Comparative Activities of Thyroxine and its Monosodium and Disodium Salts. (19981)

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Alleviation of the symptoms of thyroid disfunction has been accomplished in the past by the use of thyroid extracts, desiccated thyroid gland, and to a much lesser extent by the use of the pure thyroid hormone, thyroxine. These substances have as a general rule been administered by mouth. More recently, with the development of more effective methods for the synthesis of thyroxine, consideration is being given to the more widespread use of the pure hormone. The advantage to be gained by the use of the pure material is that the drug is a uniform, chemically pure compound, which can be standardized by chemical and physical methods. An apparent disadvantage, based on thyroxine content, is that the thyroxine of desiccated thyroid is apparently better absorbed when given by mouth than is the pure synthetic hormone. Some confusion exists in the literature relative to the comparative effectiveness of free acid thyroxine and its monosodium and disodium salts. It has been reported that in the human, monosodium salts of thyroxine were less effective orally than when given subcutaneously or intravenously (1). It has also been reported that synthetic thyroxine (free acid) was less active when given orally than the monosodium salt(2,7,8). The absorption of crystalline thyroxine from the intestine of the chick was found to be about 20% while the sodium salts were absorbed to the extent of approximately 45% (3). The use of thyroxine tagged with radioactive iodine indicated that about 70% of an oral dose of sodium DL-thyroxine is taken into the blood stream from the intestine(4). Another investigator found that sodium DL-thyroxine has only one-half the activity orally as compared to its parenteral activity(5). In the cow DL-thyroxine was found to be only 12½% as effective orally as when given subcutaneously(6).

Considering the reports that when thyroxine compounds are given by mouth, or parenterally, activity differences occur, which are supposedly dependent upon the route of administration, it seemed advisable to re-evaluate the activity from this standpoint. It also seemed to be important to determine the comparative activities of the synthetic compounds, L-Thyroxine (free acid), monosodium-L-Thyroxine,* and disodium-L-Thyroxine when given by different routes. These compounds were administered by gavage, and by subcutaneous injection, and the data are here recorded.

Materials and methods. Young adult male rats of the Sprague-Dawley strain, weighing approximately 110-120 g, were used as the test animal. All rats were maintained on a standard 18% casein diet during the experimental period. The animals used in each assay were divided into 3 major groups: 1) Normal, untreated controls, 2) Propylthiouracil controls, and 3) Experimentals. All animals were weighed daily, and the average weight changes calculated at the termination of the test period. *Propylthiouracil* was administered according to the technic of Dempsey and Astwood(9). Thirty milligrams of the antithyroxine compound was added to each 100 g of diet. The diet was offered *ad lib.*, and the average food consumption per rat was approximately 225 g in 14 days. Calculated from the average food consumption records, each animal received 67.5 mg of propylthiouracil during the assay period.

Solutions of L-Thyroxine and disodium-L-Thyroxine were prepared from pure crystalline monosodium-L-Thyroxine. Dosages were in μg/100 g of body weight. All dose levels of each of the 3 Thyroxine compounds were administered to two experimental groups, one group receiving the Thyroxine by gavage and the other by subcutaneous injection. A single stock solution of the required concentration was used for both routes of administration. The syringes used for the injections were 0.25 cc graduated in 0.01 cc, and the needles were No. 27 gauge. Gavage was given with a No. 8 French catheter. The animals received treatment for 14 days and were killed on day 15.

* Syntheroid®, Travenol Laboratories.

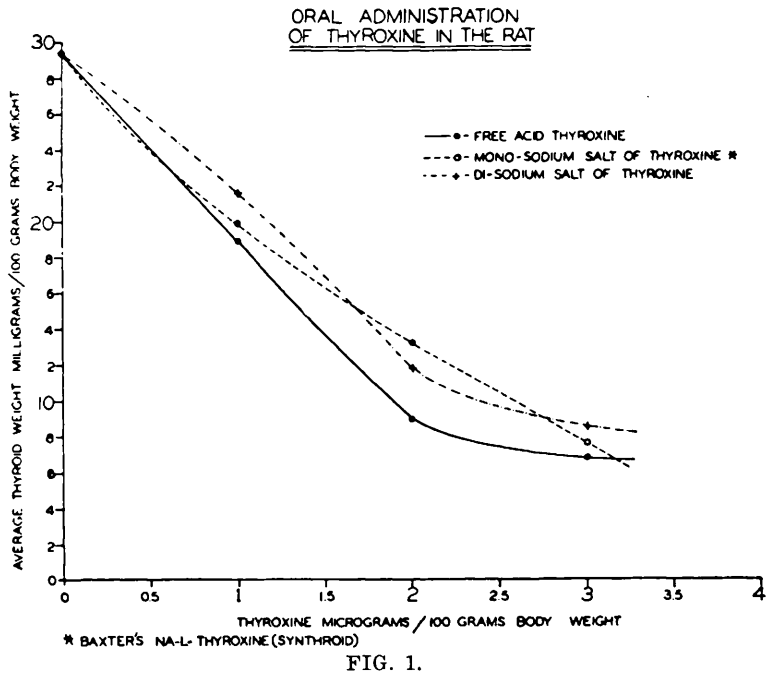

FIG. 1.

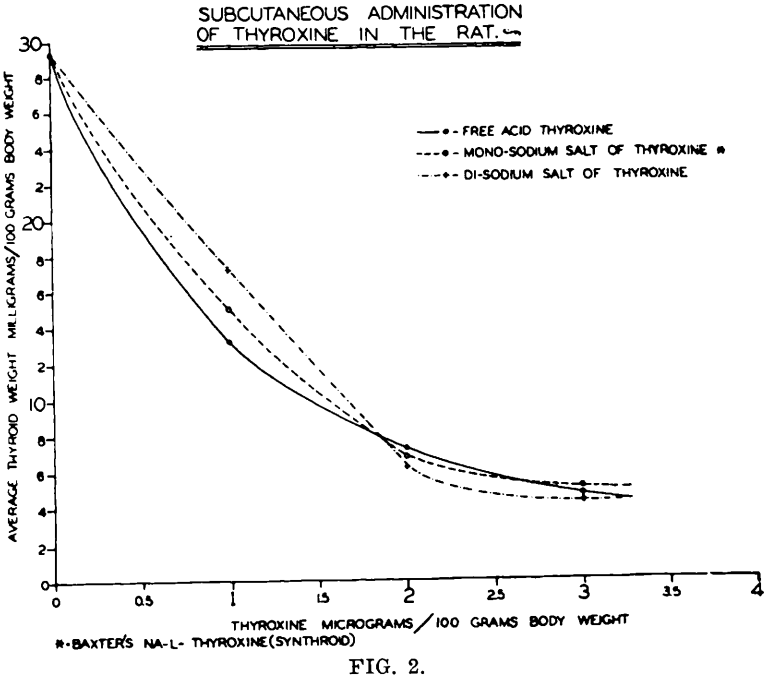

FIG. 2.

The thyroid glands were carefully removed by dissection. The average weight of the thyroids and their average weight per 100 g of body weight was calculated for all the groups in each experiment.

Results. A total of 570 rats were used in the 6 experiments here reported. The average weight of the thyroids of untreated controls was 6.0 μg/100 g of body weight, while those from animals treated with propylthiouracil averaged 29.4 μg/100 g of body weight. A graph of dose-weight relationship when the

thyroxine compounds are given orally, is shown in Fig. 1. It can be seen that to inhibit the effect of PTU, the strength of the dose necessary is 2.5-3.5 μg/100 g of body weight. Fig. 2 is the dose-weight ratio when the thyroxines are given subcutaneously. The amount of the hormone required to maintain the weight of the glands within a normal range is 2.0-2.5 μg/100 g of body weight which is somewhat lower than when the compounds are given orally.

Discussion. The data for the most part are self-explanatory, but two points need further consideration. The first is that oral administration requires a larger dose of thyroxine to bring the propylthiouracil treated thyroid weights into line with normal weights than do subcutaneous injections of the same compounds. Adsorption of the thyroxine in the intestine is a factor in dose requirement (Fig. 1 and 2). The thyroid weight in most of the groups shows a large standard error. Despite the large standard error values, further statistical analysis shows that these values are not too significant because of the great differences between the mean thyroid weight of the control as compared to the mean thyroid weight of the experimental groups. This fact is further emphasized in that the P values for all the groups are less than 1×10^{-4}. A P value of 5×10^{-2} is statistically significant in most experiments.

Summary and conclusions. Experiments, using 110-120 g Sprague-Dawley male rats, were conducted to compare the activity of L-Thyroxine, sodium-L-Thyroxine and disodium-L-Thyroxine administered by subcutaneous and oral routes. There are no significant differences in the antipropylthiouracil effect of the three synthetic thyroxine compounds when administered by the same route. Considering that the gavage method permits some technical error, the amount of thyroxine necessary to inhibit the effect of propylthiouracil is approximately 50% more by the oral method than that necessary by subcutaneous injection.

Addendum. Since this paper went to press, a report of clinical work with sodium L-thyroxine has been published (Salter, William T., and Rosenblum, Ira, *Am. J. Med. Sc.*, 1952, v224, 628). An assimilation by the patients of 67% of the orally given sodium L-thyroxine was reported.

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Effect of Arginine on Growth and Formation of Arginine Dihydrolase in *Streptococcus faecalis.**† (19982)

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Gale(1) showed in strain ST of *Streptococcus faecalis* that cells formed during the first few hours of incubation on an arginine "rich" medium contained a more active arginine dihydrolase enzyme system than cells formed at any later stage of the growth cycle. However, Slade and Slamp(2) found in strain D10 of *S. faecalis* that the first formed cells possessed very little dihydrolase activity. Enzyme formation in this strain commenced after

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