Most of the data used in this inquiry were collected or abstracted from existing records by Mrs. Eileen Armstrong, Miss Ann Cooper, Miss Ida Giles, Mrs. Betty Mann, and the health visitors of the City of Birmingham, with the help of Miss Milner, Miss Greening, and Miss Cook. Hospital and necropsy records were made available to us by Mr. O. T. Mansfield, Dr. K. W. Cross, the pathologists and records officers of local hospitals, and the City of Birmingham Coroner. Particulars of distaval sales were supplied by Dr. D. M. Burley, of the Distillers Co. (Biochemicals) Ltd. We are grateful to all these people for their ready co-operation.

ADDENDUM.—Since this paper was submitted data have been published by W. Lenz and K. Knapp (*Dtsch. med. Wschr.*, 1962, 87, 1232), G. Pliess (*Lancet*, 1962, I, 1128), and R. W. Smithells (*Lancet*, 1962, I, 1270) which indicate that syndactyly, dislocation of the hip, intestinal malrotation, biliary atresia, absence of the gall-bladder, horseshoe kidney, bicornuate uterus, and abnormal lobulation of the lungs and liver should be added to our list (Table III) of malformations which may occur in association with stunted limbs after the administration of thalidomide. Our data suggest that the incidence of these additional malformations in children with limbs of normal size has not risen recently. The reports of Lenz and Knapp and of Smithells also show that microtia is an exception to our generalization that thalidomide does not usually cause malformations in children with normal limbs. In their series most of those affected had stunted limbs, but between a sixth and a twelfth had limbs of normal size and microtia. Our data are consistent with this finding: absence of the auricle or external auditory meatus was notified in three Birmingham births in 1961 and none in 1957–60.

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STUDIES ON EFFECT OF
D-THYROXINE ON NORMAL SUBJECTS

BY

R. BARNES, M.B., B.S.

J. A. P. TRAFFORD, M.B., M.R.C.P.

AND

P. M. F. BISHOP, D.M., F.R.C.P.

Guy's Hospital, London

Clinical trials of various preparations of D-thyroxine have been undertaken in patients with myxoedema, coronary artery disease, and hypercholesterolaemia (Greene and Farran, 1958; Starr *et al.*, 1960; Greene *et al.*, 1961; Oliver and Boyd, 1961) which have shown that it is possible to produce a sustained depression of serum cholesterol level with no change of the basal metabolic rate or E.C.G. Few reports of the response of normal individuals to sodium D-thyroxine have appeared in this country. The present communication is a report on the effect of this compound on the blood cholesterol level and thyroid function of "normal" subjects—that is, individuals not suffering from myxoedema, coronary artery disease, or hypercholesterolaemia.

Material and Methods

Fifty-five euthyroid individuals volunteered to take part in the trial, which was conducted "double blind," in order to assess the significance of any possible side-effects which might have suggested that the compound has calorogenic properties. The subjects were given either a 4-mg. tablet of D-thyroxine twice a day or a placebo tablet of identical appearance. Fifty-one subjects completed the trial. Before and after one month's tablet administration the basal metabolic rate was determined in 38 according to our modification of the method of Robertson and Reid (1952) and the percentage of ¹³¹I uptake was measured in 32 by the method of Fields and Seed (1957). Only four subjects in each group ("treated" and "placebo") had their serum protein-bound iodine level estimated (method of Grossman and Grossman, 1955). It was not known to us, of course, which patients were given D-thyroxine and which the placebo until the end of the trial, when it transpired that 32 subjects received D-thyroxine and 19 the placebo. Blood cholesterol estimations were performed (method of Zlatkis *et al.*, 1953) immediately before and after the 28-day tablet administration in every case. (The normal range in the department of clinical pathology at Guy's Hospital, where these estimations were carried out, is 150–300 mg./100 ml.)

Most of the subjects were taken at random from the endocrine clinic and no weight-reducing diet was recommended during the period of the trial in those who were obese. The volunteers were not told the exact nature of the tablet nor of any possible side-effects, but were asked at the end of the trial whether they had noticed any untoward effects and were questioned in particular concerning the occurrence of increased sweating, palpitations, angina, or nervousness. No patient complained of any side-effect or complication.

Results

The results obtained with D-thyroxine (32 cases) and with the placebo (19 cases) are set out in the Table.

Serum Cholesterol.—In the group of 32 subjects that received 8 mg. of D-thyroxine a day the serum cholesterol level fell in 30, the average decrease being 48 mg./100 ml. The Chart shows the distribution of the number of cases in each initial serum cholesterol level group and indicates that the greatest fall occurred in the group with the highest initial serum cholesterol. Cases 31 and 32 showed a rise of 25 mg. and 45 mg./100 ml. respectively in the blood cholesterol level instead of a fall. So far as we know both subjects took their tablets as prescribed and made no change in their diet. Cases 33–51 received the placebo and showed no significant fall in serum cholesterol levels with the exception of Case 35, in which a fall of 45 mg./100 ml. remains unexplained. A marked rise of 58 mg./100 ml. in the cholesterol level during administration of the placebo was recorded in Case 39.

Thyroid-function Tests.—(1) *B.M.R.*: In 38 patients the basal metabolic rate was determined before and after tablet administration. None of the subjects receiving the placebo showed a significant change. Two of the subjects (Cases 6 and 11) receiving D-thyroxine, having initial B.M.R. determinations in the high normal range, recorded slightly raised percentages at the end of the trial which were not thought to be significant. (2) *Radio-iodine Uptake*: Radio-iodine (^{131}I) uptake

tests were performed on 32 subjects. No significant change was noted in the placebo group, whereas a marked depression of the radio-iodine uptake occurred in all but two of the individuals receiving D-thyroxine. The depression in Case 16 is within the margin of

Table of Results

Case No.	Sex and Age	Diagnosis	Blood Cholesterol mg./100 ml.		B.M.R.		¹³¹ I% Uptake				P.B.I. μ g./100 ml.		Weight Change	
			Before	After	Before	After	Before		After		Before	After	lb.	g.
							4 hr.	24 hr.	4 hr.	24 hr.				
Subjects given D-Thyroxine														
1	F 25	Normal	266	178									+6	+2,720
2	F 21	Hirsutism	200	110	+1	+1							-1½	-565
3	F 23	Mild obesity	217	170	+7	+9	26	41	20	32	4.8	4.9	+2	+907
4	F 20	Obesity	210	120	-1	-2	20	38	7.4	1.2			Nil	
5	F 32	Normal	230	192	+4	+3	28	42	7	9			Nil	
6	F 23	Hirsutism	165	110	+10	+14	24	33	2.3	2.5	6.4	10	Nil	
7	F 22	Normal	200	148									+1	+453
8	F 25	Obesity	190	126	+2	+4	26	38	6	14			-4	-1,815
9	M 28	Impotence	250	160	+6	+6							Nil	
10	F 25	Obesity	210	160	-2	-6	20	32	1.4	0.4			-3½	-1,585
11	F 20	Hirsutism	190	160	+9	+12					5.1	7.3	Nil	
12	F 33	Normal	215	180	-3	-3	20	34	1.2	1.0			-5	-2,268
13	F 30	Amenorrhoea	200	146	-1	-1	22	38	17	24			Nil	
14	F 24	Mild obesity	190	150	+8	+6	28	45	12	21			+1½	+680
15	F 30	"	246	196	+10	+10	32	39	4	11			-2	-907
16	F 47	Normal	270	210	+4	+8	26	38	24	36			Nil	
17	F 23	Mild obesity	220	190	-1	+3							-2	-907
18	F 22	Normal	190	113	+4	+7	18	28	1	3.4			-1	-453
19	F 46	Obesity	200	150	+5	+8	30	41	12	17			-4	-1,815
20	F 23	Mild obesity	185	129	+4	+6	24	37	1.7	2.7			+1	+453
21	M 35	Normal	290	220	+2	+2	24	38	7	15			+1	+453
22	F 20	Obesity	250	220	-5	-8	20	32					-3	-1,360
23	F 44	"	200	164	-6	-2							+1	+453
24	F 31	Normal	220	204	+2	+4					4.1	6.1	Nil	
25	F 24	Mild obesity	165	140	+4	+6	21	36	4	7			-2	-907
26	M 28	Normal	250	175									Nil	
27	F 26	"	300	210									Nil	
28	F 28	"	270	210									Nil	
29	F 25	"	170	150									Nil	
30	F 27	"	176	150									Nil	
31	M 27	"	170	195									Nil	
32	M 27	"	190	235									Nil	
Subjects given Placebo														
33	M 30	Normal	270	260									Nil	
34	M 26	"	165	165									+4	+1,815
35	F 23	"	265	229									Nil	
36	F 44	Obesity	200	200									-2	-907
37	M 25	Impotence	160	180	+6	+4	18	36	19	29			Nil	
38	M 28	"	170	180	+4	+4	16	34	16	30			Nil	
39	F 25	Obesity	188	246	+7	+3	17	28	16	34			+4	+1,815
40	F 41	"	164	180	+2	+4	18	26	20	29			+2	+907
41	F 22	Mild obesity	168	178	-1	-2	14	31	19	38			+3	+1,360
42	F 22	Normal	110	120	+1	+1	18	34	15	32			-1	-453
43	F 24	Hirsutism	265	268	-3	-2	16	22	15	26	4.1	4.3	Nil	
44	M 26	Impotence	260	254	+1	+2	20	28	18	30			Nil	
45	F 27	Normal	220	224	+3	+2	19	32	16	33	4.7	4.8	Nil	
46	F 24	"	196	193	+6	+5	18	38	17	37			Nil	
47	F 28	Mild obesity	222	231	+3	+1	17	41	18	38	4.8	4.9	-1	-453
48	M 31	Impotence	206	213	+8	+8	16	28	15	31			-2	-907
49	M 30	Normal	200	204	+9	+6	18	31	17	34	5.3	5.1	-1	-453
50	F 22	"	196	188	+2	-3	14	34	15	31			Nil	
51	M 23	"	236	241	+2	-1	20	32	18	35			Nil	

experimental error, but in Case 3 there is probably a slight but significant depression. (3) *Serum Protein-bound Iodine*: In only four cases in each group were serum protein-bound iodine estimations performed. These studies, however, are inadequate to entitle us to reach any conclusion on the effect of D-thyroxine on the serum protein-bound iodine level.

Weight Change.—The Table indicates that there was no significant change of weight in either group.

Discussion

Comparatively few reports of the effect of D-thyroxine in normal subjects have been published. Greene *et al.* (1961) have reviewed the recent literature on the properties of D-thyroxine and have reported its effect in 30 patients: 24 suffered from a variety of pathological conditions associated with raised serum cholesterol levels. These included three cases of primary hypercholesterolaemia, one of myxoedema, and 11 of diabetes mellitus. There were only six normal individuals among his 30 subjects, and Starr (1960) had 22 "controls" in his series. Boyd and Oliver (1960) refer to 12 normal subjects in evaluating the effects of a variety of thyroid analogues on plasma lipids.

Greene and Farran (1958) reported on the physiological activity of D-thyroxine. Earlier estimates of the relative activity in human beings of D- and L-thyroxine were vitiated by the fact that the preparations used were partly racemic. Pitt-Rivers and Lerman (1948) found, on the criteria of clinical response and B.M.R., that the potency of D-thyroxine was only 1/8 to 1/10 that of L-thyroxine. Starr and Liebhold-Schueck (1953) compared the effects of D- and L-thyroxine, triiodothyronine, and a placebo on the level of protein-bound iodine and on the uptake of radio-iodine. They concluded that D-thyroxine in five times the dosage of L-thyroxine showed an equal effect on the P.B.I. and that D-thyroxine had very little effect on the level of serum cholesterol. They also found that in hypothyroid patients even a fivefold dosage of D-thyroxine was unable to maintain a B.M.R. originally stabilized by L-thyroxine and that the E.C.G. of myxoedematous patients which can be affected by as little as 0.1 mg. of L-thyroxine daily required 10 mg. of D-thyroxine to produce an equivalent change. When they gave a dose of D-thyroxine similar to the dose of L-thyroxine which would cause almost complete suppression of radio-iodine uptake they obtained only 40% suppression.

Greene and Farran (1958) found that the dosage of D-thyroxine required to control hypothyroidism was between 10 and 50 times as high as that of L-thyroxine, but that they could depress the radio-iodine uptake in 10 patients with as low a dose as 0.25 mg. daily, although a daily dose of at least 1 mg. was necessary to maintain this depression. Only 4 of the 10 patients were thought to be euthyroid.

Starr *et al.* (1960) reported on the effect of sodium D-thyroxine on 22 normal subjects. The pretreatment mean serum cholesterol value was 210 mg. and administration of 6 mg./day of sodium D-thyroxine produced a reduction in only an occasional case. The post-treatment mean cholesterol was 190 mg./100 ml., a reduction of only 9%. They therefore concluded that the drug is effective only "when an abnormal accumulation of serum cholesterol has occurred." This is in contrast to our own findings in 32 normal subjects, 30 of whom responded to D-thyroxine. Our pre-

treatment mean serum cholesterol was 215.8 mg./100 ml. compared with his level of 210 mg., but our post-treatment mean level was 167.8 mg./100 ml. This represents a mean reduction of 22.3%. It is of interest that a reduction of this order was reported by Starr (1960) in patients with initial hypercholesterolaemia and that the reduction was greater the more elevated the initial level. Cohen and Bindelglass (1960) also found that the reduction was proportional to the initial level and this appears to be the case in our own series (see Chart).

Greene and Farran (1958), Boyd and Oliver (1960), and Starr *et al.* (1960) have all emphasized that sodium D-thyroxine has little effect on the E.C.G. and B.M.R. It is the separation of its calorogenic and lipid properties that enables sodium D-thyroxine to be used as a cholesterol-reducing agent. Thyroid-function studies in our subjects confirm the previous report of Greene and Farran that the ^{131}I uptake is depressed. In only two of the subjects receiving D-thyroxine was the radio-iodine uptake not significantly depressed, though there was little change in the B.M.R. in any of the cases studied. It has been suggested (Greene and Farran, 1958) that the suppression of radio-iodine uptake is due to inhibition of T.S.H. release, though Alexander *et al.* (1961) have shown, at least in thyrotoxic patients, that this effect is due to liberation of iodine from the D-thyroxine and is therefore a "dilution" effect, the uptake of ^{127}I being unaltered.

Summary and Conclusions

A double-blind trial using sodium D-thyroxine was carried out in 51 euthyroid volunteers, at the conclusion of which it transpired that 32 had been taking D-thyroxine, two 4-mg. tablets daily, while 19 had been taking placebo tablets of an identical appearance. Of the 32 individuals on D-thyroxine, 30 responded with a fall in the serum cholesterol level, whereas no change was noted in the subjects taking the placebo tablets. The mean reduction of serum cholesterol in the subjects on D-thyroxine was 48 mg./100 ml., the mean fall being 22.3%. There was no significant alteration in the weight or B.M.R. in either group. In all but two of the subjects in whom the radio-iodine uptake was studied it was found to be reduced when sodium D-thyroxine had been given. In our experience, therefore, sodium D-thyroxine is effective in reducing the cholesterol level in normal euthyroid subjects though this is contrary to previous reports.

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