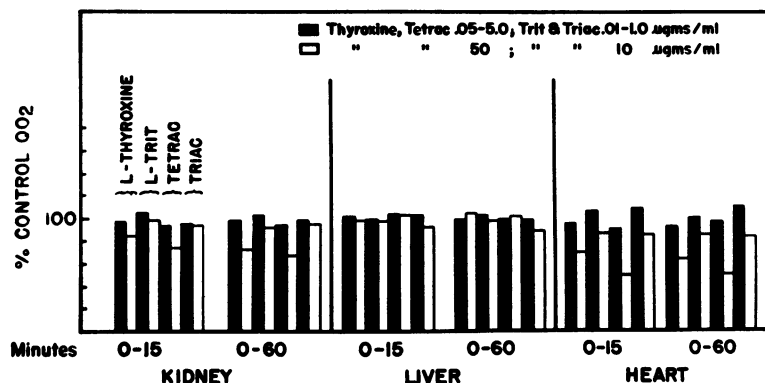


FIG. 1. OXYGEN CONSUMPTION OF SLICES OF KIDNEY, LIVER AND HEART FROM THYROIDECTOMIZED RATS. Studies were made in Krebs-Ringer phosphate glucose solution to which were added the quantities shown of thyroxine, tetrac, trit or triac. Values are expressed as per cent of the control flasks containing the same amount of alkali (0.005 N, final concentration) as that used to dissolve the thyroactive materials. Each bar is the average of eight experiments with readings covering the first 15 minutes and first 60 minutes after a preliminary 15 minute equilibrium period at 37° C.

types of studies were made: *a*) the *in vitro* response of kidney, liver and heart slices to the thyroactive materials; *b*) the response of heart, diaphragm and skeletal muscle oxygen consumption to single large doses of the thyroactive materials injected into thyroidectomized rats; *c*) the action of similar single large doses of these compounds on the basal metabolic rates of thyroidectomized rats; and *d*) the effects of repeated subcutaneous injections of the thyroactive substances on the metabolic rate of seven selected tissues of thyroidectomized rats. In every case the animals were etherized, exsanguinated and the desired tissues removed. These were kept moist with Ringer's solution at 5° C while making suitable preparations (blunt-dissected muscle fiber bundles, isolation of portions of diaphragm and razor blade slices of other tissues) for study of their oxygen consumption. These measurements were made with the standard Barcroft-Warburg technic in a phosphate-buffered Krebs-Ringer solution with glucose as the substrate.

Clinical studies. Clinical effects of these compounds were evaluated in three patients with primary hypothyroidism who were studied while being treated with one or more of the following compounds: trit, triac, tetrac, triprop, tetprop, thyroxine or desiccated thyroid substance.

All patients were studied on the metabolic ward of Birmingham Veterans Administration Hospital. Basal

for some of the acetic acid analogs; and *d*) Dr. Michael C. Barry, Division of Clinical Research, The Warner-Lambert Research Institute, for the majority of the acetic and all of the propionic acid analogs.

metabolic rates (BMR) were determined by a member of the research group using a Benedict-Roth machine. Measurements were made at 8:00 a.m. prior to the patients' daily medication. Pentobarbital, 90 mg, was routinely given orally at bed time the night before the measurement was made. The serum protein-bound iodine levels (PBI) were determined by a modification of the Barker Humphrey and Soley alkaline-ash method (30). The serum cholesterol levels were determined by the method of Pearson, Stern and McGavack (31). Thyroxine and desiccated thyroid were administered orally in a single morning dose. Trit, triac, tetrac, triprop and tetprop were administered orally in two or three divided daily doses. Measurements of the BMR, serum cholesterol and serum protein-bound iodine levels were made at one to three day intervals. In general, medication was held constant at each dose level until stabilization of these measurements had been obtained.

Clinical summaries. Case 1. F.S., a 62 year old male retired farmer, was admitted with typical primary myxedema. He was found to have a BMR of -37 per cent, a serum cholesterol level of 452 mg per 100 ml, less than 1 per cent uptake of I¹³¹ over the thyroid at 24 hours, and a serum protein-bound iodine level of 1.7 μg per 100 ml. Forty-eight hours after administering 30 units of thyroid-stimulating hormone (TSH) intramuscularly, the 24 hour thyroidal I¹³¹ uptake was 6 per cent, which was interpreted as indicating primary hypothyroidism.

He was treated with increasing doses of trit until he gradually became euthyroid. Treatment was then withheld until he was again myxedematous. At this time therapy was instituted with tetrac which was gradu-

ally increased until he was again euthyroid. He was then placed successively on triac, thyroxine, and desiccated thyroid. The doses of the last three compounds were adjusted so as to maintain clinical euthyroidism and normal basal metabolic rates.

Case 2. T.H., a 62 year old male construction worker, entered the hospital with signs and symptoms suggesting primary hypothyroidism. The BMR was -43 per cent. The serum protein-bound iodine level was 1.0 μg per 100 ml and the serum cholesterol was 386 mg per 100 ml. The I^{131} uptake over the thyroid was 8.9 per cent in 24 hours; two days after administering 20 units of TSH intramuscularly the thyroïdal uptake of I^{131} was 7.6 per cent.

Therapy was started with small doses of triiodothyronine, which were gradually increased until he was clinically euthyroid and had normal basal metabolic rates. He was then placed on triac and tetrac successively, at dose levels which were adjusted to maintain clinical euthyroidism and normal basal metabolic rates. Therapy was then withdrawn until he was again myxedematous, after which he was treated with triprop in gradually increasing doses until euthyroidism was again established. He was then placed on thyroxine and desiccated thyroid in turn at dose levels adjusted to maintain clinical euthyroidism and normal basal metabolic rates.

Case 3. R.M., a 48 year old male carpenter, was admitted to the hospital with a history of hypothyroidism following a therapeutic dose of I^{131} given five months previously for toxic nodular goiter. His BMR was

-38 per cent, the serum protein-bound iodine level was 3.1 μg per 100 ml, and the serum cholesterol level was 410 mg per 100 ml. The 24 hour thyroïdal uptake of a tracer dose of I^{131} was 3.9 per cent. He was treated with tetprop in gradually increasing doses until clinical euthyroidism and normal basal metabolic rates were established.

OBSERVATIONS

Animal studies. Many unsuccessful attempts to demonstrate an acceleration of tissue oxygen consumption by the *in vitro* addition of thyroactive substances are summarized in Figure 1. Thyroxine and tetrac were without effect on slices of kidney, liver and heart from thyroidectomized animals when 0.05 to 5.0 μg were added per ml of incubation medium, as were trit and triac at dose levels of from 0.01 to 10.0 μg . At a level of 50 μg of thyroxine or tetrac per ml, depression of heart and kidney metabolism was evident.

To answer the possibility that the compounds applied *in vitro* above were not adequately penetrating the tissues, thyroidectomized animals were injected subcutaneously with one of the following: 2.0 mg thyroxine per kg body weight, 2.0 mg tetrac, 1.0 mg trit or 1.0 mg triac. After allow-

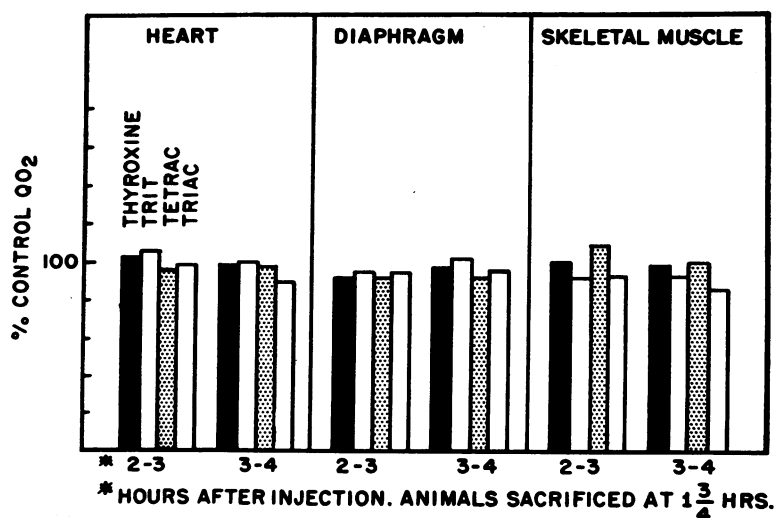


FIG. 2. THE OXYGEN CONSUMPTION OF HEART, DIAPHRAGM AND SKELETAL MUSCLE REMOVED FROM THYROIDECTOMIZED RATS AFTER A SINGLE SUBCUTANEOUS INJECTION OF THYROXINE (2 MG PER KG), TRIT (1 MG PER KG), TETRAC (2 MG PER KG) OR TRIAC (1 MG PER KG). ANIMALS WERE SACRIFICED AT 1.75 HOURS AFTER INJECTION AND TISSUE METABOLISM WAS STUDIED AT 37° C FROM TWO TO THREE AND FROM THREE TO FOUR HOURS AFTER THE INJECTION. EACH VALUE, THE AVERAGE OF SIX EXPERIMENTS, IS EXPRESSED AS THE PER CENT OF A CORRESPONDING SALINE CONTROL-INJECTED ANIMAL.

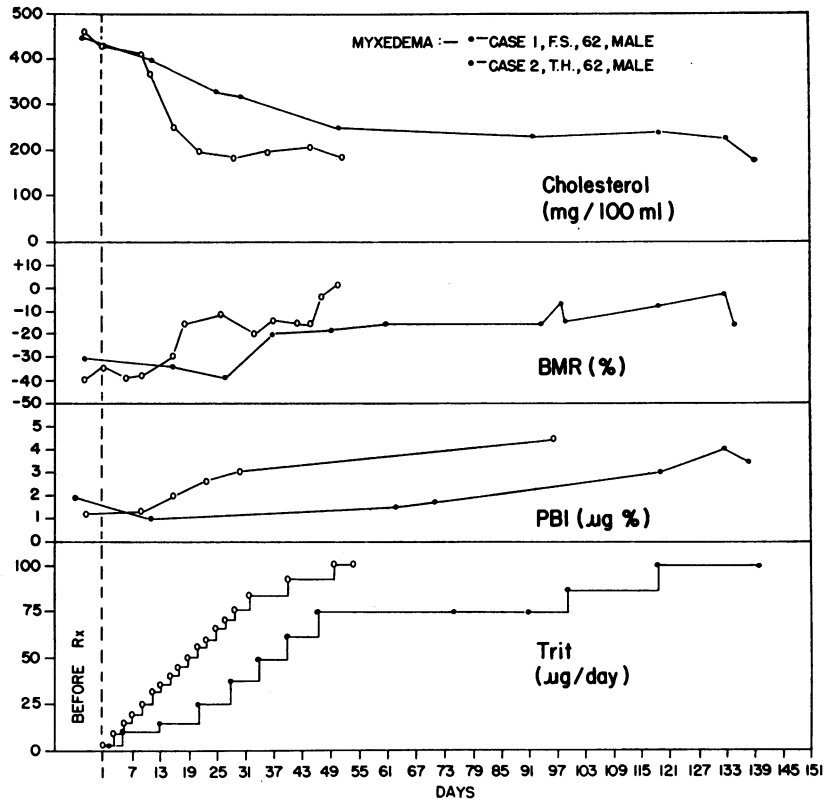


FIG. 3. THE EFFECT OF GRADUALLY INCREASING DOSES OF TRIT ON THE BASAL METABOLIC RATE, SERUM CHOLESTEROL LEVEL, AND SERUM PROTEIN-BOUND IODINE LEVEL OF TWO PATIENTS WITH PRIMARY HYPOTHYROIDISM.

ing 1.75 hours for absorption, the animals were sacrificed, and heart, diaphragm and skeletal muscle were prepared at 5° C for oxygen consumption studies. It is evident from Figure 2 that no consistent metabolic changes were produced in these tissues during the third and fourth hours after injection of the animals, the time of maximum effect previously reported for the acetic acid analogs (5).

Paralleling the lack of *in vitro* or immediate *in vivo* oxygen consumption effects just demonstrated was a similar series of whole-animal BMR measurements covering the four hour time range after a single subcutaneous injection of the same compounds. The results are shown in Table I, as percentage of BMR determinations obtained on the same uninjected thyroidectomized animals. There was a slight elevation in metabolic rate from 0.5 to 1.5 hours postinjection, probably because of the necessary handling of the animals. After that period, the BMR's settled down to the

± 10 per cent range usually encountered with such animals.

In contrast to the absence of *in vitro* or immediate *in vivo* oxygen consumption responses to these

TABLE I
Basal metabolic rates of thyroidectomized rats after subcutaneous injection of thyroxine, trit, tetrac or triac

| Hours after injection | Thyroxine 2 mg/kg | Trit 1 mg/kg | Tetrac 2 mg/kg | Triac 1 mg/kg |
|-----------------------|----------------------|-----------------|-------------------|------------------|
| Control* | 80.6 | 82.3 | 79.4 | 77.0 |
| | % | % | % | % |
| 0.5-1.0 | 106.7 | 109.9 | 112.7 | 103.1 |
| 1.0-1.5 | 118.4 | 107.2 | 110.8 | 96.7 |
| 1.5-2.0 | 95.1 | 93.5 | 95.2 | 102.8 |
| 2.0-2.5 | 104.0 | 104.7 | 103.3 | 111.6 |
| 2.5-3.0 | 112.6 | 96.1 | 109.2 | 110.3 |
| 3.0-3.5 | 105.0 | 107.9 | 107.5 | 104.2 |
| 3.5-4.0 | 108.6 | 100.0 | 105.3 | 108.9 |

* Postabsorptive oxygen consumption is given as milliliters per 100 g body weight per hour prior to injection; all other figures are percentages of control. There were eight animals in each group.

thyroactive substances are results (Table II) showing that the compounds given to thyroidectomized animals in adequate doses over a more extended time are capable of causing appreciable increases in metabolic rate. These data were obtained by injecting subcutaneously the dose shown once each day for four days, then sacrificing the animals on the fifth day. The doses shown were selected because the increases in metabolic rates of the various tissues were all in the range of 25 to 35 per cent above controls. Computed on such a basis, both triac and triprop were 3.4 and 3.8 times as active as tetrac and tetprop, respectively, an enhancement approaching the 4.3 ratio of trit to thyroxine.

Clinical studies. Improvement in hypothyroidism was obtained from all substances studied when given in large enough doses. Cases 1 and 2 were treated initially with trit, starting with small

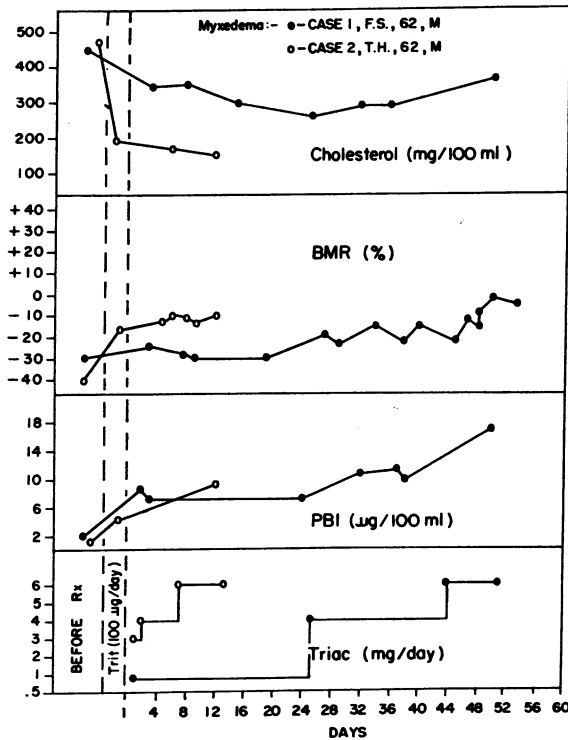


FIG. 4. THE EFFECT OF TRIAC ON THE BASAL METABOLIC RATE, SERUM CHOLESTEROL LEVEL, AND SERUM PROTEIN-BOUND IODINE LEVEL OF TWO PATIENTS WITH PRIMARY HYPOTHYROIDISM. Although Case 1 was myxedematous, the serum protein-bound iodine level remained elevated as a result of tetrac administration which had been withdrawn one month previously. Triac was given to Case 2 immediately after stopping trit.

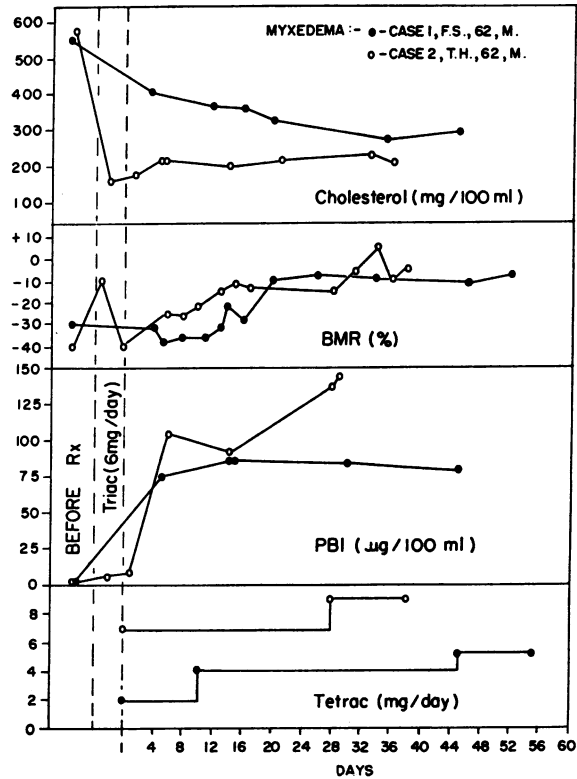


FIG. 5. THE EFFECT OF TETRAC ON THE BASAL METABOLIC RATE, SERUM CHOLESTEROL LEVEL, AND SERUM PROTEIN-BOUND IODINE LEVEL OF TWO PATIENTS WITH PRIMARY HYPOTHYROIDISM. Tetrac was given to Case 2 immediately after stopping triac.

oral doses and gradually increasing to a maximum maintenance dose of 100 µg per day. Increments of 5 µg were made every third day up to a dose of 80 µg in Case 2, and somewhat more slowly in Case 1 (Figure 3). The basal metabolic rate did not start to rise until a dose of approximately 40 µg was reached. In both cases, however, it was observed that the cholesterol was consistently reduced on doses of 20 to 30 µg per day (Figure 3). At this dose level clinical improvement was also manifest. Both patients were clinically slightly hyperthyroid on a dose of 100 µg per day and were euthyroid on 90 µg per day. The BMR returned to normal and the serum PBI level remained in the myxedematous range as expected (32-34).

As illustrated in Figure 4, triac was begun in Case 1 when the patient was myxedematous, with elevated serum cholesterol levels and low BMR's, but with a persistently elevated serum PBI level as

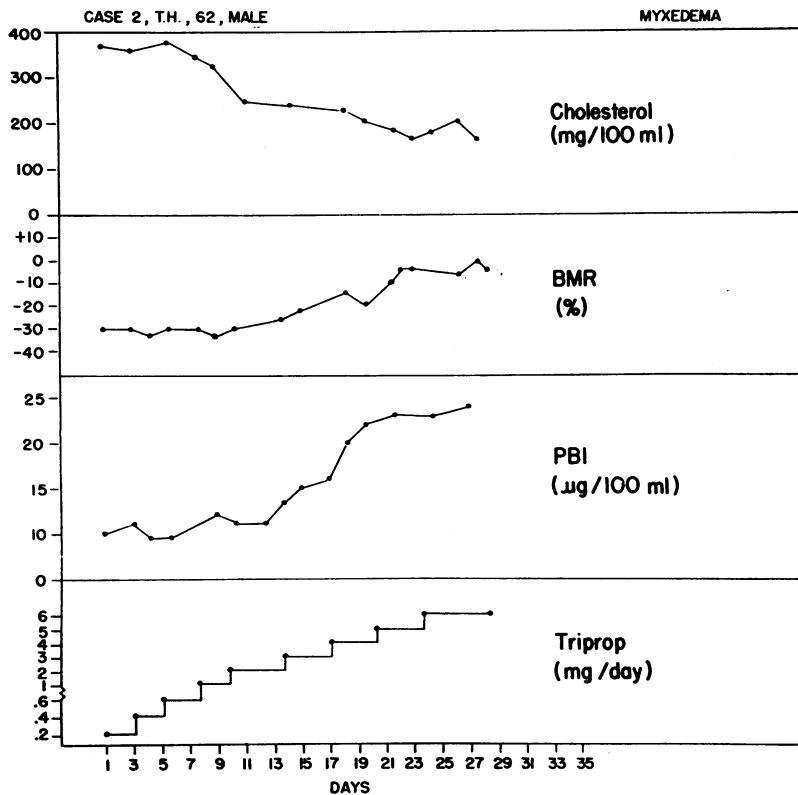


FIG. 6. THE EFFECT OF TRIPROP ON THE BASAL METABOLIC RATE, SERUM CHOLESTEROL LEVEL, AND SERUM PROTEIN-BOUND IODINE LEVEL OF A PATIENT WITH PRIMARY HYPOTHYROIDISM.

a result of tetrac administration which had been discontinued one month previously. In Case 2, triac was substituted for trit in doses which were adjusted to maintain euthyroidism. Triac was found to be weakly thyroactive, and 6 mg per day was required for maintenance of euthyroidism in both Cases 1 and 2. The response of Case 1 to triac again demonstrates a depression of the serum cholesterol level without a concomitant increase in BMR when small amounts of thyroactive substances were given. The serum PBI levels were variable, but were definitely elevated out of proportion to the metabolic state (Figure 4).

As illustrated in Figure 5, the administration of tetrac to Case 1 was begun when he was myxedematous; whereas in Case 2, tetrac was substituted for triac in doses adjusted to maintain euthyroidism. As with trit and triac, it was noted that the serum cholesterol level dropped significantly in Case 1 on small doses of tetrac, without a significant change in the BMR (Figure 5).

This effect was quantitatively slightly greater than that obtained with trit. As would be expected, the serum PBI level was tremendously elevated out of proportion to the metabolic state, and rose in a roughly linear response to the dose of tetrac employed. In Case 2, 9 mg of tetrac was required to maintain normal BMR's and clinical status, and Case 1 was still slightly hypothyroid on 5 mg per day. When tetrac was discontinued in Case 2, the metabolic response was dissipated rather rapidly; the BMR stabilized at -30 per cent within seven days, the serum cholesterol level rose, and the patient appeared myxedematous two weeks later. The serum PBI level, however, was still 10 µg per 100 ml three weeks after tetrac had been discontinued.

At this time, as illustrated in Figure 6, triprop was started in very small doses, and reproducible BMR's were obtained on successive days before increments were made. On 2 mg per day, the BMR had not appreciably changed, while the se-

rum cholesterol level had decreased 120 mg per 100 ml (Figure 6). The patient was clinically euthyroid on 6 mg of triprop per day. The PBI was again elevated out of proportion to the clinical response, reaching levels approximately equivalent to those obtained with triac, but not as high as those with tetrac, in accord with the amounts of iodine administered.

Case 3 was treated initially with tetprop, starting with doses of 2.0 mg daily, which were gradually increased to a maintenance level of 14 mg daily (Figure 7). Despite prolonged training, this patient continued to have marked variability in his BMR's. There was, however, an obvious response in both the BMR and the serum cholesterol level to 2.0 mg of tetprop daily. The serum cho-

lesterol levels continued to fall, but did not reach normal levels until tetprop was given in doses of 12 mg daily, at which time the patient was clinically euthyroid. There was very little change noted in any parameter when the dose was increased to 14 mg daily. As would be expected, the serum PBI levels were markedly elevated although not as high as those obtained following tetrac administration.

Both Cases 1 and 2 were subsequently treated with thyroxine and desiccated thyroid. On 0.3 mg of thyroxine they were clinically euthyroid and the BMR and serum cholesterol levels remained normal, although the serum PBI levels were again slightly elevated out of proportion to the metabolic state. The daily oral dose of desiccated thyroid

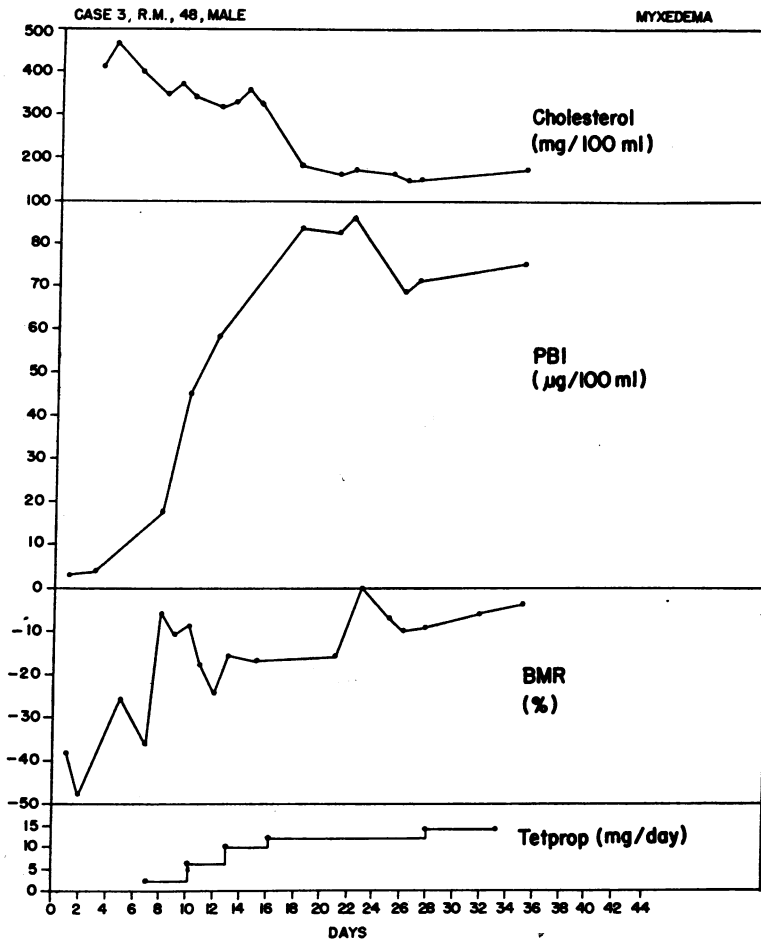


FIG. 7. THE EFFECT OF TETPROP ON THE BASAL METABOLIC RATE, SERUM CHOLESTEROL LEVEL, AND SERUM PROTEIN-BOUND IODINE LEVEL OF A PATIENT WITH PRIMARY HYPOTHYROIDISM.

TABLE II
Effect of repeated injections of thyroactive substances on metabolism of tissues from thyroidectomized rats*

| Substance injected | Thyroxine | Trit | Tetrac | Triac | Tetprop | Triprop |
|------------------------------|-----------|-------|--------|--------|---------|---------|
| Dose (mg/kg)† | 1.0 | 0.25 | 2.0 | 0.6 | 6.0 | 2.0 |
| No. of animals | 6 | 5 | 4 | 4 | 6 | 4 |
| Tissue | % | % | % | % | % | % |
| Kidney | 35.9 | 31.8 | 22.9 | 36.9 | 17.8 | 36.6 |
| Liver | 36.7 | 40.1 | 30.8 | 30.9 | 31.3 | 39.8 |
| Heart | 38.6 | 51.6 | 22.2 | 28.4 | 38.6 | 42.0 |
| Diaphragm | 19.8 | 24.3 | 17.9 | 15.1 | 23.3 | 18.4 |
| Skel. musc. | 31.8 | 32.2 | 20.6 | | 15.9 | |
| Pancreas | 39.1 | 37.4 | 34.0 | | 39.1 | |
| Saliv. gl. | 32.9 | 35.5 | 27.6 | 14.2 | 29.4 | 22.8 |
| Average | 33.5 | 36.1 | 25.1 | 25.1 | 27.9 | 31.9 |
| Per cent‡ | 100 | 431.1 | 37.5 | 127.5§ | 13.9 | 52.8§ |

* Data are expressed as per cent increase above control tissue oxygen consumption.

† Milligram per kilogram of body weight injected subcutaneously once daily for four days; tissue metabolism studied on fifth day.

‡ Relative activity compared to thyroxine as 100 per cent.

§ Based on average of corresponding five tissues.

required to maintain euthyroidism with normal BMR's and serum PBI and cholesterol levels in these two patients ranged from 90 to 120 mg.

DISCUSSION

Gross and Pitt-Rivers (2) found trit to have three to five times the potency of thyroxine in the goiter prevention assay in rats (35). Subsequent work has confirmed a high level of activity (36-38). In this laboratory, we have found that the injection of 0.25 mg trit per kg animal body weight produces the same metabolic stimulation as 1.0 mg L-thyroxine, as shown in Table II. The metabolic response is due to that of tissues such as liver, kidney, skeletal muscle, heart and the exocrine glands. Other tissues such as brain,

spleen, gastric smooth muscle, gonads and accessory reproductive structures of both sexes show no change in oxygen consumption. The pattern of metabolic response is thus the same for triiodothyronine as it is for thyroxine. In man (32, 39-41), trit has been shown to produce all of the metabolic effects of thyroxine. As one would anticipate from the low dose levels required, the serum PBI levels remain in the hypothyroid range when the patient is clinically euthyroid (33, 42). Starr, Snipes and Liebhold-Schueck (34) have demonstrated that trit is adequately measured by the Barker PBI method, and conclude that it is rapidly utilized by the tissues and leaves the blood promptly. In the present study, both patients were slightly hypermetabolic on a daily oral dose of 100 μ g of trit, and were euthyroid on 90 μ g daily. It is apparent that serum cholesterol levels decreased on small doses of trit before there was a significant change in BMR (Figure 3).

Pitt-Rivers and Harrington synthesized and studied both triac and tetrac in the goiter-prevention assay and found that both had a potency of about 0.1 that of triiodothyronine (4, 43). Other studies (Table III) have shown variation in the relative potencies of these analogs. Thibault and Pitt-Rivers (5) reported that triac and tetrac had a profound effect on biological oxidations both *in vitro* and *in vivo*. The results reported in the present study do not confirm these *in vitro* effects nor the immediate effects *in vivo*. However, it is clear that these compounds do have biological properties similar to thyroxine. Although the acetic acid analogs have been demonstrated to be normal products of thyroxine and trit degradation (10-17), there is no clear basis

TABLE III
Relative potencies of thyroactive substances in rats, obtained by various assay technics, and in man

| | Summated tissue response in rats | Human | Maintenance | Goiter prevention in rats* | Calorigenic action in rats* | Thyroid I ¹³¹ uptake block in rats† |
|-------------|----------------------------------|-------|-------------|----------------------------|-----------------------------|--|
| | % | % | mg | % | % | % |
| L-Thyroxine | 100 | 100 | 0.3 | 100 | 100 | 100 |
| L-Trit | 431 | 333 | 0.09 | 800 | 800 | 300 |
| Triac | 128 | 5 | 6.0 | 51 | 21 | 75 |
| Tetrac | 38 | 3 | 9.0 | 57 | 11 | 75 |
| Triprop | 53 | 5 | 6.0 | 28 | 10 | 60 |
| Tetprop | 14 | 2.5 | 12.0 | 14 | 7 | 60 |

* Data from Stasilli, Kroc and Meltzer (37).

† Data from Money, Meltzer, Feldman and Rawson (38).

for assuming that this change is obligatory before the amino acid forms of the hormones can be active.

Lerman and Pitt-Rivers first used triac in the treatment of myxedema (44), giving it daily by intravenous injection in doses of 0.1 to 1.0 mg. Clinical improvement was noted, along with loss of weight and reduction in the serum cholesterol level. There was little alteration in basal metabolic rate. However, when the dose was increased to 4 mg daily the basal metabolic rate returned to normal (19). Trotter, employing 6 mg of triac daily, produced clinical recovery and a return of the basal metabolism to normal levels in a case of myxedema (45). Similar findings have been reported by other investigators, (9, 26, 28, 29). Both patients in the present series receiving triac were clinically euthyroid on 6 mg daily. When small doses were given, a depression of the serum cholesterol level was again demonstrated without a concomitant increase in BMR. The serum PBI level was elevated out of proportion to the clinical state, as one might expect from the large amounts of the drug which are required to maintain euthyroidism.

Goolden found that it required 8 mg orally per day of tetrac to maintain clinical euthyroidism, and that a therapeutic response was evident within 48 hours (27). He also noted that the serum cholesterol level fell on doses less than that needed for maintenance of euthyroidism.

Other workers have confirmed the metabolic activity of this compound (9, 26-29). In the present study tetrac was also found to be a relatively weak thyroactive substance in man, since 9 mg per day was required to restore euthyroidism. At this dose level, the serum PBI was 141 μ g per 100 ml, and rose in a roughly linear response to the dosage employed (Figure 5). On small doses the serum cholesterol level fell without elevation of the BMR. On discontinuance of therapy, one patient was markedly myxedematous at the end of the second week, although the serum PBI level was still slightly elevated.

It is apparent from the present studies in man that, although they are less active, both triprop and tetprop also have metabolic properties similar to thyroxine. The effects of triprop and triac were comparable, the approximate daily dose for maintenance of euthyroidism being 6 mg in both

instances. Tetrop was considerably less active than triprop and slightly less active than tetrac, since 12 mg daily was required to maintain euthyroidism (Table III). Maintenance doses of thyroxine and desiccated thyroid in these patients were established at levels of 0.3 mg and 120 mg daily, respectively.

These studies illustrate that a dissociation of cholesterol and metabolic rate responses may be obtained with trit, thyroxine, triac, tetrac, triprop and tetprop when small enough doses are used. Although this may be a phenomenon shared by all thyroactive substances, it is conceivable that an even more marked dissociation of responses might be obtained by suitable alterations of the thyroxine molecule. Such an achievement has already been approached in the specific case of tadpole metamorphosis, where tetprop and triprop exhibit 120 and 290 times, respectively, the activity of thyroxine (46). This possibility should also be viewed along with the now well established dissociation of responses obtained by altering the molecular structure of the adrenal cortical steroids (47-49).

No peculiarly specific role of the acetic acid analogs in thyroid physiology has been established. It seems unlikely that these weakly thyroactive compounds are obligatory forms of the thyroid hormone utilized by the tissues. Since amino acids in general are broken down through oxidative deamination and decarboxylation, the thyroacetic compounds would be expected as metabolic degradation products of thyroxine and trit. The same cannot be said of the propionic acid analogs, and they should probably be considered as the outstanding contemporary example of purely synthetic thyroactive substances.

SUMMARY

Studies have been done to evaluate, both in animals and in man, the metabolic actions of the acetic and propionic acid derivatives of L-thyroxine and 3,5,3'-triiodo-L-thyronine. The effects of these substances were compared, both qualitatively and quantitatively, with those of the parent compounds. The acetic acid analogs produced an acceleration of oxygen consumption in animal tissue preparations only when they were preinjected in the animals. Both the acetic and propionic acid analogs

were weakly thyroactive in man, with 5 per cent or less of the activity of thyroxine. All of the analogs had metabolic properties similar to the parent compounds. A dissociation of cholesterol and metabolic rate responses was obtained with all compounds, when small enough doses were used.

ACKNOWLEDGMENTS

The authors are grateful for the assistance given by Miss Mary Sheffield, Mrs. Hilda Harris, Miss Joyce Faught and Mrs. W. W. Tofft.

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