Sodium Dextro-Thyroxine in Coronary Disease and Hypercholesteremia

By Richard J. Jones, M.D., and Louis Cohen, M.D.

A striking reduction in serum lipids as a consequence of the administration of thyroid substance has long been appreciated. However, thyroid analogues have not been regarded as practical agents for lowering the serum cholesterol of euthyroid patients because of their more primary calorigenic and cardiac stimulating effects\(^1,2\) and because of the reported escape from this effect.\(^2,5\) More recently fairly substantial evidence has suggested that various other measures of thyroid activity, including serum lipid reduction, do not necessarily parallel the calorigenic activity of many analogues of thyroxine and triiodothyronine,\(^4,5\) and the escape of serum lipids after prolonged administration of such compounds has been found to occur only at low dosage.\(^6\)

Of these analogues particular interest has centered about the dextro-isomer of thyroxine. Pitt-Rivers and Lerman\(^7\) found that the calorigenic effect of the dextro-isomer was one tenth that of the naturally occurring 1-thyroxine. According to Starr\(^8,9\) a dose of dextro-thyroxine 50 times the usual therapeutic dose of levo-thyroxine had a suppressive effect upon the serum cholesterol with little, if any, calorigenic effect in diverse patients showing serum cholesterol elevation. He\(^8,9\) has further suggested that it has a minimal effect on the heart in comparison with a calorigenically equivalent dose of levo-thyroxine. Oliver and Boyd\(^11\) have claimed that, among many compounds studied, dextro-thyroxine showed the greatest disparity between its calorigenic and hypcholesteremic effect. Larson and co-workers\(^12\) found no deiodination of dextro-thyroxine in an in vitro system. However, comparative isotope studies on the disposition of d- and l-thyroxine in the rat by Tapley and co-workers\(^13\) revealed not only that d-thyroxine was excreted more rapidly, but also that it was concentrated twice as much in the liver while only one sixth as much in other tissues (e.g., heart muscle) as was l-thyroxine.

Material and Methods

Outpatients of the University of Chicago Clinics with coronary disease or hypercholesteremia, and on whom monthly values of serum cholesterol were available for 6 months before treatment, were given 4 to 8 mg. of sodium d-thyroxine\(^*\) daily. The larger dose was used initially, but the 4 or 6 mg. dose was later used, even as the starting dose, when adverse effects on the larger dose became apparent. Basal metabolic rate, pulse rate, and blood pressure were measured initially and at least once more, after about 3 months of treatment. In addition the patients were seen in regular clinic visits and examined for signs of hyperthyroidism or worsening cardiac symptoms at appropriate intervals.

Of 20 patients initially considered for this study, one did not cooperate; three developed a sharp increase in the frequency of angina pectoris and discontinued the treatment; and one patient died suddenly at work, while in the tenth week of treatment. Two of those developing angina and the uncooperative patient were excluded; hence the study included one hypothyroid and 16 euthyroid patients, all followed for at least 10 weeks.

Total lipids and phospholipids of sera, drawn from patients in the fasting state, were measured initially, and at 3 months; the serum cholesterol was determined biweekly throughout the first 3 months of treatment. The total lipids were determined gravimetrically from a Bloor extract,\(^14\) the cholesterol by the technic of Abell and co-work-

*Generously supplied by Baxter Laboratories as Choloxin.

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ers,\textsuperscript{15} and the phospholipid by the Gomori tech-
nic.\textsuperscript{16} In four subjects serial observations were 
also made on the cholesterol partition among the 
three lipoprotein fractions separated by two pre-
parative centrifugations at densities of 1.063 and 
1.019, as described by Havel et al.\textsuperscript{17} with minor 
modifications described elsewhere.\textsuperscript{18}

Results

In figure 1 may be seen the time course of 
the serum cholesterol in all the euthyroid pa-
tients who continued the treatment for 9 
weeks or longer. Except for two patients 
who fluctuated rather widely at first, the in-
dividual cholesterol curves showed a sharp 
reduction in serum cholesterol levels within 
2 weeks, which was sustained for the first 3 to 
6 months at an average level of about 73 per 
cent of the control level.

Except for one patient, each showed a sta-
tistically significant ($p < .01$) reduction in 
mean serum cholesterol level averaging 27 
per cent below his mean control level. From 
table 1, it may also be seen that there was 
a somewhat less striking reduction in serum 
phospholipid and total lipid values so that the 
cholesterol:phospholipid ratio was re-
duced. In table 2, the serial observations in 
four of our subjects suggest that the only lipop-
protein fraction consistently contributing to 
the serum cholesterol reduction was that of 
density 1.019 to 1.063. The heavy density 
($> 1.063$) lipoprotein cholesterol was but 
little affected and the low density ($< 1.019$) 
lipoprotein cholesterol was not significantly 
affected by this administration of sodium 
dextro-thyroxine except in the hypothyroid 
patient A.P.

Calorigenic and Other Side Effects

All patients lost weight during the first 3 
months of treatment, the average weight loss 
being 31\textsuperscript{1/2} lb. This loss is reflected in the 
increased daily basal caloric requirement, as 
estimated from the basal oxygen consumption, 
which averaged 174 calories on the 8-mg. dose 
and 87 calories on the 4- to 6-mg. dose. This 
loss was not disadvantageous to many of these 
patients who had been trying to lose weight 
for years, and some patients volunteered an 
increase in energy, in stamina, and in a sense 
of well-being. Two patients developed an 
obvious lid lag and tremor of the tongue on 
the larger dose.

Much more disturbing was the increase in 
intensity of cardiac symptoms. One man 
(R.B.) developed severe classical angina of 
effort for the first time since a myocardial in-
farction 3 years earlier. Of the patients ex-
cluded from the study, one who had a stable 
anginal syndrome experienced a sharp in-
crease in frequency of pain from once to 
several times a day, often in the absence of 
precipitating exertion, on the 8-mg. dose. An-
other whose anginal pattern had been stable 
for years also had a decrease in exercise tol-
erance and the new development of nocturnal 
angina. Two of these patients could tolerate 
the drug no better when it was reinstituted 2 
weeks later at 4 mg. per day. The last pa-
tient was able to tolerate a dose of 2 mg. per 
day of sodium-d-thyroxine, even though he 
still felt a questionable and subjective redu-
tion in frequency of angina on final discon-
tinuation of that dose. His mean serum level 
of cholesterol (not included in table 1) was 
reduced from 296 mg. per cent during the 
control period to 260 mg. per cent by this 
dose. Of the other 11 patients (including
### Table 1
Response of the Basal Metabolic Rate, Weight, Pulse Rate, and Serum Lipid Levels to Administration of Sodium D-Thyroxine in 16 Euthyroid Patients

| Patient | Age | Sex | Diagnosis* | D-thyroxine dose mg./day | Treatment interval weeks | B.M.R. | Body wt. Kg. | Basal pulse min. | Serum lipid mg. % | Cholesterol mg. % | Phosphorus mg. % | Total lipid mg. % | B.M.R. % | Body wt. Kg. | Basal pulse min. | Cholesterol mg. % | Phosphorus mg. % | Total lipid mg. % |
|---------|-----|-----|------------|--------------------------|--------------------------|-------|--------------|------------------|------------------|-----------------|----------------|----------------|-----------------|---------|--------------|------------------|------------------|----------------|------------------|
| M.L.B.  | 63  | F   | AS         | 8                        | 14                       | -4    | 50.5         | 59               | 360              | 78              | 318            | 1495            | +17    | 48.0         | 67               | 239              | 307            | 1095            |
| P.E.    | 55  | M   | AS         | 8                        | 17                       | -6    | 7.99         | 77               | 192              | 35              | 245            | 880             | +4     | 76.4         | 79               | 192              | 222            | 750             |
| V.F.    | 58  | F   | AS, PMI    | 8                        | 19                       | -3    | 53.5         | 70               | 327              | 73              | 377            | 978             | +11    | 50.6         | 76               | 234              | ...            | ...             |
| R.G.    | 50  | M   | AS, PMI    | 8                        | 14                       | -1    | 56.1         | 58               | 289              | 66              | 248            | 885             | +6     | 53.5         | 61               | 176              | 205            | 665             |
| M.L.    | 50  | F   | AS, PMI    | 8                        | 13                       | -17   | 73.2         | 57               | 303              | 265            | 555            | 930             | +9     | 72.3         | 71               | 219              | 237            | 700             |
| M.B.    | 65  | F   | AS, PMI    | 8                        | 9                        | +4    | 49.1         | 59               | 352              | 305            | 797            | 970             | +22    | 47.2         | 64               | 245              | 255            | 805             |
| R.S.    | 52  | M   | PMI        | 8                        | 10                       | -12   | 69.6         | 68               | 306              | 317            | 1160           | -7    | 69.0         | 74               | 287              | 265            | 925             |
| R.B.    | 59  | M   | PMI        | 8                        | 3                        | -10   | 79.8         | 66               | 300              | 325            | 1215           | -2    | 79.0         | 71               | 239              | 257            | 875             |
| Average |     |     |            |                          |                          | 12    | 6.1          | 65.5             | 308              | 294            | 1061           | 6.2   | 63.3         | 70               | 227              | 250            | 831             |
| H.H.    | 44  | M   | AS, PMI    | 6                        | 13                       | -16   | 76.8         | 71               | 340              | 327            | 1365           | -9    | 75.6         | 70               | 230              | 227            | 760             |
| H.I.    | 44  | F   | NCVD       | 6                        | 17                       | -9    | 64.8         | 63               | 272              | 255            | 805            | -5    | 62.2         | 72               | 221              | 232            | 760             |
| S.S.    | 47  | F   | AS, XT     | 6                        | 26                       | -6    | 51.7         | 84               | 488              | 367            | 1345           | +2    | 50.3         | 89               | 335              | 282            | 1010            |
| L.L.    | 59  | F   | NCVD       | 6                        | 26                       | -13   | 52.4         | 63               | 383              | 285            | 1140           | -9    | 51.0         | 71               | 293              | 280            | 960             |
| M. W.   | 60  | M   | AS, PMI    | 4                        | 24                       | -4    | 56.9         | 62               | 346              | 345            | 1190           | +4    | 55.4         | 61               | 276              | 282            | 925             |
| H.C.    | 45  | M   | PMI, AD    | 4                        | 13                       | -16   | 62.3         | 61               | 362              | 362            | 1455           | -9    | 61.4         | 76               | 265              | 327            | 1345            |
| D.G.    | 52  | F   | PMI        | 4                        | 26                       | -11   | 36.8         | 64               | 336              | 287            | 1095           | -7    | 36.7         | 69               | 244              | 230            | 875             |
| F.B.    | 56  | M   | AS, PMI    | 4                        | 18                       | -14   | 82.9         | 64               | 270              | 267            | 910            | -9    | 82.6         | 59               | 255              | 262            | 975             |
| Average |     |     |            |                          |                          | 20    | -11.1        | 59.3             | 341              | 301            | 1115           | -4    | 58.2         | 71               | 265              | 265            | 951             |

*Diagnostic initials: AS, anginal syndrome; CHF, congestive heart failure; PMI, previous myocardial infarction; EH, essential hypertension; NCVD, no cardiovascular disease; XT, xanthoma tendinosum; AD, Addison's disease.

†Mean of 6 or more determinations.
A.P.) afflicted with the anginal syndrome, some more severely than the above three, none had any such gross change in his pain pattern and two thought that perhaps it had improved. Actually, no intensification of the anginal syndrome occurred in those patients started on the 4 or 6 mg. daily dose, and a graded increase to full dosage was not regularly prescribed.

A return of the symptoms of congestive heart failure was noted in two women (M.B. and V.F.) after 10 weeks on the 8-mg. dose, and after 1 year on the 6-mg. dose, respectively. These symptoms were not easily controlled until the d-thyroxine was stopped and, in M.B., later adjusted to the 4-mg. dose. One patient, receiving long-term Dicumarol therapy for a previous myocardial infarction, died suddenly at work while in his tenth week on the 8-mg. dose. No autopsy was obtained, and clinical information was too limited to permit any conclusion regarding a possible relationship between dextro-thyroxine administration and his death.

In 11 patients pursuing long-term Dicumarol therapy, great variability in prothrombin times occurred during their first month of treatment. In all but three, a reduction in dosage of Dicumarol was necessary because of a prolonged prothrombin time; two of these three had a shortened time followed later by a prolonged prothrombin time, also requiring adjustment of dosage. Thus only one patient, F.B., whose response to the d-thyroxine was weak in every other way, showed no unusual fluctuation in Dicumarol requirement. None of these patients suffered a hemorrhagic episode. No equivalent disturbance in prothrombin time regulation occurred on withdrawal of the thyroxine isomer.

Escape of the Serum Cholesterol

Seven of these patients have continued to take the thyroxine isomer for long periods of 11 to 20 months, and their serum cholesterol is plotted as the percentage of the control level against time in figure 2. It may be seen that there is generally a return from maximum cholesterol depression in the first month to a leveling-off at a stable serum concentration for the next 6 months. In two patients (M.B. and M.W.) dosage adjustments in the first 4 months complicate interpretation, but there is a definite tendency for the serum cholesterol to be higher in the second 6 months than in the first 6 months. In all but two subjects (H.H. and H.C.) a gradually rising trend was apparent by the end of 1 year. The serum cholesterol still remained about 15 to 20 per cent below control levels, however, and an increase in the daily dose from 6 mg. to 8 mg. in S.S. restored the lower level of 12 months earlier. Always, when the drug had been terminated, a sharp rise in serum cholesterol has been noted (e.g., V.F. and D.G. of fig. 2).

Comparison between the response to so-
Distribution of Cholesterol among the Three Major Lipoprotein Fractions in Four Patients in Mg. per 100 Ml. Serum before and during the Administration of Sodium-d-Thyroxine, 8 Mg. per Day

<table>
<thead>
<tr>
<th>Period Lipoprotein density</th>
<th>Control</th>
<th>D-thyroxine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1.019</td>
<td>&gt;1.063</td>
</tr>
<tr>
<td>mg. %</td>
<td>mg. %</td>
<td>mg. %</td>
</tr>
<tr>
<td>S. S.</td>
<td>27</td>
<td>378</td>
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<td>M. B.</td>
<td>44</td>
<td>195</td>
</tr>
<tr>
<td>M. L.</td>
<td>34</td>
<td>179</td>
</tr>
<tr>
<td>A. P.*</td>
<td>55</td>
<td>301</td>
</tr>
</tbody>
</table>

*I*<sup>131</sup> induced myxedema.

Diuretic d-thyroxine and sodium l-thyroxine was made in one patient, A.P., who had been made hypothyroid by radioiodine treatment of a hyperthyroid state. This patient was clinically myxedematous, with puffy facial edema, slow mentation, thickened speech, weight gain, and constipation on February 21, 1959, and later on December 12, 1959, when he was receiving no medication. On the latter occasion, d-thyroxine was reinstituted without waiting for the basal metabolic rate to fall lower. The serial basal metabolic rate and serum cholesterol analyses may be seen in table 3. From this comparison, it may be concluded that the dose of sodium d-thyroxine required to maintain this patient in the euca-
loric state is roughly 50 times that of l-thyroxine. In this particular case, the hypocholesteremic effect and calorigenic effect seem to be disproportionate: the serum cho-
lesterol was much lower on the d-thyroxine than on the calorically comparable dose of l-thyroxine and a dose only 20 times as great still effected a lower level of serum cholesterol than was seen with the largest dose of l-thyroxine.

Discussion

The marked hypcholesteremic effect of thyroid-active compounds is well observed in these 16 euthyroid subjects. Our hypothy-
roid patient experienced a hypcholesteremic effect much more dramatic with d-thyroxine than on a calorically equivalent maintenance dose of 1-thyroxine. These two observations confirm those first made by Starr. The effect of serum cholesterol reduction on the d-thyroxine preparation is similarly disproportionate to its caloric effect, in comparison with l-thyroxine, in the euthyroid patient cannot be determined from these data. However, Strisower et al. treated 16 euthyroid sub-
jects with roughly 1 mg. per day of an l-thy-
roxine preparation: about 10 times the usual replacement dose of l-thyroxine employed here. Precise caloric data were not reported but, from the observed weight loss and in-
crease in pulse rate, their subjects, though enjoying a serum cholesterol reduction comparable to that reported here, sustained a much greater calorigenic effect.

The practical advisability of using this dextro-isomer of thyroxine for the control of serum cholesterol in euthyroid patients is somewhat impaired by the fact that it does have a weak but definite calorigenic effect. While it seems to be true that this is weaker than its hypcholesteremic effect, when com-
pared with other thyroxine analogues, it is still capable of provoking cardiac symptoms in patients who may otherwise be quite com-
fortable. Even this risk might be worth tak-
ing, if the assurance were great that this hypcholesteremic effect would halt the process of atherogenesis or prevent further occlusive episodes. It is still uncertain, however, what benefit serum cholesterol reduction may pro-
vide to the patient with coronary artery disease: certainly our fatality had an unsuc-
sessful outcome.

Our limited data on lipoprotein cholesterol concentrations suggest that, as has been demonstrated in the case of thyroid extract and l-thyroxine, the suppressive effect is vir-
tually limited to the medium density (1.019 to 1.063) beta lipoprotein. While some evi-
edence relates hyper-beta-lipoproteinemia to
DEXTRO-THYROXINE AND HYPERCHOLESTEREMIA

Table 3

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose mg./day</th>
<th>Date*</th>
<th>B.M.R. %</th>
<th>Serum total cholesterol mg. %</th>
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<tr>
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<td>185</td>
</tr>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>12/3/58</td>
<td>-5</td>
<td>395</td>
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<tr>
<td></td>
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<tr>
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<td>-12</td>
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<td>345</td>
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<tr>
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<tr>
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<td>10/17/59</td>
<td>+2</td>
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<td>11/7/59</td>
<td>-9</td>
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<td>-15</td>
<td>463</td>
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<td>Na-d-thyroxine</td>
<td>6</td>
<td>1/29/60</td>
<td>-9</td>
<td>225</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>195</td>
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<tr>
<td></td>
<td></td>
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<td>219</td>
</tr>
<tr>
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<td>-10</td>
<td>202</td>
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<td></td>
<td>10/29/60</td>
<td>-10</td>
<td>212</td>
</tr>
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</table>

*The new dosage always started on the date above the preceding horizontal line.

Atherogenesis, there are those who feel that the lighter density alpha₂ material (S, 20-400 or d < 1.019) may be more important in this regard.20,21 Thus, in the present state of our knowledge, the accomplishment of such a hypocholesteremic effect with the attendant hazards recorded here does not seem warranted except perhaps in subjects with minimal or no symptoms of heart disease.

The disturbance in Dicumarol therapy as indicated by the rise and fall of prothrombin times was unexpected. No effort at initial graded dosage was made in this study, and this may have emphasized that effect. Two incomplete reports have suggested that the feeding of thyroid substance to rats did enhance the prolongation of the prothrombin times induced by a salicylate22 or warfarin.23 In any case, the observation suggests that patients receiving these two drugs should have frequent determinations of the prothrombin time initially.

Conclusion

A marked hypocholesteremic effect (27 per cent) was seen with the administration of sodium d-thyroxine given in doses of 4 to 8 mg. per day. It was primarily, as with l-thyroxine, the beta lipoprotein (d 1.019 to 1.063) cholesterol that was affected. The reduction in serum cholesterol was better sustained at the higher dosage levels than at 4 mg. per day but a slight tendency for the cholesterol to rise after 1 year could be overcome by a fractional increase in dosage. Sodium d-thyroxine showed the same capacity to elevate basal caloric requirement, enhance the frequency of the anginal syndrome, and occasionally aggravate symptoms of congestive heart failure that has been reported with other active thyroid compounds. In this study these adverse effects were seen predominantly at the 8-mg. daily dose, but even smaller doses were not always tolerated in susceptible patients and the tendency of
the serum cholesterol to return to pretreatment values was more often seen after 6 to 9 months at lower dosage levels.

A puzzling alteration in the prothrombin time of patients maintained on Dicumarol therapy was frequently observed early in the course of d-thyroxine therapy.

Although it is clear that a hyper-beta-lipoproteinemia can be partially corrected by the administration of sodium d-thyroxine, the usual caution observed in the administration of thyroid compounds to patients with heart disease is still deserved. In view of the present uncertainty of the goal of serum lipoprotein manipulations in coronary artery disease, the use of this preparation for that disease cannot be recommended without qualifications and should best be reserved for patients free of cardiac symptoms.

References
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