Effect of Prolonged Use of Estrogens on Circulating Lipids in Patients with Idiopathic Hyperlipemia or Idiopathic Hypercholesteremia

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The low incidence of atherosclerosis in premenopausal women and the effects of gonadal extracts on serum lipids indicate the desirability of further clinical and biochemical studies. Ethinyl estradiol was administered to 12 persons with idiopathic hyperlipemia or idiopathic hypercholesteremia. Medication was given for an average period of 16 months and was well tolerated, despite moderate gynecomastia, diminished libido, or uterine bleeding. The effects on the levels of circulating lipids and the clinical feasibility of this therapy are discussed.

The lower incidence of coronary atherosclerosis in premenopausal women as compared to men is well established. Sex and age differences in levels of serum lipids and lipoproteins suggest an important role of the gonads in the regulation of circulating lipids. Administration of estrogenic hormones to men and women is followed by a fall in serum lipid levels and alteration in serum lipoprotein patterns. A number of studies have been concerned with the administration of estrogens to patients with coronary artery disease.

Patients with idiopathic hyperlipemia or idiopathic hypercholesteremia provide a unique material for the study of disturbances in circulating lipids per se and in relation to lipid deposition in the tissues that often accompanies these disorders. Therefore, a study was undertaken of the long-term use of orally administered ethinyl estradiol, at minimum effective doses, in men and women with either disorder. A preliminary report appeared previously.

Materials and Methods

Selection of Patients. The group with idiopathic hyperlipemia included 4 men, age 39, 47, 49, and 52, and 2 women, age 49 and 56 (both postmenopausal). Four patients, 3 men and 1 woman, had xanthomata tuberosa; 1 man also had tendinosa. Other pertinent clinical data are summarized in table 1.

In the group with idiopathic hypercholesteremia, there were 3 men and 3 women. The men were age 47, 50, and 54 and the women were 47 (still menstruating), 48, and 50 years old (postmenopausal) at the inception of the study. One woman and 1 man had xanthomata tendinos. Other clinical manifestations are noted in table 1.

The individual pretreatment levels of serum lipids and lipoproteins are presented in table 2. In the group with idiopathic hyperlipemia mean levels of total and esterified cholesterol were 579 and 384 mg. per cent; phospholipid levels averaged 647 mg. per cent, triglycerides 2,642 mg. per cent, and total lipids 3,878 mg. per cent. α-lipoprotein was 11.2 per cent. β-lipoprotein 37.1 per cent, and the O-fraction 51.7 per cent of the total stainable lipoprotein, with a β plus O: α ratio of 7.9. In the group with idiopathic hypercholesteremia the mean levels of total and esterified cholesterol were 434 and 330 mg. per cent, phospholipids 412 mg. per cent, triglycerides 452 mg. per cent and total lipid 1,298 mg. per cent. Average level of α-lipoprotein was 17.4 per cent, β-lipoprotein 65.0 per cent, and O-fraction 17.5 per cent; β plus O: α ratio was 4.7.

All patients had been observed by at least one of the investigators for a period of 1 to 5 years prior to the study. During this period of time, determinations of serum lipids and lipoproteins had been serially recorded. All patients had been maintained on a low-fat diet which was not altered throughout the course of treatment. Treatment with digitalis, diuretics, or nitroglycerin was continued as needed. No patient received any anticoagulant during the period of the study. Under the conditions of this study each patient served as his own control for at least 1 year.

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Method. Measurements followed at bimonthly or monthly intervals included body weight; stig mata of the disordered lipid metabolism such as symptoms and signs of coronary artery disease, number and size of skin and tendon lesions; fasting levels of serum total and esterified cholesterol, phospholipids, and total lipids by chemical methods (triglycerides calculated by difference)18-21; levels of lipoproteins (α, β, and O-fraction) and proteins (albumin, α, β, and γ globulins) by paper electrophoresis and subsequent staining with oil red O for lipids and amidoblack for proteins followed by quantitative densitometric evaluation with a Spinco Analytrol.22,24

Dosage of Ethinyl Estradiol. Patients were initially started on ethinyl estradiol* in dosage of 0.1 mg. twice a day which after 4 weeks was reduced to 0.05 mg. 3 times a day. If a satisfactory lipid-lowering effect was obtained, the dose was reduced to 0.05 mg. twice a day or sometimes once a day. Dosage was later altered in some patients to interrupt therapy by administering medication for 3 weeks and discontinuing it for 1 week. In 1 man with hyperlipemia and 1 man and 3 women with hypercholesteremia the course of ethinyl estradiol was interrupted for from 2 to 5 months, during which time patients were maintained on a placebo. These patients were otherwise followed in the same manner as those on the drug.

To date, 12 patients have been studied from 2 to 26 months, with an average duration of 16 months of therapy. In 3 men with hyperlipemia and 1 with hypercholesteremia the study was terminated after 2, 3, 4, and 11 months, respectively. Eight patients are still receiving treatment: all women in both groups, 1 man with hyperlipemia and 2 men with hypercholesteremia.

RESULTS

In all patients in both groups there was a significant fall in serum total and esterified cholesterol (table 2). Phospholipid levels declined in all the hyperlipemic patients and in 4 patients with hypercholesteremia and were unchanged in 2 patients in the latter group. Triglyceride and total lipid levels fell in all except 1 patient with hypercholesteremia. In all except 1 patient with hyperlipemia the lipoprotein pattern "improved" significantly in both groups in that there was an increase in α-lipoprotein with a corresponding decrease in β-lipoprotein or the O-fraction.

*We should like to thank Dr. J. Black, of the Schering Corporation, Bloomfield, N. J. for the generous supplies of estinyl and placebo used in this study.

The response to and course of therapy of 1 representative patient in each group is depicted in figures 1 and 2. Levels of lipid and lipoprotein fractions are graphed in relation to therapeutic regimen over a 2-year period. Representative lipoprotein patterns for each of these patients are shown in figures 3 and 4.

The mean results in each group before and after therapy are presented in graphic form in figures 5 and 6. In the group with idiopathic hyperlipemia (fig. 5) on therapy the mean levels of total and esterified cholesterol fell by 47 and 45 per cent to 309 and 210 mg. per cent. Phospholipid levels declined by 30 per cent to 454 mg. per cent. Triglyceride levels were reduced 69 per cent to 822 mg. per cent while a 59 per cent fall occurred in total lipids to a mean level of 1,586 mg. per cent. α-lipoprotein increased to 22.0 per cent, β-lipoprotein was increased slightly to 43.1 per cent, and the O-fraction declined to 34.9 per cent of the total stainable lipid, resulting in a 56 per cent fall in the β:α lipoprotein ratio.

<p>| Table 1.—Clinical Manifestations in Patients with Idiopathic Hyperlipemia or Idiopathic Hypercholesteremia Treated with Ethinyl Estradiol |
|---|---|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Xanthoma tuberosum</th>
<th>Xanthoma tendinum</th>
<th>Coronary artery disease</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipemia</td>
<td>1 M 39</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>26*</td>
</tr>
<tr>
<td>2 M 47</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>3 M 49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>4 M 52</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Diabetes</td>
<td>17*</td>
<td></td>
</tr>
<tr>
<td>5 F 49</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>Pancreatitis</td>
<td>26*</td>
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<tr>
<td>6 F 56</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesteremia</td>
<td>7 M 47</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>25*</td>
</tr>
<tr>
<td>8 M 50</td>
<td>+</td>
<td>Gout</td>
<td></td>
<td></td>
<td>11*</td>
<td></td>
</tr>
<tr>
<td>9 M 54</td>
<td>+</td>
<td></td>
<td></td>
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<td>11</td>
<td></td>
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<tr>
<td>10 F 42</td>
<td>+</td>
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<td></td>
<td></td>
<td>26*</td>
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<tr>
<td>11 F 48</td>
<td>+</td>
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<td>24*</td>
<td></td>
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<tr>
<td>12 F 50</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>24*</td>
<td></td>
</tr>
</tbody>
</table>

*Still on therapy.
Table 2.—Maximal Effect of Estinyl Therapy on Serum Lipids and Lipoproteins in Idiopathic Hyperlipemia or Idiopathic Hypercholesteremia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total cholesterol</th>
<th>Esterified cholesterol</th>
<th>Phospholipids</th>
<th>Triglycerides</th>
<th>Total lipid</th>
<th>α</th>
<th>β</th>
<th>α:β ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/100 ml.</td>
<td>mg/100 ml.</td>
<td>mg/100 ml.</td>
<td>mg/100 ml.</td>
<td>α %</td>
<td>β %</td>
<td>% of total stainable lip</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hyperlipemia

1 Pretreatment
- 1
- 2
- 3
- 4
- 5
- 6

Hypercholesteremia

7 Pretreatment
- 7
- 8
- 9
- 10
- 11
- 12

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In the group with idiopathic hypercholesteremia (fig. 6) on therapy there was a fall of 35 and 39 per cent in the mean levels of total and esterified cholesterol to 283 and 201 mg. per cent. Phospholipid levels declined 11 per cent to 368 mg. per cent. Reduction of 17 per cent occurred in triglycerides, to 375 mg. per cent and total lipid levels fell 23 per cent to a mean of 1,026 mg. per cent. α-lipoprotein increased to 37.6 per cent and β-lipoprotein fell to 46.9 per cent while the O-fraction declined slightly (15.5 per cent) resulting in a 64 per cent drop in the β:α lipoprotein ratio.

Significant declines in lipid levels were apparent after 4 weeks and maximal effects were usually noted after about 6 weeks of therapy. Efforts to lower the minimum effective maintenance dose of estinyl to below .1 mg. daily were uniformly unsuccessful. The serum lipid levels of most patients were stabilized on a regimen of .1 to .15 mg. daily for 3 weeks, with 1 week off therapy.

In all 5 patients on the placebo regimen, lipid and lipoprotein levels gradually reverted...
Fig. 2. Effect of prolonged estinyl therapy on circulating lipids in patient 12, with idiopathic hypercholesteremia. Legends as in figure 1.

toward pretreatment values (table 2). In 1 instance of hypercholesteremia, the levels after 7 weeks on placebo were actually higher than before therapy. The time required for reversion of the lipid levels in the other patients was 5 months in the male patient with hyperlipemia and 3 and 4 months in 2 hypercholesteremic women. The rate of increment in total cholesterol when estrogen therapy was stopped averaged 49 mg. per cent per week, ranging from 20 to 85 mg. per cent.

Side Effects. The therapy was generally well tolerated by the patients. There were no complaints of fatigue, weakness, or malaise as had been reported in other studies.12 Weight was maintained in all instances. Three patients had occasional mild nausea. All men developed moderate gynecomastia or nipple sensitivity while the latter was noted by 2 women. Diminished libido was described by 5 men. Occasional uterine bleeding of mild degree and short duration was noted by 4 women. Institution of placebo administration was followed by return of full libido in 4 weeks in a man with hyperlipemia who had been on estrogen therapy for the preceding 8 months. In another man who stopped estinyl after 2 months, full libido returned in 3 weeks.

While on the study there was no instance of worsening of the course of coronary heart disease as manifested by angina, myocardial infarction, or of congestive heart failure. No deaths occurred during the study. In 1 hyperlipemic man with xanthomata tuberosa of knees and elbows there was almost complete disappearance of these lesions after 14 months of therapy. They began to regress after about 3 months of therapy (fig. 1).

Discussion

It is apparent that the therapeutic scheme of the study, which provided for a minimal effective dose of estrogen and interrupted therapy, is suitable for the long-term management of patients with elevated levels of serum lipids. Therapy is particularly well tolerated by women. In more than half the men, side
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Fig. 3 Left. Serum lipoproteins by paper electrophoresis of patient 1 with idiopathic hyperlipemia before treatment, while on therapy with ethinyl estradiol, and on placebo. The abnormally low α-lipoprotein increased while on therapy with ethinyl estradiol and the O-fraction decreased. On placebo α-lipoprotein was again depressed. α—α-lipoprotein; β—β-lipoprotein; O—O-fraction (triglycerides adsorbed at point of origin, i.e., of application of serum).

Fig. 4 Right. Serum lipoproteins by paper electrophoresis of patient 12 with idiopathic hypercholesteremia, before treatment, while on therapy with ethinyl estradiol, and on placebo. Legends as in figure 3. The abnormally low α-lipoprotein fraction increased under ethinyl therapy while the β and O-fractions decreased. On placebo, there was again decided depression of α-lipoprotein.

effects were not sufficient to exclude their participation for a prolonged period of time. The effect of estrogen therapy on serum lipids and lipoproteins is constant, predictable, and continuous at a dosage range considerably lower than that employed in other studies, although still above the physiologic level even for the female.
the course of the present study. Similar results were reported by others using estrogen therapy, and in our laboratory as a concomitant of the lipid-lowering effect of marked restriction of fat intake, after thyroid therapy, or after large doses of nicotinic acid.

The use of hormonal agents provides a practical means of controlling abnormal serum lipid and lipoprotein levels. Such therapy might be improved by the use of synthetic estrogen analogues which preserve the lipid-lowering effect and eliminate the feminizing action in a moderate dose range. Studies of this sort, in progress in numerous laboratories, may lead to more definitive measures for the management of disturbances in lipid metabolism and, perhaps their clinical complications.

**Summary**

Ethinyl estradiol in minimal effective doses of 0.2 to 0.1 mg. daily in interrupted courses was administered to 7 men and 5 women with idiopathic hyperlipemia or idiopathic hypercholesteremia for an average period of 16 months. In the group with idiopathic hyperlipemia mean levels of total and esterified cholesterol, phospholipids, triglycerides, and total lipids fell 30 to 69 per cent from pretreatment values. There was an increase in a-lipoprotein and a fall in b-lipoprotein and the b:a lipoprotein ratio. In the group with idiopathic hypercholesteremia mean levels of lipid fractions fell 11 to 39 per cent from pretreatment values. a-lipoprotein increased and b-lipoprotein and the b:a lipoprotein ratio decreased. A return toward pretreatment values within 2 to 5 months occurred in 5 patients placed on a placebo regimen.

Therapy was well tolerated. Side effects included moderate gynecomastia, sensitive nipples, diminished libido, and uterine bleeding. Almost complete disappearance of extensive xanthomata tuberosa occurred in 1 man with idiopathic hyperlipemia after 14 months of therapy.

The use of ethinyl estradiol provides a practical means of controlling abnormal serum lipid and lipoprotein levels.

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**Fig. 5** Top. Mean levels of circulating lipid and lipoprotein fractions in group of patients with idiopathic hyperlipemia before therapy with ethinyl estradiol and at point of maximum lipid-lowering effect under treatment.

**Fig. 6** Bottom. Mean levels of circulating lipid and lipoprotein fractions in group of patients with idiopathic hypercholesteremia before therapy and at point of maximum lipid-lowering effect under treatment with ethinyl estradiol.

Whether this type of therapy aimed at a long-term reduction of serum lipid fractions and the b:a lipoprotein ratio to approximately the normal range has any influence on the morbidity, mortality, or course of atherosclerosis, and its complications in these patients with decidedly disturbed lipid metabolism cannot be answered at present. Only prolonged observation of such patients treated with various lipid-lowering agents may provide such an answer at some future time. One external manifestation of hyperlipemia, tuberous xanthomas, was seen to disappear during
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SUMMARIO IN INTERLINGUA

Estradiol ethinylic in doses minime efficace de 0,2 a 0,1 mg per die in cursus interrumpite esseva administrate a 7 masculos e 5 femininas con hyperlipemia idiopathica o con hypercholesterolemia idiopathica durante un periodo medie de 16 menses. In le gruppo con hyperlipemia idiopathica, le nivellos medie de cholesterol total e esterificate, de phospholipidos, de triglyceridos, e de lipidos total descendeva per 30 a 69 pro cento del valores pretracamental. Esseva constatate un augmento de lipoproteina alpha e reductiones del lipoproteina beta e del proportion de lipoproteina beta a lipoproteina alpha. In le gruppo con hypercholesterolemia idiopathica, le nivellos medie del fractiones lipidic descendeva per 11 a 39 pro cento del valores pretracamental. Lipoproteina alpha se augmentava e lipoproteina beta e le proportion de lipoproteina beta a lipoproteina alpha se reduciva. Un retorno al valores pretracamental occurreva intra 2 a 5 menses in 5 patientes recipiente un medicament fictitie.

Le therapia esseva ben tolerate. Le effectos lateral includeva grados moderate de gynecmastia, sensibilitate del papillas, regressio del libido, e sanguination uterin. Le disparition quasi complete de extense xanthomas tunerose occurreva in 1 masculo con hyperlipemia idiopathica post 14 menses de therapia.

Le uso de estradiol ethinylic representa un medio practic pro regular anormal nivellos de lipid e lipoproteina in le sero.

REFERENCES

20. —: Electrophotometric microdetermination of


There are 3 main types of atrial septal defects, any of which may be associated with anomalous pulmonary venous drainage. They are the high defect or sinus venous type, the fossa ovalis or ostium secundum defect, and the ostium primum defect. The volume of the shunt is the chief surgical indication. The authors considered pronounced elevation of the pulmonary vascular resistance as a contraindication to surgery. The electrocardiogram should show right ventricular hypertrophy and right axis deviation. A tendency to left axis deviation may suggest an ostium primum defect. The reported surgical experience in this series is 49 patients—46 secundum defects, 2 primum defects, and 1 sinus venous defect. The basic surgical approach was described and emphasis was placed on the importance of a well-trained surgical team. Four operative deaths occurred in the first 10 patients and in none thereafter. Open-heart surgery was used in combination with hypothermia. All survivors were symptomatically improved.

Krause
Effect of Prolonged Use of Estrogens on Circulating Lipids in Patients with Idiopathic Hyperlipemia or Idiopathic Hypercholesteremia

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