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Lester C. shell
University of Dubuque

Louis Farrugia
University of Dubuque

Danzil Hawes-Davis
University of Dubuque

Alexander Philip
University of Dubuque

Tom Merritt
University of Dubuque

See next page for additional authors

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Authors

Lester C. shell, Louis Farrugia, Danzil Hawes-Davis, Alexander Philip, Tom Merritt, and Dan Lock

Some Effects of Thyroxine-Reserpine Treatment on Growth of Mice

LESTER C. SHELL, LOUIS FARRUGIA, DENZIL HAWES-DAVIS,
ALEXANDER PHILIP, TOM MERRITT, AND DAN LOCK¹

Abstract. Thyroxine, reserpine, and a combination of the two drugs were given to white mice over a ten-week period. Effects on growth rate were noted. Data are presented which indicate that a sequence of thyroxine for two days and reserpine for one day, with the sequence repeated over the experimental period, proved to have greatest effect on growth rate.

Beginning with the early experimentation of Gudernatsch (1912) in feeding thyroid substances to frog tadpoles and continuing to the rather recent and extensive experimentation using birds as a favorable vertebrate for study, much work has been done concerning the effect of thyroid substances on growth patterns. Although thyroid feeding accelerates differentiation, growth is definitely retarded or kept at a minimum in many instances. The basal metabolic rate may be elevated, body temperatures raised, appetite accelerated, respiration excited and general activity much increased, but the growth rates are not often accelerated accordingly.

Man from the earliest time, has had an innate desire to find means of ameliorating the stresses of his environment. The calming and hypotensive effects of Rauwolfia seemed to be the answer until recent scientific methods began to elucidate the fact that the effects were even more than sedation or hypnosis. The discovery of the tranquilizing action of reserpine, one of the alkaloids of Rauwolfia, is of such recent date that the full significance of its alterations are still speculative. Apparently, no work has been done with reserpine on growth effects on mice. Some work has been done, however, with the rat.

The purpose of this investigation was to study the effects of thyroxine and reserpine on growth patterns in mice. Observing that many of the results of use of these drugs were of an opposite nature, these studies were expanded to include certain combinations of the two drugs in our study of growth in mice.

MATERIALS AND METHODS

White mice at age four weeks were given approximately .18 mg. thyroxine per day per mouse in drinking water and were

¹ Department of Biology, University of Dubuque, Dubuque, Iowa.

² This research was aided by a gift of Sandril Reserpine (Lilly) by the Lilly Research Corporation.

weighed each week over a ten week period. Five groups of four mice were used for each determination. Food in the form of Purina commercial laboratory chow was kept before them at all times.

Groups of the same size were given Reserpine.² Each mouse received approximately 0.25 mg per day in drinking water. Control groups, given only laboratory chow and tap water, were observed for comparison in each determination.

In order to see if the toxicity produced in animals given thyroxine over a long period of time could be neutralized by the use of the tranquilizer, Reserpine, a similar group of mice was given the same amounts of thyroxine for two days followed by reserpine for one day and this sequence of dosage repeated over the ten week period. Another group was given the same amount of thyroxine for one day and reserpine for two days and this sequence of dosage repeated over the experimental period. Growth increase each week, measured in grams and averaged for the five groups, was plotted and compared with control groups.

RESULTS

The thyroxine-treated mice showed a slight increase in weight each week, with the increase reaching a peak at the end of the fourth week of experimentation. The increase per week dropped slightly, then gave an irregular pattern during the weeks that followed. These results are shown in Figure 1. The mice were exceedingly active, had excessive thirst, and consumed great quantities of food.

The reserpine treated group showed a very rapid increase in weight each week and reached the peak of increase at the end of the fifth week of experimentation. In this way they followed the same pattern as the control animals. After the fifth week, the rate of increase fell rapidly as the animals became toxic and showed increased defecation and dehydration. Ptosis and miosis were noticeable.

The action of reserpine given alone was characterized by a very slow onset; animals appeared to move about normally for two or three weeks, then their movements were greatly diminished. Treated animals ate larger quantities of food initially than did the control animals, but as their quiescence increased over the experimental period the amount of food consumed dropped steadily. There was no change in the amount of water containing reserpine consumed daily. Results of this part of the experiment are shown graphically in Figure 1.

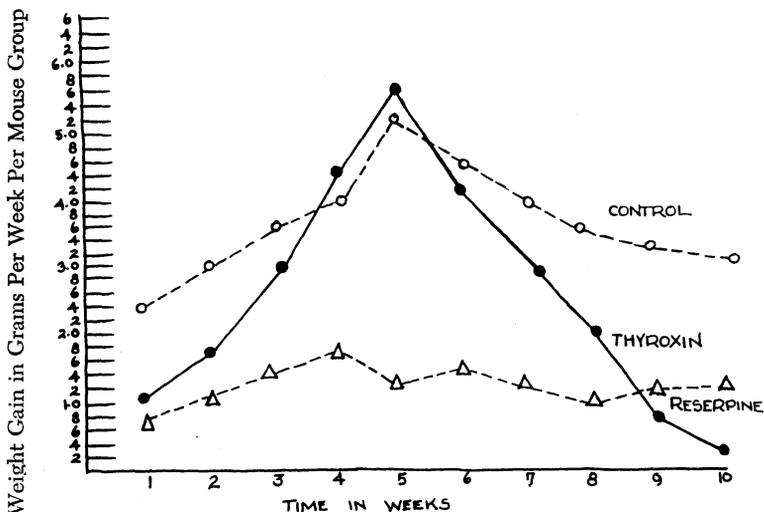


Figure 1. Results of experimentation with five groups of mice, four individuals per group, given thyroxine and reserpine alone showing average weight gain in grams per week per group.

The group given thyroxine for two days and reserpine for one day gave a growth pattern which increased steadily and the increase was sustained at a high rate over a period of several weeks. This rate increase did not show signs of diminishing at the end of the experimental period. Results are shown in Figure 2.

The combination of thyroxine for one day and reserpine for two days gave a slower rate of increase and reached a peak two to three weeks later than the peak reached by the controls, the reserpine group or the thyroid group. The drop from the peak increase was less abrupt than that shown with reserpine alone, and the rate did not level off as was true when the thyroxine-reserpine sequence was given. Results are shown in Figure 2.

DISCUSSION

Thyroxine given alone caused an appetite increase, an increase in activity and excitability but no loss in weight as had been reported by the early work of Magnus-Levy (1939), and in the more recent work of Dobyns and Steelman (1953) on rabbits and dogs. Energy was squandered excessively. The animals appeared toxic and a condition simulating diabetes appeared.

At first the action of the reserpine seemed to be rather slow, which was in accord with the findings of Bein (1953) and

Plummer (1955), as well as those of other workers with a number of different animals being used, but mice not included. The voluntary food intake steadily diminishing followed the same pattern as observed by Gaunt et al. (1954) with rats. With reserpine available at all times in the water, symptoms produced by the drug did not diminish. The mice showed an increased rate of defecation but not the severe type diarrhea Schneider (1955) found with cats and dogs.

The increased defecation and accompanying dehydration could have been responsible for slower weight gain and the eventual severe loss of weight beginning with the tenth week of experimentation. After the experimental period was concluded, it was found that few of the mice lived through more than twenty weeks of continuous treatment. Restoring them to normal conditions with no drugs being administered checked the dehydrating effect. This substantiated the findings of Plummer et al. (1954) that symptoms lasted for some time after the drug ceased to be administered.

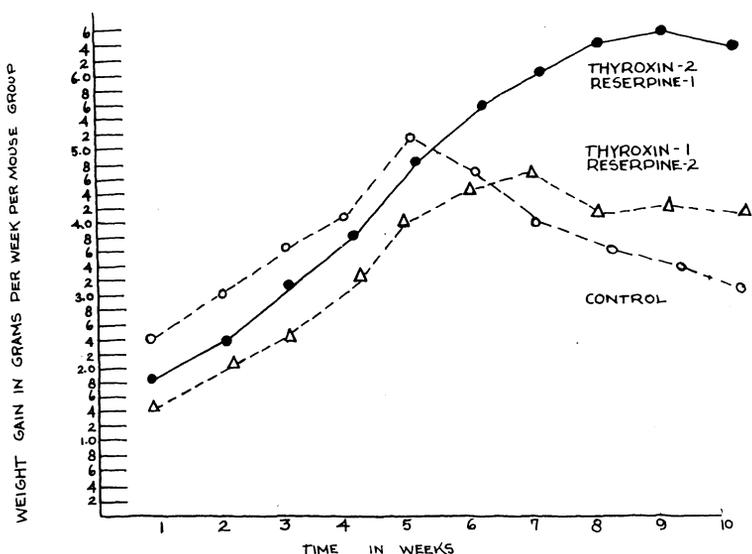


Figure 2. Results of experimentation with five groups of mice, four individuals per group, given thyroxine-reserpine in two different sequences showing average weight gain in grams per week per group.

With the combination treatment of thyroxine-reserpine in the sequence of two days thyroxine and one day reserpine, none of the toxic effects of thyroxine were noticed, energy was seemingly not dissipated, animals displayed normal activity and gained weight steadily. There was no evidence of dehydration as was noticed with the reserpine alone, appetite remained

at a high level, and animals were alert. However, they were not as alert and active as when treated with thyroxine alone. It would appear that many of the undesirable effects of giving thyroxine alone were not noticeable with this particular combination.

Reversing the procedure and giving the reserpine for two days and the thyroxine for one day, growth increase was steady but slower. Defecation was nearly normal and no dehydration effects were noticeable. Ptosis was evident and some miosis, but not as much as was observed when reserpine was given alone. These facts were in accord with those found by Schneider and Earl (1954), working with rats, rabbits, cats and dogs.

CONCLUSIONS

The combination of thyroxine-reserpine treatment with the thyroxine being given for two days and the reserpine for one day, with the sequence repeated over the ten week period of experimentation, gave best results in growth pattern. Growth increase was steady and remained high over the experimental period.

Thyroxine given alone did not bring about a definite decrease in weight, as had been reported by others; neither did it result in as great an increase as was true with control groups.

Reserpine given alone resulted in a much greater increase in weight than in the control animals, but this increase fell rapidly as animals became toxic and showed dehydration.

The combination of reserpine for two days and thyroxine for one day did not approximate the increase shown by the sequence of thyroid two days and reserpine for one day. It more closely approximated the control group, but increases were less per week and the increase was maintained over a longer period than the control group.

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