The Effect of Desiccated Thyroid on Plasma and Tissue Lipids and Atherogenesis in the Stilbestrol-Treated Chick


Repeated implantations of diethylstilbestrol pellets cause a sustained hyperlipemia in the chick, and atherosclerosis eventually supervenes. Desiccated thyroid significantly reduces the incidence and degree of the stilbestrol-induced atherosclerosis in the chick, although it is without sustained effect upon the plasma and tissue lipids.

The exhibition of estrogenic substances elicits an increase in the concentration of plasma lipids in the chick.\(^1\)\(^2\)\(^3\) If the hyperlipemia is maintained for several months by repeatedly implanting pellets of diethylstilbestrol, atherosclerosis is induced.\(^4\)\(^5\) We have previously shown that desiccated thyroid lowers hyperlipemia and hypercholesterolemia in cholesterol-fed chicks. Concomitantly, this hormone reduces the incidence, extent and severity of cholesterol-induced atherosclerosis.\(^6\)\(^7\) These findings led us to study the effect of desiccated thyroid in stilbestrol-implanted chicks, in order to determine if hormone interrelations known to affect endogenous lipid metabolism manifest themselves in an altered incidence and degree of atherosclerotic lesions.

Methods

One day old Hy-Line cockerels were obtained from a certified hatchery and raised in a battery brooder. They were fed a commercial chick starter mash (plain mash) of known composition.\(^*\) At 8 weeks of age, 30 birds were divided into 3 groups of 10 chicks each: Group 1 birds subsisted on plain mash and received subcutaneous implantations of diethylstilbestrol pellets (25 mg)\(^*\) at 3 week intervals. Group 2 chicks were implanted with stilbestrol and fed thyroid mash (99.5% plain mash + 0.5% desiccated thyroid).\(^†\) The control group (Group 3) received only plain mash.\(^†\)

All birds were weighed weekly and a record of feed intake was maintained. They were bled periodically from the carotid vein. Pooled aliquots of plasma were analyzed for the various lipid fractions by the methods of Schoenheimer and Sperry\(^*\) and Man et al.\(^11\) Plasmas from 3 or 4 birds of a group were pooled, and 2 sets of pooled plasmas were analyzed each time. Autopsies were done on all birds which succumbed during the course of the experiment. After twenty-five to twenty-seven weeks on the diet, surviving chicks were sacrificed by decapitation and exsanguination. All the viscera were examined and the gross findings recorded. The hearts and great vessels (aorta, brachiocephalic and iliac arteries) were carefully inspected for evidence of gross atheromatous plaques. Lesions, if any, were described and recorded graphically on special forms; the aortas were graded 0 to 4 for atheroma, according to criteria previously described.\(^12\) During grading, specimens from different groups were indiscriminately mixed and examined consecutively as unknowns. Blocks of tissue were taken for microscopic examination and fixed in 10% aqueous formalin. Frozen sections were stained with hematoxylin-eosin. At the end of the experiment, pooled aliquots of liver and aorta were analyzed for lipids (total and free cholesterol, lipid phosphorus, total fatty acid) according to procedures previously described.\(^11\) Livers and aortas of 2 or 3 chicks of a

\(^*\) We are indebted to Drs. J. R. Mote and L. P. Anderson of the Armour Laboratories, Chicago, Illinois, for donating the desiccated thyroid for this study.

\(^†\) Concomitantly we studied the effects of thyroid on lipid metabolism and atherogenesis in chicks fed plain mash. The findings, which are being prepared for publication, are not significant with respect to control data for the present study.
group were pooled, and 2 analyses per group were conducted.

Results

Growth and development. No significant differences in feed intake were noted among the three groups. The stilbestrol–plain mash chicks (Group 1) became heavier than any of the other groups, apparently because of hormone-induced deposition of fat.\textsuperscript{8,12,14} The stilbestrol-thyroid mash birds (Group 2) exhibited the slowest rate of weight gain.

Plasma lipids. The mean data on plasma lipids are presented in figures 1 and 2 and table 1. In accord with previous reports,\textsuperscript{3,5} stilbestrol implantation induced a hyperlipemia involving all plasma lipid elements. Lipid phosphorus exhibited the greatest increment; the increase in plasma cholesterol was less marked. Consequently the ratio total cholesterol/lipid phosphorus decreased (fig. 2). Stilbestrol implantation also consistently induced an increase in the plasma ratio free cholesterol/total cholesterol (table 1).

The exhibition of desiccated thyroid to stilbestrol-implanted chicks led to a decrease in hypercholesterolemia and hyperphospholipemia during the first weeks of the experiment (figs. 1 and 2, table 1). Thus, at one week, the stilbestrol–plain mash birds had a mean plasma total cholesterol and lipid phosphorus of 226 and 31.3 mg. per cent respectively (ranges: 215–237 and 29.2–33.3 mg. per cent). The stilbestrol–thyroid mash birds (Group 2, table 1) had significantly lower mean values, i.e. 101 and 13.3 mg. per cent respectively (ranges: 93–109 and 12.2–14.3 mg. per cent respectively). These plasma cholesterol levels are well within the normal range. The lipid phosphorus values are elevated. Hence the ratio total cholesterol/lipid P was decreased. The
desiccated thyroid diet also tended to keep the plasma ratio free cholesterol/total cholesterol at normal levels (table 1). At five weeks, the plasma lipid pattern was similar to that observed at 1 week, except that thyroid exhibition no longer completely prevented moderate hypercholesterolemia and elevation of the ratio free cholesterol/total cholesterol. By ten weeks the two stilbestrol-implanted groups had similar plasma-27 weeks and aortic cholesterosis and lidiposis (table 1).

These tissue lipid levels in the two treated groups represent significant elevations. Consistent with plasma findings at this time, no significant differences between Group 1 and 2 in degree of tissue lidiposis were recorded. In both the stilbestrol–plain mash and the stilbestrol–thyroid mash chicks, the hepatic cholesterol concentration was significantly in-

Table 1.—Mean Plasma and Tissue Lipids of Stilbestrol (Group 1), Stilbestrol-Thyroid (Group 2) and Control (Group 3) Chicks

<table>
<thead>
<tr>
<th>Group</th>
<th>Lipid P</th>
<th>Phospholipid*</th>
<th>Phospholipid Fatty Acid†</th>
<th>Total Chol.</th>
<th>Free Chol.</th>
<th>Esterified Chol.</th>
<th>Ratio: F/T Chol.</th>
<th>Ratio: Esterified Chol. Fatty Acid‡</th>
<th>Esterified Chol. Fatty Acid§</th>
<th>Total Fatty Acid</th>
<th>Neutral Fat Fatty Acid¶</th>
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<td>*Phospholipid Fatty Acid = phospholipid X .67.</td>
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<td>†Ratio F/T Chol. = Ratio: free cholesterol/total cholesterol.</td>
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<td>§Esterified Chol. Fatty Acid = Esterified cholesterol X .73.</td>
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<td>¶Neutral Fat Fatty Acid = Total fatty acid — (phospholipid fatty acid + cholesterol fatty acid).</td>
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<td>‡Total Lipid = phospholipid + total cholesterol + esterified cholesterol fatty acid + neutral fat fatty acid.</td>
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ilar plasma lipid phosphorus levels (fig. 2), although hypercholesterolemia remained less severe in the thyroid-fed birds. At fifteen weeks and thereafter the pattern of hypercholesterolemia and hyperphospholipemia was essentially similar in the 2 groups of stilbestrol-implanted chicks (figs. 1 and 2, table 1).

After twenty-seven weeks of treatment, both experimental groups had a moderate hepatic creased about one-third above control values, with the ester fraction accounting for most of this increment (table 1). Liver phospholipids were similarly elevated. The two experimental groups had an aortic cholesterolosis and lidiposis approximately equal in degree. These findings contrast with the significant differences between the 2 groups in gross pathologic grading for atheroma (see below and fig. 1).
In contrast to the plasma lipid pattern, aorta cholesterol rose more than phospholipid (table 1). Hence the ratio total cholesterol/lipid phosphorus increased, whereas in the plasma it decreased. If these excess aortic lipids are derived from the hyperlipemic plasma, this predominance of aortic cholesterol over phospholipidosis may reflect a relative inability of the organism to remove cholesterol from the vessel wall.

Morphologic findings. Grading of aortas of individual birds is presented in detail for all three groups in table 2. This data is summarized in figure 1 with the data corrected to eliminate age variations as a factor accounting for differences in pathologic findings. In contrast to the aortic lipid findings (table 1), the stilbestrol-thyroid mash chicks had a significantly lower incidence, extent and severity of gross atherosclerosis than the stilbestrol-plain mash birds. Thus only 37 per cent of the stilbestrol-thyroid mash birds (Group 2) had any gross evidence of atheroma; the average overall grading of lesions in the birds with plaques was 0.4; no birds had a grading of 1 or greater. Corresponding data for the stilbestrol-plain mash birds (Group 1) was: per cent with lesions, 67 per cent; average overall grading, 1.1; per cent with overall grading of 1 or greater, 33 per cent. The control chicks (Group 3) and the stilbestrol-thyroid mash birds (Group 2) exhibited a very similar incidence, severity and extent of atherosclerosis (figure 1). Unlike the controls, the stilbestrol-thyroid mash chicks were not entirely free of thoracic aorta lesions (table 2).

Routine microscopic sections were taken from the thoracic and abdominal aorta of chicks from each group. In general, the histologic picture of both stilbestrol-induced and spontaneous plaques was in accord with previous descriptions from this and other laboratories. Also in agreement with previous

**Table 2.—Gross Pathologic Grading for Atheroma in Aortas and Great Vessels of Individual Birds**

<table>
<thead>
<tr>
<th>Group</th>
<th>Bird No.</th>
<th>Weeks on Diet</th>
<th>Grading</th>
<th>Bird No.</th>
<th>Weeks on Diet</th>
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<td>0</td>
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<td>0</td>
<td>274</td>
<td>12</td>
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Group 1—Stilbestrol-implanted, plain mash fed.
Group 2—Stilbestrol-implanted, thyroid mash fed.
Group 3—Control—plain mash fed, no hormone treatment.

* Thor. = Thoracic aorta and brachiocephalic vessels.
† Abd. = Abdominal aorta and iliac vessels.

findings, two birds in Group 1 (chicks 63 and 698) without evidence of gross evidence of atheroma at twenty-seven weeks had microscopic infiltration of the intima and subjacent media with sudanophilic material. The microscopic droplets of sudanophilic material were intra- and extracellular; they were not associated with either intimal foam cell cushioning or fibrotic thickening. Three birds of Group 2 (chicks 283, 287 and 719) exhibited the same phenomenon. Thus both stilbestrol-plain mash and stilbestrol-thyroid mash chicks were susceptible to this diffuse microscopic lipid infiltration of the aorta. This morphologic finding correlates well with the biochemical data on
aortic lipidosis in the 2 experimental groups, and is at variance with the group differences in degree of gross atherosclerosis. The relationship of this diffuse aortic lipidosis to atherogenesis remains to be elucidated.19, 21

**DISCUSSION**

Desiccated thyroid decreased the incidence, extent and severity of stilbestrol-induced atherosclerosis in the chick. This protective action of thyroid hormone was only partial; complete prevention of lesions was not accomplished. These findings are similar to our previous observations on the partial prophylactic effect of desiccated thyroid in chick cholesterol-induced atherosclerosis.6, 7

It is difficult to correlate the degree of atherosclerosis with the plasma and liver lipid levels observed in the present study. Thus the stilbestrol and the stilbestrol-thyroid treated chicks had similar lipid levels during the latter half of the experiment. Nevertheless, the stilbestrol-thyroid birds had significantly less atherosclerosis. This finding may be related to the retardation of hyperlipemia induced by thyroid during the initial weeks of the study. However, this early depression of hyperlipemia was never complete. In relation to their level of plasma lipids over the entire course of the experiment, the stilbestrol-thyroid chicks were remarkably free of lesions. Thus the possibility arises that thyroid hormone exerted its effect on atherogenesis via mechanisms other than depression of hyperlipemia.6, 7, 22-26

Stilbestrol-induced atherosclerosis in chicks differs from the cholesterol-induced lesion in the duration of time required for development of atheroma. Cholesterol-fed birds with a hypercholesterolemia of the same degree as stilbestrol-implanted chicks develop gross atheroma in one-third to one-half the time. Two possible explanations for this finding are suggested on the basis of present knowledge: (1) Compared to stilbestrol-implantation, cholesterol feeding probably requires the transport, turnover and metabolism of a greater load of cholesterol for a corresponding level of hypercholesterolemia24, 26; (2) unlike stilbestrol-implantation, cholesterol feeding induces a hyperlipemia characterized by a predominance of hypercholesterolemia over hyperphospholipemia. The ratio of cholesterol to phospholipid in the plasma rises. The opposite change is seen in the stilbestrol-treated chick. Several workers maintain that an elevated ratio plasma total cholesterol/plasma lipid phosphorus leads to lipid instability, macrochylomicronemia and atherosclerosis.27 The predominant hyperphospholipemia of the stilbestrol-implanted chick may retard the atherogenesis presumably induced by hypercholesterolemia. However, estrogen-treated chicks eventually develop atherosclerosis. Hence it would appear that an increased ratio of total cholesterol to lipid phosphorus in the plasma is not essential for the ultimate development of atherosclerosis. Apparently atherogenesis is promoted by any derangement of lipid metabolism inducing hyperlipemia with hypercholesterolemia and an alteration of the normal quantitative relations among the plasma lipid elements.

In the present study, thyroid exhibition had a variable effect on plasma lipid levels in the stilbestrol-implanted chick. During the first weeks of the experiment, desiccated thyroid depressed hypercholesterolemia and hyperphospholipemia. This is similar to its effect in the cholesterol-fed chick.6, 7 However, the stilbestrol-thyroid chicks eventually developed a hyperlipemia as marked as that of the birds receiving only stilbestrol. These findings are consistent with the previous observations of other workers. Thus, Fleischmann and Fried noted that thyroxine “neutralized” the effect of estradiol on serum cholesterol if equal doses of the two agents were given.28 When estrogen dosage exceeded thyroxine dosage, hyperlipemia ensued. This situation probably obtained in our stilbestrol-thyroid chicks during the latter weeks of the present study as a result of repeated pellet implantations.

This apparent predominance of stilbestrol over thyroid was also reflected in the liver lipid pattern at the end of this study. Both the stilbestrol and the stilbestrol-thyroid treated chicks had a slight hepatic cholesterolosis and phospholipidosis.21, 22 No significant quantitative differences between the two groups were noted. Thus, at least during the latter
weeks of this experiment, thyroid was ineffective as a prophylactic lipotropic agent.\textsuperscript{29}

The mechanisms of these hormone influences on lipid metabolism remain obscure. Fleischmann and co-workers have concluded that both stilbestrol and thyroid exert their opposing effects on plasma cholesterol concentration by shifting sterol to and from blood plasma, rather than by altering the relationship between sterol accumulation and disposal.\textsuperscript{28, 30} Others, working with radioactive tracers, have obtained data tending to support different conclusions. Stetten has recently suggested that hyperthyroidism leads to a disproportionate increase in hepatic degradation of fat.\textsuperscript{31} Lipid depletion results.\textsuperscript{12, 29} Taurog et al. have shown that excised liver slices of stilbestrol-treated chicks form radiophospholipid at an enhanced rate.\textsuperscript{23} They suggest that this is the source of stilbestrol-induced hyperphospholipemia. We have recently obtained data indicating that chronic stilbestrol administration alters the organism's overall lipid balance. In addition to hyperlipemia, the body total cholesterol, phospholipid and neutral fat increase.\textsuperscript{14}

The interrelationships between thyroid and estrogenic hormones extend beyond lipid metabolism, and apparently operate in many physiologic situations considerably different from those of the present experiment.\textsuperscript{34-37} Thus estrogens have been shown to suppress thyroid and plasma protein-bound iodine, probably via a pituitary action.\textsuperscript{38, 39} The significance of these hormonal interconnections for atherogenesis remains to be elucidated.

**Summary**

1. Desiccated thyroid reduced the incidence and degree of stilbestrol-induced atherosclerosis in the chick.

2. During the first few weeks, thyroid hormone suppressed stilbestrol-induced hypercholesterolemia and hyperlipemia. After this period, plasma lipid levels and ratios in stilbestrol and stilbestrol-thyroid groups were essentially similar.

3. At the end of the study, both of the experimental groups had a moderate hepatic and aortic lipidosis, the degree of which in each tissue was essentially similar in each group.

4. The possible mechanisms involved in the interplay of the two hormones, thyroid and stilbestrol, in suppressing stilbestrol-induced atherosclerosis are discussed.

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The Effect of Desiccated Thyroid on Plasma and Tissue Lipids and Atherogenesis in the Stilbestrol-Treated Chick

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