EFFECT OF D-THYROXINE ON SERUM CHOLESTEROL

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In the past few years much attention has been focused on the possibility of finding a thyroid "analogue" possessing one desired property of the natural hormone without the other, undesired, ones. In particular, repeated attempts have been made to find a substance which would depress the level of cholesterol in the serum without raising oxygen consumption or in any other way embarrassing the heart.

Starr and Liebhold-Schueck (1953) and Starr (1958) found that in human beings the metabolic activity of D-thyroxine (DT_4) is very slight compared with that of L-thyroxine (LT_4), the "D:L ratio" varying from 1:2 to 1:100 according to the method by which the activities were tested. They then thought that DT_4 had little effect upon the serum cholesterol in the doses used, though a response was shown by one patient treated with 10 mg. daily. However, Greene and Farran (1958) differed from Starr in finding that the level of cholesterol fell when the dose of DT_4 was raised enough, a minimum of 4 mg. a day and in some patients 10 mg. a day being needed. They found that the minimum dose needed to improve the clinical condition of hypothyroid patients was 4 mg. daily, but that some patients failed to improve when given 20 mg. daily. In no case was the B.M.R. raised by a dose smaller than 4 mg., and most patients needed 10 mg. or more. The D:L ratio in different patients varied between 1:10 and 1:50 or more.

At a symposium held in Chicago in December, 1959, much further information became available. Gesler *et al.* (1959) confirmed the previous work of Starr *et al.* and of Greene and Farran in showing that whereas DT_4 is only one-tenth as active calorigenically as LT_4 , it is one-quarter as active in goitre inhibition, and therefore probably in T.S.H. suppression. Tapley *et al.* (1959) produced a possible explanation of the differing effects of the two isomers. They showed that three hours after their intravenous injection into rats there is twice as much DT_4 as LT_4 in the liver and kidney, whereas in the blood and other organs, including heart muscle, there is twice as much LT_4 as DT_4 . One might therefore expect DT_4 to have a more profound effect on the liver (and therefore on cholesterol metabolism) and LT_4 a more profound effect upon the heart. That DT_4 (in equivalent "goitre-prevention doses") has a greater effect than LT_4 in diminishing liver cholesterol in the rat and rabbit was shown by Best and Duncan (1959) and by Kritchevsky and Langan (1959) respectively. Starr (1959) presented a series of cases of myxoedema

with hypercholesterolaemia, diabetes with hypercholesterolaemia, idiopathic hypercholesterolaemia, and healthy controls treated with DT_4 . In all hypercholesterolaemic cases the serum cholesterol levels fell, the doses used varying between 2 mg. and 26 mg. Usually 4 mg. was needed to lower a high cholesterol level. The effects were less consistent with a normal initial level. Changes in the B.M.R. and E.C.G. were rarely observed at a dose level below 10 mg. These results confirmed the findings of Greene and Farran. One patient with myxoedema, angina, and hypercholesterolaemia ceased to have angina when treated with 4 mg. of DT_4 daily, a finding consistent with that of Beaumont and Robertson (1939) and of the later workers who have reported relief of angina in myxoedema by treatment with thyroid. Hoobler, Caldwell, and Beierwalter (1959) obtained an average drop in the level of serum cholesterol to 21% below the initial level with a dose of 8 mg. The drop was sustained and there was no "escape" during long periods of observation. All 14 patients had hypercholesterolaemia without myxoedema; 8 had angina. None of these had an increase in angina, but in two the dose was lowered to 4 mg. because of thyrotoxic symptoms. Goldstein (1959) presented a series, which included cardiac patients. He concluded that at a dose level of 6 mg. daily DT_4 is a safe and innocuous drug. He was less impressed than other speakers by the decrease in serum cholesterol observed, but gave no figures. McCullagh and Sylvester (1959) treated 15 hypercholesterolaemic patients, all euthyroid, of whom nine had diabetes, three had previously had thyrotoxicosis, and one had arteriosclerosis. With doses of DT_4 , which lay between 2 and 12 mg. there was a consistent return of the serum cholesterol to normal levels. One patient became hypermetabolic, a woman who had previously had Graves's disease. Jones (1959) made the important observation, not hitherto confirmed, that DT_4 produces an increase in prothrombin time in patients receiving anticoagulant therapy. He treated 14 patients with coronary disease with doses of 4 to 8 mg. daily. A 27% decrease in serum cholesterol was obtained and maintained for three to six months. Slight increases in metabolism and angina were observed when the dose was 8 mg., but the 6-mg. dose proved safe. Larson and Card (1959) did a "reversed double-blind test" using 4 mg. daily. In subjects with normal or slightly elevated levels of serum cholesterol there was a slight but consistent fall without any increase in metabolism.

At a symposium on derivatives and isomers of the thyroid hormones held in Philadelphia in February, 1960, further evidence was produced. Ruegamer (1960) stated that "diac" and DT_4 caused the greatest reduction in the liver cholesterol of rats of all the substances tested, with no effect on oxygen consumption or growth rate. Starr and Lepp (1960) described further clinical experiences. Oliver and Boyd (1960) called attention to the specific effect of thyroid analogues on cardiac muscle. They had seen angina increased under treatment with DT_4 , but thought that this was the most promising of the substances tested. Starr (1960) administered DT_4 to three patients with myxoedema in a dose of 1 to 2 mg. daily. The serum cholesterol was lowered in three to four weeks from 500 to 300, 330 to 215, and 375 to 280 mg./100 ml. There was no significant change in the electrocardiograms or the basal metabolic rates. At the end of the study the latter were -36, -40, and -40% respectively.

Starr (1961), at the Fourth International Goitre Conference in London, presented a series of some 50 patients. He had found that, in untreated myxoedema, a dose of DT₄ as small as 1 or 2 mg. significantly lowered the serum cholesterol in 30 days without raising the metabolic rate or changing the E.C.G. In idiopathic and diabetic hypercholesterolaemia without hypothyroidism, the same results were achieved with doses of 2 to 8 mg. Patients suffering from angina had been maintained safely on 2 to 4 mg. The decrement was maintained during long periods of observation.

Boyd and Oliver (1960a), working with rats, showed that some iodothyronines cause a relatively greater depression of cholesterol levels with a relatively smaller

increase in heart rate than others. They calculated a serum cholesterol/heart rate ratio and found this to be greatest for LT₂ and LT₄ and lowest for DT₄. They found (Boyd and Oliver, 1960b) that in human subjects the dose of most thyroxine "analogues" needed to keep low the cholesterol level was dangerously near the dose which produced angina, even when the B.M.R. was not increased. The exception was DT₄, which rarely led to angina in euthyroid men with coronary heart disease at a dosage of 7.5 mg. daily, though it reduced the level of cholesterol in the serum by an average of 25%. Cuthbertson *et al.* (1960) found that in rats fed on a diet which raised the serum cholesterol, three times as much DT₄ as LT₄ was required to affect the heart rate.

It would therefore seem that there is ample evidence that DT₄ lowers the level of serum cholesterol to normal in many cases; that the effective dose is from 2 to 10 mg.; that such doses rarely produce a significant rise in the B.M.R. and are in all other respects innocuous in the absence of ischaemic heart disease; and that in this condition DT₄ should be used with care but is probably safe when given in a dose of 4 mg. daily.

Before this information became available we had begun a trial of DT₄ in patients with hypercholesterolaemia, using the dosage suggested by previous work at New End Hospital (Greene and Farran, 1958).

TABLE I

Group	Diagnosis	No. of Patients Examined	No. with High Serum Cholesterol	No. Admitted to Series
I	Diabetes	214	23	11
II	Diabetes with atherosclerosis	69	11	3
III	Atherosclerosis	108	10	5
IV	Idiopathic hypercholesterolaemia	3	3	3
V	Idiopathic hypercholesterolaemia and myxoedema	1	1	1
VI	Disseminated lupus erythematosus	1	1	1
VII	Controls	6	0	6
		402	49	30

TABLE II.—Effects of Treatment with DT₄ on Level of Serum Cholesterol

Case No.	Cholesterol Levels Before Treatment (Averages in Parentheses)	Cholesterol Levels During Treatment (Time in Weeks from Beginning)												Maximum Depression from Average Level before Treatment	
		2	4	6	8	10	12	14	16	18	20	22	24		26
Group I															
1	298, 280 (289)	..	..	177	..	191	217	146	..	207	..	210	..	215	50
2	333, 358 (345)	..	..	203	..	..	..	..	..	..	..	..	..	..	41
3	295, 291, 267 (285)	..	..	..	205	..	187	..	182	..	222	..	255	..	36
4	294, 273, 332 (299)	..	240	318	297	259	..	238	260	290	..	294	318	27	
5	400, 454, 413, 457, 411 (425)	..	255	358	400	..	288	305	225	..	..	..	..	47	
6	325, 315, 317 (319)	..	..	250	282	..	..	..	..	..	..	..	..	22	
7	324, 357, 321 (334)	..	..	203	241	..	282	..	..	..	..	..	..	40	
8	308, 318, 304 (310)	..	..	280	..	278	..	..	..	..	..	..	249	20	
9	375, 427 (401)	..	325	238	209	..	257	291	312	..	..	..	..	48	
10	465, 443 (454)	..	389	371	..	372	333	304	296	..	..	..	..	35	
11	351, 299, 306 (317)	..	257	309	..	..	..	..	..	..	..	..	..	38	
Group II															
12	402, 362, 300 (355)	..	..	205	197	287	..	384	..	276	..	225	232	45	
13	319, 327, 326 (324)	..	257	181	..	..	291	245	265	..	383	441	44		
14	420, 370, 345 (378)	..	280	294	..	..	..	291	250	..	265	..	..	34	
Group III															
15	240, 261, 400 (300)	..	272	..	246	..	256	214	252	..	..	..	..	29	
16	331, 352, 351, 351 (346)	..	305	267	268	..	..	..	277	..	316	319	272	29	
17	324, 283, 400, 295 (323)	..	..	232	218	..	..	..	..	301	..	..	..	23	
18	405, 459 (432)	..	350	..	..	..	302	..	..	238	..	..	..	45	
19	277, 293, 277 (282)	..	254	189	204	..	234	219	233	..	278	..	266	34	
Group IV															
20	308, 308 (308)	..	262	251	..	..	..	189	205	..	225	..	..	39	
21	299, 298 (298)	..	278	237	..	267	..	312	..	299	..	300	279	18	
22	474, 471, 466 (472)	..	388	356	369	322	267	288	274	..	295	..	320	23	
Group V															
23	315, 318 (316)	..	253	225	230	..	237	203	218	..	209	208	185	212	22
Group VI															
24	310, 309, 313 (310)	..	233	309	313	..	278	318	..	276	..	263	25		
Group VII															
25	261, 235, 259 (252)	..	246	289	..	314	..	290	..	225	244	252	276	11	
26	231, 302, 278 (270)	..	225	293	..	..	..	..	..	..	..	..	..	17	
27	272, 296, 278 (282)	..	322	318	..	..	..	..	..	..	..	..	..	+12	
28	285, 275, 285 (261)	..	239	221	..	271	..	286	..	..	..	..	..	16	
29	306, 296, 254 (244)	..	226	298	..	..	..	..	..	..	..	..	..	3	
30	254, 232, 258 (248)	..	257	..	..	..	223	..	..	..	..	..	294	10	

Case 1: 10 mg. No side-effects. Levels normal after further three months. Case 2: 5 mg. No side-effects. Levels normal after further three months. Case 3: 10 mg. No side-effects. Levels normal after further three months. Case 4: 10 mg. Throbbing head. Dose reduced to 5 mg. after four weeks. No side-effects. Case 5: 5 mg. No side-effects. Case 6: 10 mg. Tachycardia. Experiment abandoned. Case 7: 10 mg. No side-effects. Case 8: 5 mg. No side-effects. Case 9: 10 mg. No side-effects. Case 10: 5 mg. Dose increased after 12 weeks to 10 mg. No side-effects. Case 11: 5 mg. No side-effects. Patient left district. Case 12: 5 mg. Despite coronary infarction dose increased after 16 weeks to 10 mg. No side-effects. Case 13: 10 mg. Despite absence of side-effects, dose reduced after 12 weeks to 5 mg. Case 14: 5 mg. Previously severe angina relieved. Case 15: 5 mg. No side-effects. Case 16: 5 mg. No side-effects. Case 17: 5 mg. After 20 weeks dose increased to 10 mg. No side-effects. An uncooperative patient who ceased to attend. Case 18: 5 mg. for 18 weeks. Dose then increased to 10 mg. for 4 weeks, then increased to 15 mg. No side-effects, but for safety's sake dose reduced to 10 mg. after 34 weeks. Levels normal (211 to 268, average 234) for a year since. Case 19: 10 mg. No side-effects, but dose reduced to 5 mg. after 4 weeks. Case 20: 5 mg. Dose increased to 10 mg. after 8 weeks. No side-effects. Case 21: 5 mg. No side-effects. Case 22: Treatment initially with DT₄ reduced level to 350 in 10 weeks. Addition of 5 mg. and later 10 mg. of DT₄ produced no further effect. The effect of 15 mg. of DT₄ is shown. In the next 6 months the levels remained between 205 and 379, average 317. Case 23: See text. Case 24: 10 mg. No side-effects. Cases 25-30: See text.

Present Study

In order to determine the effect of DT_4 on the level of serum cholesterol, cholesterol determinations were made in the blood of patients in the groups shown in Table I. The maximum normal level of cholesterol in the serum was assumed to be 275 mg./100 ml. The discrepancy between the last two columns was due to practical, domestic, or geographical difficulties.

Methods.—In most cases periodic measurements of the B.M.R. and recordings of the E.C.G. were made before and during treatment. With few exceptions at least two, and usually three, determinations of the serum cholesterol were made before treatment. The initial "screening test" was performed in the hospital laboratory, but thereafter tests were performed at intervals of a fortnight in the Glaxo laboratories in order to obviate any differences in technique between the two hospitals in which the trial took place. Only the figures obtained in the Glaxo laboratories are recorded here. The method used was a modification of that of Zlatkis *et al.* (1953) after extraction by the technique of Abell *et al.* (1952). The doses of DT_4 are recorded in Table II. They varied between 5 and 15 mg. daily.

Results

Levels of Serum Cholesterol

The levels of serum cholesterol before and after treatment are shown in Table II. In group I (patients with uncomplicated diabetes mellitus) all patients but one showed a sustained drop in the level, the exception being a patient whose level dropped satisfactorily when he received 10 mg. but rose when, owing to "throbbing in the head," the dose was reduced to 5 mg. Of the patients in group II, one, who had had a coronary infarction, showed at first a satisfactory reduction on 5 mg. but "escaped"; 10 mg. produced sustained reduction without any deleterious effects on the heart. One in whom a good reduction was obtained with 10 mg. (without side-effects) could not be maintained by a dose of 5 mg. and relapsed. The third has been well maintained on 5 mg. for a year, his severe angina being completely relieved. In group III three patients showed a satisfactory reduction which has been maintained; one has shown a tendency to "escape" although the dose has been raised from 5 to 10 mg.; and one responded well to 10 mg. but has not maintained so low a level on 5 mg. In group IV one patient with a cholesterol level only slightly above normal failed to respond. Group V consisted of a single patient suffering from myxoedema. He was treated initially with triiodothyronine, which restored him to normal health. However, his serum cholesterol, which had averaged 458 before treatment, was reduced only to an average level of 350. When DT_4 (10 mg. daily) was added to his treatment no change in his B.M.R. or general health occurred, but the level of serum cholesterol sank to normal, and has remained since between 180 and 250 mg./100 ml. for a period of 14 months.

In group VI (one case of lupus erythematosus) the level of serum cholesterol fell from 313 to 233 mg. under treatment with DT_4 (5 mg. daily) in two months; when treatment was stopped it rose to an average of 311 mg. over a period of four months. Treatment with 10 mg. produced little effect, the range over the next five months being 263 to 318 (average 290 mg.).

In group VII were six diabetics who were not given DT_4 . During the course of the experiment their levels

of serum cholesterol, compared with the average before the experiment, varied greatly, the maximum reduction being of 16%—a warning to the optimists.

Effects on the Heart

In a previous experiment, abandoned and unpublished, we produced with "triac" a temporary angina in a healthy house-physician who was acting as a control. In consequence we were especially watchful for any deterioration in the cardiac condition of our eight atherosclerotic patients, all of whom had ischaemic heart disease. One patient in group I complained of "throbbing in the head" without tachycardia. Two patients in group I and one in group III developed tachycardia. In each case the dose was reduced to 5 mg., when the symptom disappeared, the cholesterol remaining normal. No patient developed angina *de novo* or experienced an exacerbation of pre-existent angina. One patient in group II, previously the victim of severe and frequent attacks, rapidly lost his pain, despite the fact that he had presented no evidence of myxoedema.

Effects of Metabolism

In no instance was there any change in the E.C.G., B.M.R., or pulse rate. The weights of the patients were not significantly affected.

Summary

D-Thyroxine (DT_4) in doses of 5 to 15 mg. daily is capable of reducing an abnormally high level of serum cholesterol, usually into the normal range. This effect is produced by doses too low to affect the E.C.G. or B.M.R. In ischaemic heart disease the drug should be used with caution, but no ill effects have been observed by us with doses not exceeding 5 mg. daily, and some patients in this category can tolerate larger doses. Some need a daily dose of 10 mg. to achieve the desired result. The drug is usually satisfactory in cases of atherosclerosis and diabetes, but in idiopathic hypercholesterolaemia the number of patients treated is too small for conclusions to be drawn.

The question of whether any benefit accrues to the patient when the level of serum cholesterol is reduced to a normal level remains still to be answered.

We are grateful to Dr. T. B. Binns, of Glaxo Laboratories, for supplies of DT_4 and for much helpful criticism; and to Mr. Michael Curwen, statistician to the Royal Northern Hospital, for his valuable advice on the presentation of our findings.

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LONG-CONTINUED INHIBITION OF GASTRIC SECRETION BY POLDINE METHOSULPHATE IN PATIENTS WITH PEPTIC ULCER

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Antacids are widely used to control pain and promote healing in patients with peptic ulcer. Although antacids, provided they are taken often enough and in large quantities (Clark and Hunt, 1958), are unquestionably effective in maintaining a lowered acidity in the gastric contents during the day, they have no influence on the acidity of the gastric contents during sleep. Instead of neutralizing the acid after it is secreted, it would seem better to try to inhibit the secretion of acid continuously even when the patient is in remission. This paper is concerned with treatment of patients with peptic ulcer along these lines, using an anticholinergic substance, poldine methosulphate ("nacton"), which reduces by about one-half the gastric secretion of acid without producing noticeable side-effects.

Present Investigation

In-patients of a previous trial (Douthwaite and Hunt, 1958) and several new patients have been followed as out-patients for periods up to three years. All those studied were admitted to the wards under the care of the consultant physicians because a full course of medical treatment under the best conditions was necessary. With the permission of the clinicians concerned, the trial was discussed with the patients. All except one of those approached accepted the offer.

Relevant facts about the patients, who are all men, are summarized in Table I. The mean duration of their dyspepsia was 10 years, two patients had gastric ulcers and 14 had duodenal ulcers. For the most part the diagnosis rested on the clinical history and radiology. In two there had been a perforation and in two others melaena. Ten had lost more than five weeks from work.

Procedure.—The patients were studied in the wards with test meals first while on dummy tablets and then on poldine, the dose being slowly increased until the patients noted some side-effect attributable to anti-

cholinergic action. The amount was then reduced by 1 mg., or occasionally 2 mg., for each of the four daily doses, until the side-effect was abolished. During their treatment as in-patients they received in addition diets and antacids in accordance with the custom of the clinicians concerned. On their discharge, arrangements were made for the patients to attend for a test meal once a month, having taken their poldine on rising. On these occasions they were encouraged to report even mild dyspeptic symptoms that had occurred during the previous month. Their food was entirely of their own choosing, and antacids in the form of "prodexin" were made freely available.

Test-meal Method.—The method used for assessing the effect of poldine on gastric secretion has been described by Douthwaite and Hunt (1958). In essence it allows the total amounts of acid and chloride secreted in response to a test meal in 30 minutes to be measured by adding the amounts of acid and chloride recovered from the stomach to the amounts calculated to have passed into the duodenum. The amounts of acid and chloride can then be converted into the volumes of the acid component and the volumes of bicarbonate-containing secretion formed by the stomach (Hunt, 1954). The test-meal consists of 750 ml. of a solution containing 50 g. of glucose per litre, which is given down a tube into the stomach after an initial washout.

Dose of Poldine and its Side-effects

The dose of poldine was adjusted for each patient so that he did not notice any side-effects, such as dryness of the mouth, slowness in passing urine, or blurring of vision. As experience accumulated it became apparent that there were sometimes other side-effects that might indicate overdosage.

One patient took a double dose of poldine by accident and complained of severe headache, which ended very abruptly. One patient (Case 5, Fig. 2) noted eructations in the afternoon with an unpleasant odour after eating eggs. The symptom disappeared on reducing the dose. One patient reported reduced potency in the sexual act without loss of libido. As he was able to judge which of two lots of tablets were dummy, using his potency as an index, it was presumably a genuine side-effect. The other patients have not had the same experience. Potency was restored by a small reduction of the evening dose. One man, aged 35, noted slight breathlessness as a possible side-effect. No one noted constipation as a side-effect, although physicians using larger doses of poldine have reported it in their patients.

Tachycardia and extrasystoles, both unnoticed by the patients, have been found. It has been taken as a general rule, possibly overcautiously, that the heart rate should not be allowed to exceed 90 a minute at about two to three hours after the last dose of the drug. This has been made the limiting factor for 3 patients out of 16. In two patients extrasystoles were found occasionally, these were abolished by reducing the dose of the drug.

In one patient (Case 8), who had an excessive hypersecretion before treatment, it appeared that in spite of dryness of the mouth, the gastric effect of the drug was sometimes inadequate to relieve his symptoms. He was given his treatment in five divided doses instead of four, and in this way was able to take more poldine with fewer side-effects and with concurrent more effective control of his dyspepsia. Presumably, by giving the poldine more frequently the concentration at the