LONG-TERM TRIAL OF D-THYROXINE IN HYPERCHOLESTEROLAEMIA

BY

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So far there is no proof that reduction of the blood cholesterol decreases the incidence of ischaemic heart disease and atherosclerosis. Before such proof can be obtained a satisfactory cholesterol depressant suitable for use over many years must be found. It is well recognized that analogues of thyroxine will reduce the level of the blood cholesterol (Boyd and Oliver, 1960; Cuthbertson *et al.*, 1960; Starr *et al.*, 1960; Oliver and Boyd, 1961) by increased excretion or catabolism of cholesterol (Kritchevsky, 1960; Rabinowitz *et al.*, 1962). D-Thyroxine will lower the cholesterol in a dose which does not greatly raise the basal metabolic rate (Boyd and Oliver, 1960; Hoobler *et al.*, 1960). This effect is probably due to the more rapid disappearance from the blood and greater concentration in the liver of dextro- than of laevo-thyroxine (Tapley *et al.*, 1959; Starr, 1960). The present trial was carried out to assess the value of D-thyroxine (sodium salt or free acid) when given over a two-year period in lowering the hypercholesterolaemia of patients with cardiovascular disease and xanthomatosis.

Methods

Patients.—Table I shows the clinical findings in: (a) 19 hypercholesterolaemic patients with evidence of ischaemic heart disease, peripheral vascular disease, or hypertension; Patients 7 and 15 also had retinal vein thrombosis; and (b) eight patients with idiopathic hypercholesterolaemic xanthomatosis, two of whom (Nos. 26, and 27) had idiopathic hyperlipaemia. The xanthomata were measured with callipers at the beginning and end of treatment. Angina was graded in severity, grade 1 being the least and grade 4 the most severe (Wood, 1956). An electrocardiogram was recorded at the beginning and end of treatment in all patients. Intermittent claudication was also graded, grade 1 being the least and grade 3 the most incapac-

citated (Boyd, 1954). To assist in this grading an exercise test was performed in which the distance a patient could walk at approximately 4 (6.4 k.m.) m.p.h. was measured. The basal metabolic rate (B.M.R.) was measured by the Benedict-Roth method, using Robertson-Reid standards (normal range 85 to 120%), before and at the end of treatment. The serum protein-bound iodine (normal 4 to 8 $\mu\text{g.}/100\text{ ml.}$) and inorganic iodine (normal less than 10 $\mu\text{g.}/100\text{ ml.}$) were estimated at the end of treatment.

Blood Cholesterol.—The serum from 10 ml. of venous blood was obtained by centrifuging at 3,500 g for 10 minutes. The serum cholesterol was estimated by method one of Billimoria and James (1960). In all patients a minimum of three estimations of the serum cholesterol at intervals of at least a week were made before treatment was started, and the mean of these was taken as the control level. In all patients this was greater than the normal of 270 mg./100 ml. (range 291–518 mg./100 ml.) During treatment the serum cholesterol was estimated monthly.

Treatment.—Those patients with symptoms of angina or intermittent claudication were given placebo tablets during the preliminary period of observation; these were then replaced by identical tablets containing D-thyroxine. The initial dose of 15 mg./day of D-thyroxine was found to be too high, and was reduced to 7.5 or 5 mg./day. This was given in divided doses and gradually increased until a satisfactory reduction of cholesterol was obtained. The maximum dose tolerated was 12.5 mg./day.

Clinical Results

Treatment was continued for one to two years in all except two patients, one of whom (No. 11) withdrew from the trial, and in the other (No. 1) treatment was stopped after nine months because of increasing angina. The effect of treatment on clinical manifestations is seen in Table II.

TABLE I.—Clinical Manifestations. Patients 1–19, Hypercholesterolaemia; 20–25, Familial Xanthomatosis; 26 and 27, Idiopathic Hyperlipaemia

Patient	Age	Sex	Xanthoma	Angina	Ischaemic E.C.G.	Intermittent Claudication	Hypertension mm. Hg
1	64	M		+	+	+	
2	55	M	XI	+	+		
3	64	F		+			
4	61	M				+	165/95
5	49	F	XI				150/95
6	55	F					185/95
7	60	F		+	+		210/130
8	51	F		+			
9	59	M		+	+		
10	42	M		+	+		
11	23	M		+			
12	64	M	XI	+	+	+	175/95
13	58	M		+	+		
14	61	F		+	+		155/95
15	47	M		+	+		
16	53	M		+	+		
17	38	M		+	+		175/110
18	55	M		+	+	+	155/95
19	56	M					
20	55	F	Xt XI				
21	16	F	Xt				
22	39	M	Xt				
23	54	F	Xt		+		
24	17	F	Xt				
25	42	F	Xt Xu		+		170/100
26	33	M	Xu				
27	41	M	Xu			+	

Xt=Xanthoma tendinosum. Xu=Xanthoma tuberosum. XI=Xanthelasma.

* Previous myocardial infarct.

TABLE II.—Effect of D-Thyroxine on Clinical Manifestations

Patient	Months of Treatment	Xanthomata			Angina	Ischaemia on E.C.G.	Intermittent Claudication
		Xt	Xu	XI			
1	9				Incr.	Unch.	Unch.
2	25				Unch.	Decr.	
3	25			Unch.			
4	25						Decr.
5	26						
6	25						
7	27					Incr.	
8	25						
9	26					Unch.	
10	23						
11	4						
12	23			Decr.		Incr.	Unch.
13	23					Unch.	Unch.
14	24					Incr.	
15	23					Unch.	
16	20				Decr.		
17	19					Unch.	
18	20					Incr.	Incr.
19	17						
20	12	Unch.		Incr.			
21	18						
22	13	Decr.				?	
23	13						
24	16	Incr.	Unch.			Decr.	
25	14		Decr.				
26	16						Incr.
27	18						

Incr.=Increased. Decr.=Decreased. Unch.=Unchanged.

Xanthoma tendinosum was not significantly affected, but xanthoma tuberosum decreased considerably in size in two of the three patients. There was no consistent effect on xanthelasma. Angina was present in 13 patients and it had diminished in two, increased in two, and was unaffected in nine. Temporary increase in angina due to too large a starting dose of D-thyroxine occurred in three patients (Nos. 1, 2, and 3) and in two others (Nos. 7 and 9) when the dose was increased from 5 to 7.5 mg./day. While on treatment one patient (No. 9) had an episode of acute myocardial ischaemia necessitating admission to another hospital, but there was no permanent increase in his angina and the D-thyroxine was continued. On conclusion of the trial a myocardial infarct occurred one week after gradually withdrawing treatment in a patient (No. 22) with no previous angina.

The E.C.G. showed evidence of myocardial ischaemia in 12 patients, and this had increased in four, diminished in two, and was unaltered in five by the end of the trial. In two patients (Nos. 15 and 19) with an initially normal E.C.G., evidence of ischaemia appeared during treatment. There was no correlation between changes in angina and the E.C.G. Intermittent claudication and hypertension were not significantly affected by D-thyroxine.

Clinical evidence of hyperthyroidism due to the drug was found in only two patients, in one of whom (No. 4) the dose of D-thyroxine was started at 15 mg./day when the B.M.R. rose to 125% and in the other (No. 6) at a dose level of 7.5 mg./day when the B.M.R. rose to 120%. The B.M.R. returned to normal with reduction of the dose of D-thyroxine. There was usually a reduction in weight, with a mean fall of 6.9 lb. (3.13 kg.), and a significant rise in the B.M.R., which remained, however, within the normal range (Table III).

While on treatment the protein-bound iodine was elevated in 21 patients, indicating that D-thyroxine was being taken consistently, but in five patients it is possible that ingested iodide may have raised the protein-bound iodine, for the serum inorganic iodide was also raised.

TABLE III.—Effect of D-Thyroxine on Weight, Basal Metabolic Rate (B.M.R.), Protein-bound Iodine (P.B.I.), and Inorganic Iodine (I.I.) at End of Treatment

Patient	Change in Weight (lb.)		B.M.R.			P.B.I. Treatment $\mu\text{g./100 ml.}$	I.I. $\mu\text{g./100 ml.}$
	lb.	kg.	Control %	Treatment %	Change %		
1	+2	+0.9	100				
2	-15	-6.8	87	117	+30	17.4	3.0
3	-8	-3.6	93	107	+14	13.2	6.0
4	-15	-6.8	106	104	-2	17.4	1.0
5	-17	-7.7	108	112	+4	14.4	7.0
6	-8	-3.6	102	109	+7	13.0	30.0
7	-25	-11.3	106	99	-7	9.9	4.0
8	-13	-5.9	95	108	+13	15.0	10.0
9	-3	-1.36	96	95	-1	9.1	3.0
10	+9	+4.1	104	111	+7	17.0	1.0
11	-5	-2.27	97				
12	-13	-5.9	103	96	-7	10.4	8.0
13	-7	-3.17				10.2	3.0
14	-10	-4.5	118			15.1	6.0
15	-7	-3.17	92	115	+23	29.4	10.0
16	-7	-3.17	88	97	+9	11.9	5.0
17	-5	-2.27	98	109	+11	20.0	15.0
18	-15	-6.8	99	117	+18	16.5	12.0
19	+5	+2.27	114	102	-12	30.0	30.0
20	-3	-1.36					
21	-9	-4.1					
22	-2	-0.9	90			13.9	7.0
23	-2	-0.9					
24	+2	+0.9					
25	-9	-4.1				15.2	4.0
26	-3	-1.36	104	116	+12	12.5	30.0
27	-4	-1.8	98	111	+13	22.5	9.0
Mean	-6.9				+7.8		
S.E. $\pm$	1.0				2.7		
P	<0.001				0.02>		
					P>0.01		

Serum Cholesterol

As it has previously been reported that the reduction of serum cholesterol by D-thyroxine is less satisfactory in patients with xanthomatosis (Green *et al.*, 1961; Oliver and Boyd, 1961), changes in the two groups were analysed separately.

Hypercholesterolaemia without Xanthomatosis

There was a fall in the serum cholesterol from a mean control level of 335 to 265 mg./100 ml. on treatment (Table IV). This reduction of 70 mg./100 ml. was significant and represents a fall of 21%. The reduction ranged from 33% to 8%, but in one patient there was a rise of 5%.

TABLE IV.—Change in Mean Serum Cholesterol as a Result of D-Thyroxine

Patient	Mean Control Cholesterol (mg./100 ml.)	Mean Treatment Cholesterol (mg./100 ml.)	Change (mg./100 ml.)	Change as % Control
<i>Hypercholesterolaemia without Xanthomatosis</i>				
1	331	251	-80	-24
2	392	222	-80	-26
3	379	255	-124	-33
4	325	239	-86	-27
5	301	253	-48	-16
6	339	252	-87	-26
7	361	315	-46	-13
8	291	215	-76	-26
9	363	283	-80	-22
10	315	218	-97	-31
11	387	317	-70	-18
12	332	295	-37	-11
13	305	320	+15	+5
14	327	228	-99	-30
15	298	227	-71	-24
16	318	292	-26	-8
17	340	277	-63	-19
18	439	320	-119	-27
19	302	257	-45	-15
Mean	335	265	-70	-21
S.E. $\pm$			7.6	2.0
P			<0.001	<0.001
<i>Hypercholesterolaemia with Xanthomatosis</i>				
20	491	474	-17	-3
21	518	382	-136	-26
22	468	447	-21	-5
23	471	503	+32	+7
24	306	342	+36	+12
25	475	414	-61	-13
26	365	268	-97	-26
27	484	327	-157	-32
Mean	447	395	-52	-11
S.E. $\pm$			25.8	5.8
P			0.1>P>0.05	0.2>P>0.1

The month-by-month change in cholesterol (Fig. 1) showed a mean fall of greater than 20% in each of the first eight months. Thereafter the mean cholesterol began to rise up to the twelve month, showing a partial "escape." In the second year of treatment the level fell again, although by this time there were fewer observations.

It was found that there was a seasonal variation in the reduction of the serum cholesterol. In all the patients (Nos. 2, 4, 8, 10, 14, and 19) in whom the dose of the D-thyroxine was kept constant there was a rise in the cholesterol of approximately 50 mg./100 ml. during the winter with a fall in the summer (Fig. 2). The winter rise in cholesterol was accompanied by a gain in weight (2-12 lb.:0.9-5.5 kg.) in five patients, but a loss (3.5 lb.:1.6 kg.) in one. In the second winter only two patients had a gain in weight. In the other patients, although the dose of D-thyroxine was varied, there was still a tendency for the cholesterol to rise in the winter. The cyclical effect was not due simply to starting treatment in the early months of the year, for treatment in

many patients was continued for two years and peak values of cholesterol in two winters were observed.

Hypercholesterolaemia with Xanthomatosis

There was a reduction of the serum cholesterol from a mean control of 447 mg./100 ml. to a mean treatment level of 395 mg./100 ml. (Table IV). This fall of 52 mg./100 ml. (a drop of 11%) was just not significant. The two patients with idiopathic hyperlipaemia had a greater than average reduction in the cholesterol. The monthly change in cholesterol showed a progressive fall over the first three months to a maximum reduction of 24% (Fig. 3). Thereafter the effect decreased and had disappeared by the eleventh month. After this there was again a fall, but by this time only three patients (two with hyperlipaemia) continued on treatment. In the xanthomatosis group, where the dose of D-thyroxine

was kept constant for sufficient time, there was a rise in the cholesterol during the winter and a fall again during the summer, and a similar trend was observed even when the dose of the drug was varied.

Discussion

A drug which is satisfactory for the long-term control of hypercholesterolaemia should depress the blood cholesterol consistently without toxic effects. D-Thyroxine is not satisfactory on either count. There is undoubtedly a depression of cholesterol in most cases, but the effect is variable, and patients with xanthomatosis are less responsive (Greene *et al.*, 1961; Oliver and Boyd, 1961; Moses, 1962).

There appears to be a seasonal fluctuation with a tendency for the cholesterol to rise accompanied by an increase in weight during the winter. With a constant dose of D-thyroxine the level of cholesterol falls again during the summer. This seasonal variation in the effect may be due to greater metabolic requirements of thyroxine by the body or increased endogenous biosynthesis of cholesterol in the winter. In the normal human there are conflicting reports on a seasonal variation in the blood cholesterol. There is evidence against a seasonal change (Turner and Steiner, 1939; Paloheimo, 1961), and where this is reported, generally in convict communities (Thomas *et al.*, 1961), there is a small rise in the winter of less than 50 mg./100 ml. Administration of exogenous thyroxine over long periods may suppress the secretion of pituitary-thyroid-stimulating hormone (Greene and Farran, 1958; Starr *et al.*, 1960; Oliver and Boyd, 1961), and

with greater requirements due to environmental factors during the winter a relative deficiency of thyroxine could occur, with a rise in the blood cholesterol and an increase in body weight. It is of interest that there is a seasonal incidence of myocardial infarction in young adults, 60% occurring between November and March (Gertler and White, 1954).

In previous studies of the effect of D-thyroxine, an escape in the depression of the cholesterol has been described (Jones and Cohen, 1961; Oliver and Boyd, 1961), but denied by others (Starr *et al.*, 1960; Cohen, 1962). In the present investigation there was a rise in the serum cholesterol after six months in spite of continuing D-thyroxine therapy. This escape was more definite in patients with xantho-

FIG. 1.—Monthly change in serum cholesterol expressed as a percentage of control level in hypercholesterolaemic patients without xanthomatosis.

FIG. 2.—Seasonal variation in serum cholesterol in six patients (Nos. 2, 4, 8, 10, 14, and 19), on a constant dose of D-thyroxine.

matosis. After one year the cholesterol began to fall again, but by this time there were fewer patients continuing treatment, especially in the xanthoma group. This possible cyclic effect is not due to seasonal variation, and at the moment there is no adequate explanation.

FIG. 3.—Monthly change in serum cholesterol expressed as a percentage of control level in patients with xanthomatosis.

Clinically, D-thyroxine had no beneficial effect on ischaemic heart disease, peripheral vascular disease, hypertension, or xanthomata, except perhaps on xanthoma tuberosum. Few workers (Cohen, 1962) have reported on improvement in angina, and true assessment of this symptom is always most difficult. Diminution of xanthomata, particularly xanthoma tuberosum, in patients on thyroid and its derivatives has been described previously (Strisower *et al.*, 1960; Owen *et al.*, 1962), though the number of cases cited is small. Evidence of an increased metabolic rate was shown by the considerable loss of weight and elevation of the B.M.R., but hyperthyroid symptoms occurred in only two patients. The dose of D-thyroxine (5–10 mg.) which is effective in reducing the serum cholesterol is very close to that (12.5–15 mg.) which is apt to aggravate angina or induce hyperthyroidism. The manufacturers of D-thyroxine cannot guarantee that the drug is completely free from the laevo form, which may be a contaminant up to 2%. When doses of 10 mg. are used it is possible that 0.2 mg. or L-thyroxine is also present. This contaminant may account for the loss of weight, and in higher doses for the increased angina or hypermetabolic symptoms.

Summary

A prolonged study of 27 patients, extending over two years, on the effect of D-thyroxine in the reduction of hypercholesterolaemia associated with cardiovascular disease and xanthomatosis, has been carried out.

A significant reduction of the serum cholesterol in the hypercholesterolaemic patients without xanthomatosis was demonstrated but not in those with xanthomata. There was an "escape" in the effect of D-thyroxine on the serum cholesterol by the end of the first year—more definite in the patients with xanthomatosis than in those without.

A seasonal variation in the levels of the serum cholesterol, attributed to the effect of D-thyroxine, was observed with higher levels in the winter than in the summer.

There was no effect on ischaemic heart disease as judged by angina and electrocardiographic change, intermittent claudication, or xanthoma tendinosum, but xanthoma tuberosum diminished in two out of three cases.

The effective dose of the drug in reducing hypercholesterolaemia was very close to that which aggravated angina and produced hyperthyroid symptoms. This may have been due to contamination of D-thyroxine with the laevo form.

It is concluded that D-thyroxine is unsuitable for prolonged use in an attempt to assess the benefit of depressing the blood cholesterol in atherosclerosis and xanthomatosis.

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REFERENCES

- Billimoria, J. D., and James, D. C. (1960). *Clin. chim. Acta*, **5**, 644.
 Boyd, A. M. (1954). *Med. Press*, **231**, 170.
 Boyd, G. S., and Oliver, M. F. (1960). *Brit. med. Bull.*, **16**, 138.
 Cohen, B. M. (1962). *Angiology*, **13**, 69.
 Cuthbertson, W. F., Elcoate, P. V., Ireland, D. M., Mills, D. C., and Shearley, P. (1960). *J. Endocr.*, **21**, 45.
 Gertler, M. M., and White, P. D. (1954). *Coronary Heart Disease in Young Adults*. Harvard Univ. Press, Cambridge, Massachusetts.
 Greene, R., and Farran, H. E. A. (1958). *Brit. med. J.*, **2**, 1057.
 ———, Pearce, J. F., and Rideout, D. F. (1961). *Ibid.*, **1**, 1572.
 Hoobler, S. W., Colwell, B., and Beierwaltes, W. H. (1960). *J. Mich. med. Soc.*, **59**, 1704.
 Jones, R. J., and Cohen, L. (1961). *Circulation*, **24**, 164.
 Kritchevsky, D. (1960). *Metabolism*, **9**, 984.
 Moses, C. (1962). *Angiology*, **13**, 59.
 Oliver, M. F., and Boyd, G. S. (1961). *Lancet*, **1**, 783.
 Owen, W. R., Owens, J. C., and Neely, W. B. (1962). *Angiology*, **13**, 75.
 Paloheimo, J. (1961). *Ann. Med. intern. Fenn.*, **39**, Suppl. 8, p. 1.
 Rabinowitz, J. L., Rodman, T., and Smolinsky, T. L. (1962). *Angiology*, **13**, 81.
 Starr, P. (1960). *J. Amer. med. Ass.*, **173**, 1934.
 ———, Roen, P., Freiburg, J. L., and Schleissner, L. A. (1960). *Arch. intern. Med.*, **105**, 830.
 Strisower, B., Gofman, J. W., Rubin, L., Rosenthal, D., and De Lalla, O. (1960). *Amer. J. med. Sci.*, **239**, 71.
 Tapley, D. F., Davidoff, F. F., Hatfield, W. B., and Ross, J. E. (1959). *Amer. J. Physiol.*, **197**, 1021.
 Thomas, C. B., Holljes, H. W., and Eisenberg, F. F. (1961). *Ann. intern. Med.*, **54**, 413.
 Turner, K. B., and Steiner, A. (1939). *J. clin. Invest.*, **18**, 45.
 Wood, P. H. (1956). *Diseases of the Heart and Circulation*, 2nd ed., p. 711. Eyre and Spottiswoode, London.

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