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THE EFFECT OF DEXTRO-THYROXINE ON THE SERUM-CHOLESTEROL LEVEL

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With the correlation that exists between raised serum-cholesterol levels and susceptibility to ischaemic heart disease, it is not surprising that great interest is focussed on any means whereby high serum-cholesterol levels can be lowered. On the other hand, as shown by a long-term study with oestrogens,[1] it does not necessarily follow that an agent's capacity to lower serum-cholesterol levels will at the same time improve survival from ischaemic heart disease.

Many factors enter into the regulation of cholesterol metabolism. These have been well reviewed by Gordon[2] and Lewis.[3] Among these factors is the thyroid. Strisower and his colleagues[4] reported that incremental doses of thyroid extract led to sustained falls in levels in otherwise refractory cases of essential hypercholesterolaemia. The difficulty with most thyro-active substances, whether naturally occurring or synthetic, is that their serum-cholesterol-level lowering properties are accompanied by an increase in myocardial metabolism and myocardial oxygen requirements, and a decrease in effort tolerance in patients with angina pectoris — the very patients in whom therapy aimed at lowering the serum-cholesterol level is probably most desirable. The dextro-isomer of thyroxine seemed worthy of trial because of its reported property of lowering serum-cholesterol levels without stimulation of the basal metabolic rate.[5] The purpose of this report is to describe the effects seen in a small series of men, actively engaged in their occupations, who were given sodium dextro-thyroxine ('choloxin'*) and, unbeknown to them, an inert tablet of identical appearance.

CLINICAL MATERIAL AND METHODS

The subjects studied were professional and business men who for several years had attended our clinic for the investigation of the effects of agents on serum-cholesterol levels. Reference can be made to a previous report from this clinic on the long-term effects of certain saturated and unsaturated fat supplements.[6] These men were actively engaged in their occupations, partook of their ordinary diets and, with the exception of a few with ischaemic heart disease, were apparently healthy.

Twelve male subjects aged 37 - 65 years were subdivided at random into 3 groups. Two groups received 2 mg. of sodium dextro-thyroxine twice daily for 10 weeks. Unbeknown to the subjects, or the technician doing the serum-cholesterol determinations, this was replaced by an inert tablet of identical appearance for an additional 8 weeks. One of these 2 groups received in addition a supplement of 30 G. of sunflower-seed oil throughout, having been on this supplement for several weeks before the trial began. The third group received neither dextro-thyroxine nor placebo. This group merely continued on the regimen prescribed, and in this way acted as a control with regard to serum-cholesterol trends that could have occurred over this prolonged period.[6] A further form of control was achieved by overlapping treatment and placebo phases so that while some were on placebos others were on dextro-thyroxine.

Records were kept of body weight, blood pressure, side-effects, etc., and the serum-cholesterol levels were estimated fortnightly by the method of Abell *et al.*[7] as modified by Anderson and Keys.[8] The results were expressed as the change in mg. per 100 ml. in the serum-cholesterol level from the mean level obtained from the estimations during the 2 months before the trial began.

In each of the 2 treatment groups there was 1 subject with essential hypercholesterolaemia and there were 2 subjects with a history of previous myocardial infarction, 1 in each group having angina pectoris. No subject had stigmata of hypothyroidism.

RESULTS

The mean age in each group was similar. The initial mean serum-cholesterol level of the group receiving oil and dextro-thyroxine (350 mg. per 100 ml.) was slightly higher than that of the group receiving dextro-thyroxine alone (320 mg. per 100 ml.).

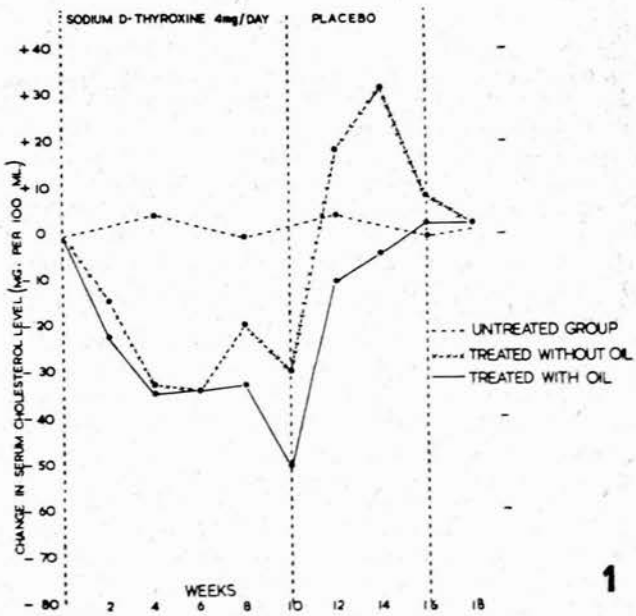

Fig. 1. The change in serum-cholesterol levels that occurred during the period dextro-thyroxine was administered compared with that seen during the administration of an inert tablet.

*Choloxin - brand of sodium dextro-thyroxine (Baxter Laboratories).

Changes in Serum-cholesterol Levels

In each individual tested, dextro-thyroxine produced an immediate and substantial fall in these levels (Fig. 1), and the levels continued to fall throughout the test period. The greatest fall (106 mg. per 100 ml.) was seen in 1 patient with essential hypercholesterolaemia whose initial level was 430 mg. per 100 ml. On switching to the inert tablet, the levels immediately rose again. The group who continued on the oil supplement in addition to dextro-thyroxine had a slightly greater fall ($0{\cdot}10 > p > 0{\cdot}05$), whether this was measured in mg. per 100 ml. or percentage fall. No subject in this series failed to respond. The untreated group showed no significant change in levels throughout the trial.

Changes in Body Weight

In all subjects receiving dextro-thyroxine there was a mean gain of 3 lb. in weight over the 10-week period. This weight gain was most marked during the first month; thereafter the weight remained stationary and did not revert to the initial values until 10 weeks later.

Side-effects

Five men on dextro-thyroxine voluntarily stated that they had noticed an increase in appetite. Otherwise at this dose no other side-effects were noted. Two men with angina pectoris did not complain of lessened effort tolerance. On the other hand, 1 remarked that the number of attacks of angina pectoris had sharply decreased. No particular significance can be attached to this, as this had occurred previously on several occasions in this man for no apparent reason. One man with intermittent claudication did not observe any change in effort tolerance.

There were no changes in blood-pressure levels or pulse rate.

DISCUSSION

Recently there have been many preparations in tablet or capsule form that claim to reduce serum-cholesterol levels. Many of these have been tried in this clinic without success. Until the use of sodium dextro-thyroxine, only sunflower-seed oil supplements, which have to be taken in large doses, and nicotinic-acid tablets, which may have unpleasant side-effects, were effective. In this study no subject failed to respond and it is perhaps of interest to note that 2 subjects had previously not responded to oil supplements. The series was small and it is quite possible that, had more subjects been studied, there might have been some who would not have responded. This statement is made in view of a recent study by Oliver and Boyd,[9] where 6 out of 38 men failed to respond to larger doses than used here, viz. 7·5 mg. and 10 mg. daily. Greene *et al.*[10] noted that in certain instances the dose had to be increased from 5 to 10 mg. daily to induce a satisfactory fall in serum-cholesterol levels, whereas Hoobler *et al.*[11] reported that the response was variable using both 8 mg. and 4 mg. daily among 14 patients with idiopathic hypercholesterolaemia. Starr *et al.*,[12] on the other hand, achieved satisfactory reductions on 4 mg. daily in hypothyroidic individuals, but Boyd and Oliver[13] pointed out that with most thyro-active substances the dose required to reduce serum-cholesterol levels in hypothyroidism is far less than that necessary in euthyroid individuals. It may be fortuitous, therefore, that in our series of euthyroid individuals all 8 subjects responded on only 4 mg. daily.

It is of interest that a slightly greater response was seen in those consuming, in addition, an oil supplement. This may have been the result of chance or it may suggest the possibility that the nature of the diet could account for the reported variability, and the mode of action may be determined at gut level. This possibility exists because Boyd[14] claimed that administration of thyro-active substances to the rat resulted in a decrease in the biological half-life of plasma cholesterol, associated with irregular changes in the apparent rate of plasma-cholesterol synthesis. By dietetic alterations, the rat responds to hyperthyroidism by regular marked depression in the plasma-cholesterol level.

Studies on the effect of thyroid hormones on the concentration of cholesterol and its breakdown products, the bile acids, by van Zyl[15] showed that there is an increase in bile flow and an alteration in the nature of the bile acids produced. The concentration of trihydroxycholanic (cholic) acid is markedly reduced, whereas the dihydroxy acids rise. Howe *et al.*[16] have shown that in mice the mono- and dihydroxycholanic acids neutralize the plasma-cholesterol-elevating effect of cholic acid. It is therefore possible that an alteration in the ratio of tri- to dihydroxycholanic acids in the gut by dextro-thyroxine in man determines the effect on the plasma-cholesterol levels, but this is a matter for future study.

At the dose of 4 mg. daily, the slight increase in weight possibly arose from an increase in appetite. There were no side-effects, but from the literature cited above it appears that doses in excess of 4 mg. daily may raise the basal metabolic rate in some individuals and lead to decreased effort tolerance in patients with angina pectoris.

SUMMARY

1. Sodium dextro-thyroxine at the dosage level of 4 mg. daily effectively reduced the serum-cholesterol levels in all 8 subjects throughout a trial period of 12 weeks. The levels rose again while the subjects continued to take inert tablets of identical appearance.

2. There was a slight gain in weight, but no side-effects were encountered even in subjects with ischaemic heart disease.

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