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THE PHYSIOLOGICAL ACTIVITY OF D-THYROXINE

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The human thyroid gland produces only the laevorotatory isomer of thyroxine (Harington and Salter, 1930); D-thyroxine has, however, been produced synthetically and its properties appraised by many workers, using many different methods. All are agreed that its potency is considerably less than that of L-thyroxine, estimates of relative strength varying between 1:2 and 1:∞.

Estimates of their relative activity in human beings have been few, and much of the earlier work was vitiated by the fact that both preparations were partly racemized. Using purer isomers, Pitt-Rivers and Lerman (1948) found, on the criteria of clinical response and B.M.R., that D-thyroxine had only one-eighth to one-tenth of the potency of L-thyroxine. Starr and Liebhold-Schueck (1953) compared the effects of L-thyroxine, D-thyroxine, triiodothyronine, potassium iodide, and a placebo on the level of protein-bound iodine (P.B.I.) and on the uptake of radio-iodine. Their results were expanded by Starr (1958), and from these two papers some important conclusions may be drawn: (1) that D-thyroxine in a dose five times as great as that of L-thyroxine had an equal effect on the P.B.I.; (2) that by means of a sufficiently large dose of D-thyroxine it was possible to raise the P.B.I. to "thyrotoxic" levels without raising the B.M.R.; (3) that D-thyroxine had very little effect on the level of serum cholesterol; (4) that in hypothyroid patients even a fivefold dosage of D-thyroxine was unable to maintain a B.M.R. stabilized by L-thyroxine; (5) that, whereas the E.C.G. of myxoedematous patients was affected by as little as 0.1 mg. of L-thyroxine, as much as 10 mg. a day of D-thyroxine given for 18 consecutive days was ineffective; (6) that when almost complete suppression of the uptake of radio-iodine was achieved with a given dose of L-thyroxine the same dose of D-thyroxine caused a suppression to only about 40% of the initial uptake; (7) that these results were not vitiated by the iodine content of the thyroxines.

To summarize previous work, it would appear that the effect of D-thyroxine on the metabolic processes considered is extremely slight in comparison with that of L-thyroxine. On the basis of the E.C.G. it may be as little as 1/100 of that of L-thyroxine, and on the basis of the B.M.R. not more than 1/5 and perhaps 1/10. Yet its effect on the uptake of radio-iodine suggests that its depressant effect on the production of thyrotrophic hormone (T.S.H.) is about half that of L-thyroxine.

This observation, if confirmed, suggests several interesting corollaries. For instance, (1) If some forms of hyperthyroidism arise in the pituitary the suppression of the output of T.S.H. (without significant rise in metabolism) by means of D-thyroxine should control the hyperthyroidism. D-thyroxine might prove to be the tool by means of which the primarily thyroid case of thyrotoxicosis could be distinguished from the primarily pituitary case, if indeed two such types exist. (2) If exophthalmos, as is still believed by some despite evidence to the contrary (Greene, 1955; Gilliland and Strudwick, 1956), is due to an excessive production of T.S.H., it should be possible to reduce it by means of D-thyroxine without detriment to the patient.

Experiment I: Clinical Effects of D-thyroxine in Hypothyroidism

In the earlier cases, treatment was begun cautiously with a dosage of 0.25 mg. daily, gradually increased at fortnightly intervals to allow observations to be made at each dosage level. As experience has accumulated the initial dose has been raised.

Eight patients, diagnosed clinically and by laboratory tests as suffering from hypothyroidism, have been treated with D-thyroxine. The results were as follows.

Case 1.—Fibrosis of the thyroid and severe myxoedema. The patient became euthyroid when treated with D-thyroxine in a dosage of 8 mg. daily for a fortnight, and has since remained well on 0.4 mg. daily of L-thyroxine. The ratio of potency of L-thyroxine to D-thyroxine (L:D) is in this case 20:1.

Case 2.—Mild hypothyroidism with impalpable thyroid. She became euthyroid after 4 mg. daily of D-thyroxine had been administered for a fortnight, and has since been maintained in good health with 0.4 mg. of L-thyroxine. L:D=10:1.

Case 3.—Hashimoto's disease and extreme myxoedema. Improvement did not begin until D-thyroxine, 20 mg. daily, had been given for a fortnight. L-thyroxine has now been prescribed in a dosage of 0.5 mg. L:D=40:1.

Case 4.—Moderate myxoedema with impalpable thyroid. Ten mg. of D-thyroxine administered for a fortnight had no effect. She has since been maintained in good health with 0.5 mg. daily of L-thyroxine. L:D=>20:1.

Case 5.—Large diffuse goitre with mild clinical hypothyroidism. She responded in a fortnight to 10 mg. daily of D-thyroxine and has since been kept well with L-thyroxine 0.2 mg. daily. L:D=50:1.

Case 6.—Nodular goitre with mild hypothyroidism. She was relieved by 10 mg. daily for a fortnight, and has since remained well with L-thyroxine 0.4 mg. daily. L:D=25:1.

Case 7.—Moderate post-operative hypothyroidism. D-thyroxine 15 mg. daily for a fortnight had no effect. L-thyroxine was effective in a dosage of 0.5 mg. daily. L:D=>30:1.

Case 8.—Severe post-operative hypothyroidism. 15 mg. daily of D-thyroxine for a fortnight relieved her and she has remained well with 0.3 mg. daily of L-thyroxine. L:D=50:1.

Results of Experiment I

These figures are admittedly meagre, but they support the contention of previous authors that the metabolic effects of D-thyroxine, judged by clinical means, are very slight, the most responsive patient having an "L:D ratio" of 10:1. In the majority of patients it appears that the ratio is far higher, and may be as high as 50:1 or more. Neither the B.M.R. nor the serum cholesterol was measured consistently in a sufficient number of patients for firm conclusions to be drawn, but in no patient was a rise in the former or a fall in the latter observed with a daily dose of less than 4 mg. In 6 of the 8 cases, 10 mg. or more was needed. The serum cholesterol (*pace* Starr, 1958) appeared to fall when the clinical condition was corrected.

Experiment II: Effect of D-thyroxine on the Immediate Thyroidal Uptake of Radio-iodine

In the earlier cases, numbering 10, the slope "S" of the immediate uptake of ^{131}I (Farran, 1958) was measured before the administration of D-thyroxine and afterwards at fortnightly intervals during its administration in various doses.

(a) Four of the patients were originally euthyroid by all criteria. A suppression of iodine uptake occurred with a dose of 1 mg. daily of D-thyroxine in three cases (two with single "hot" nodules, and one with slight diffuse thyroid enlargement). In one patient with a multinodular goitre no suppression occurred with either D-thyroxine (1 mg.) or L-thyroxine (0.3 mg.). One of the patients with a single "hot" nodule showed suppression of iodine uptake with a dose of 1 mg. of D-thyroxine but no suppression with 0.2 mg. of L-thyroxine.

(b) Six of the patients were thyrotoxic and deserve more detailed consideration.

Case 9.—Severely toxic diffuse goitre with severe exophthalmic ophthalmoplegia. The uptake expressed as "S" on 0.25 mg. daily of D-thyroxine was temporarily suppressed from 3.4 to 0.85; 1 mg. daily of D-thyroxine was needed to maintain it at this level. In 10 months no change in the eyes or in the degree of thyro-

FIG. 1.—Response of Case 9 to varying dosage levels of D-thyroxine. (a) B.M.R. (b) Urinary excretion of ^{131}I during 0-6 hours. (c) "S."

toxicosis occurred, and it was necessary to treat the exophthalmos with x-rays to the orbits and the thyrotoxicosis with carbimazole. L-thyroxine 0.3 mg. daily failed to suppress the uptake (see Fig. 1).

Case 10.—Severely toxic diffuse goitre, with severe exophthalmic ophthalmoplegia, acropachy, and pretibial myxoedema. D-thyroxine 0.5 mg. suppressed S from 2.8 to 1.1, but only temporarily; 1 mg. failed to produce any further depression, and it was necessary to terminate the experiment and give x-rays to the orbits and carbimazole.

Case 11.—Slight thyrotoxicosis with impalpable thyroid and exophthalmos. D-thyroxine 0.5 mg. daily produced suppression of S from 2.8 to 1.1; but an increase in dosage to 1 mg. produced no further depression or clinical change, and the experiment was discontinued after three months.

Case 12.—Slight thyrotoxicosis with slightly enlarged thyroid and exophthalmos and a thyroid index ("T") of 24. D-thyroxine in a dosage of 0.5 mg. daily suppressed S to 0 in four weeks; 1 mg. was required to maintain depression, but on stopping treatment S rose to 1.2. No clinical changes occurred.

Case 13.—This and the next case are worthy of special consideration. Case 13 was a male suffering from severe thyrotoxicosis judged by clinical standards. He had a slightly enlarged diffuse goitre, a severe but stationary degree of exophthalmos, a B.M.R. of +24%, a characteristic E.C.G., and pretibial myxoedema. T was 29. D-thyroxine in a dose of 0.25 mg. daily raised gradually to 1 mg. had no effect, but after a fortnight on 1 mg. a slight suppression of uptake occurred, and after 14 weeks the value of S sank gradually from 1.8 to 0. During this time his clinical condition steadily improved and at the end he was clinically euthyroid. His weight had increased by 12 lb. (5.44 kg.) and his B.M.R. had dropped to +11%. Treatment was stopped without, during nine months of clinical observation, any detriment to his clinical condition. Throughout there was no significant change in his exophthalmos, but his pretibial myxoedema disappeared (Fig. 2).

Case 14.—This case also deserves special consideration. It was that of a young woman with severe recurrent thyrotoxicosis four

FIG. 2.—Response of Case 13 to treatment with D-thyroxine. (a) The effect on the B.M.R. (b) "S."

FIG. 3.—Response of Case 14 to treatment with D-thyroxine. (a) The effect on the B.M.R. (b) "S."

years after thyroidectomy, with severe and recently progressive exophthalmos. The B.M.R. was +21%. D-thyroxine in a daily dosage of 0.5 mg. reduced the value of S from 1.6 to 0.75. The dose was gradually raised to 1 mg. daily and the value of S dropped to 0.2. During five months she steadily improved and became clinically euthyroid, with a B.M.R. of +9%. There was no change in the degree of exophthalmos. When seen six months later she remained well (Fig. 3). It would appear, therefore, that 1 mg. daily of D-thyroxine suppressed the uptake of radio-iodine in all these six thyrotoxic patients, albeit temporarily in two. In two, a complete remission of thyrotoxicosis occurred during treatment with D-thyroxine, but in neither was any improvement in exophthalmos observed.

Summary of Results of Experiment II

Of 10 patients—6 thyrotoxic, 4 euthyroid—9 showed a depression of uptake of radio-iodine, most with doses as low as 0.25 mg. daily of D-thyroxine. However, in the majority a daily dosage of 1 mg. was necessary for suppression to be maintained. The only patient in whom suppression did not occur had a multinodular goitre without evidence of either hyperthyroidism or hypothyroidism. A daily dose of 0.3 mg. of L-thyroxine likewise failed to suppress uptake, though, unlike D-thyroxine, it rendered the patient thyrotoxic.

Two patients are worthy of particular stress. Both were suffering from thyrotoxicosis with exophthalmos. A daily dose of 1 mg. of D-thyroxine apparently rendered them euthyroid but failed to improve their exophthalmos. Though the operation of chance cannot be excluded, it is difficult to escape the conclusion that in these two patients the thyrotoxicosis was due to an excessive production of T.S.H. and that the exophthalmos was not, in the period of observation, relieved by its reduction.

Experiment III: Effect of D-thyroxine on the Discharge of Radio-iodine from the Thyroid

The first experiment having shown that 1 mg. of D-thyroxine was sufficient to produce an effect on the uptake, it was decided that the discharge of radio-iodine from the thyroid would perhaps be a more reliable index of the suppression of T.S.H. production. In 12 cases ^{131}I was given orally, 50 μc to patients under 45 and 200 μc to older patients about to undergo treatment with radioactive iodine. After 48 hours, treatment was begun with carbimazole in a dosage of 20 mg. eight-hourly, given in order to prevent re-use of circulating iodide by the thyroid. This drug was chosen instead of potassium perchlorate, which might from some points of view be considered preferable, because in our clinic it is normally used for the preparation of thyrotoxic patients for thyroidectomy and often for therapy with radioactive iodine. Thenceforward counts over neck and thigh were made twice daily, using a partially collimated, wide-angle scintillation counter with an efficiency of about 10 counts per second per μc in the neck. The counting rate over the neck, minus that over the thigh, was plotted against the time in hours, using semilogarithmic paper, so that the biological half-life of the radioactive iodine in the thyroid could be plotted as a straight line. The slope of this line could usually be determined after three or four days, though in one or two cases six or seven days were necessary. When the initial slope had been determined, 1 mg. of D-thyroxine was given daily for 5–10 days, counts twice daily continuing.

Results of Experiment III

An immediate effect of D-thyroxine was observed in 5 of the 12 cases. In 5 cases no discernible change in the slope occurred during the succeeding 7 to 14 days (Figs. 4 and 5). In two cases the initial biological half-life was so long that the results could not be assessed.

An analysis of the characteristics of the five "successful" cases gives no indication of any which clearly differentiates them from the "unsuccessful" cases. All patients in both groups were thyrotoxic, most of them severely. Both groups contained examples of diffusely enlarged and nodular goitres with various degrees of enlargement, and

FIG. 4.—Effect of 1 mg. of D-thyroxine daily on the rate of discharge of ^{131}I from the thyroid. Showing suppression of T.S.H.

FIG. 5.—Effect of 1 mg. of D-thyroxine daily on the rate of discharge of ^{131}I from the thyroid. Showing no apparent effect on T.S.H. production.

of exophthalmos. It is clear that if any clinical difference exists between the two groups a larger series must be examined before it becomes manifest.

Discussion

The results of these experiments give support to previous work and strongly suggest that D-thyroxine has a very weak effect upon tissue metabolism. A numerical estimate of the relative potency of D-thyroxine and L-thyroxine cannot be made at present, but it appears that L-thyroxine is at least 10 times as effective as D-thyroxine by any criterion, and the figure may well be higher. On the other hand, small doses of D-thyroxine have, even in thyrotoxicosis, a suppressive effect on the thyroidal uptake and discharge of radio-iodine and, it may be inferred, upon the production of T.S.H. by the anterior pituitary. This finding is surprising. Werner *et al.* (1952) failed to suppress by means of desiccated thyroid the radio-iodine uptake of thyrotoxic patients. Morgans *et al.* (1952) reported a like failure using L-thyroxine, and Werner and Hamilton (1953) using triiodo-thyronine. The fact that in two of our patients suppression

was produced by D-thyroxine but not by L-thyroxine might suggest that D-thyroxine has a qualitatively different effect from that of L-thyroxine on the anterior pituitary. This seems highly improbable, and further work with both isomers is necessary to resolve the dilemma.

The expectation that cases of thyrotoxicosis might be found in which it would be possible to reduce the metabolism to normal by means of D-thyroxine has apparently been fulfilled in two of six patients treated for three months. This is not so surprising, for Means (1948) has reported a clinical improvement in cases of Graves's disease treated with desiccated thyroid, and Werner *et al.* (1952) quote a single case personally communicated to them by Greer. Moreover, these authors noted that in several of their patients treatment with thyroid was accompanied by a fall in the level of P.B.I. They advanced three possible causes for this finding—the effects of non-hormonal iodine in the desiccated thyroid, of repeated doses of ^{131}I , or of rest in bed. None of these explanations is applicable in our patients. Moreover, the danger to the patient of using thyroid or L-thyroxine is absent when the relatively non-calorigenic D-thyroxine is used.

Although the output of T.S.H. was inhibited, at least temporarily, in almost every case in our series, in no instance was any change seen in the degree of exophthalmos. This observation cannot be explained by the hypothesis that exophthalmos, originally produced by an excess of T.S.H., has become irreversible, for it is a common observation that exophthalmos may decrease or even disappear spontaneously. The doses of D-thyroxine used, smaller than in the hypothyroid patients, were large enough to depress the uptake of radio-iodine for periods up to 10 months, but not large enough to increase metabolism. Our results give support to those who have long doubted the classical hypothesis that exophthalmos is due to an excessive production of T.S.H. by the pituitary.

Summary

The metabolic effects of D-thyroxine are very slight when compared with those of L-thyroxine, the latter being at least ten times as potent. On the other hand, doses of D-thyroxine too small to effect metabolism directly are capable in most cases, even of thyrotoxicosis, of suppressing the uptake of radio-iodine and, by inference, the production of T.S.H. Suppression of the production of T.S.H. appeared to induce a remission of Graves's disease in two of six patients, but the exophthalmos was not improved.

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The fourth annual "Aircent" medical conference, dealing with aviation medicine and the medical aspects of nuclear warfare against air bases, was held at Headquarters, Allied Air Forces Central Europe, Fontainebleau, from October 8 to 10. Group Captain E. S. SIDY, Medical Branch of the R.A.F., presided. Over 50 delegates attended, including senior officers from the Medical Services of the armed Forces of the United Kingdom, the United States, Canada, France, Belgium, the Netherlands, West Germany, and Italy.

THE IMMEDIATE UPTAKE OF RADIOACTIVE IODINE AS A TEST OF THYROID FUNCTION

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The rate of uptake of radioactive iodine by the thyroid has been used as the basis of a number of tests of thyroid function (Myant, Pochin, and Goldie, 1949; Astwood and Stanley, 1947; Goolden, 1958). It is commonly agreed that in about 90% of the cases tested a good separation can be achieved between thyrotoxic and euthyroid patients with an overlap of 5 to 10% whichever method is adopted. The technique reported here has been found of value when an answer is needed immediately or when serial investigations are required on the same person. The radiation dose is extremely small, particularly when ^{132}I is used.

Material and Method

Four scintillation counters with sodium iodide crystals, $1\frac{1}{2}$ in. (3.8 cm.) diameter and 1 in. (2.5 cm.) long, are used. Each crystal is backed by a perspex light guide, $1\frac{1}{2}$ in. (3.8 cm.) in diameter and $\frac{1}{4}$ in. (1.9 cm.) long, which forms the optical connexion to a photomultiplier. The pulses from the four counters are fed into a mixer unit and from there, through an amplifier, to a ratemeter which is connected to a pen recorder (Fig. 1). The counters are mounted in cylindrical lead shields 2 in. (5 cm.) thick, which are positioned so as to form a ring 20 cm. in diameter. The patient is seated in a dental chair, which can be adjusted

FIG. 1.—General view of the equipment.

FIG. 2.—The counters in position round the patient's neck.