Effect of Estrogenic Hormone on Serum Lipids in Patients with Coronary Arteriosclerosis

By Alfred Steiner, M.D., Henry Payson, M.D. and Forrest E. Kendall, Ph.D.

The oral administration of large amounts of ethinyl estradiol daily to patients with coronary arteriosclerosis and to control subjects consistently produced a favorable effect upon the serum lipid pattern. However, toxic effects of the estrogen prohibited its prolonged use. The clinical status of the patient as evidenced by the incidence of chest pain or the electrocardiogram were not altered during the period of the study.

The cause of the greater incidence of myocardial infarction secondary to coronary arteriosclerosis in men below the age of 50 as compared with women in the same age group has been the subject of interest and conjecture for many years. The possibility that this difference may be related to endocrine factors which serve to protect the female until the menopause has recently received support by Wuest, Dry and Edwards.1 These authors observed that the incidence and severity of coronary arteriosclerosis in bilaterally oophorectomized women is greater than in control females, and approaches that found in men.

Many contradictory reports have appeared relating the gonads and their secretions to the serum lipid pattern and to the development of arteriosclerosis both in human beings and in experimental animals.2 The effect of the administration of estrogens upon the serum lipid pattern of men and women has been studied by a number of investigators. Eilert3 reported that the oral administration of ethinyl estradiol (0.05 to 0.10 mg, daily) to menopausal women resulted in an average decrease of 25 mg. per 100 cc. in the serum cholesterol level together with an increase averaging 45 mg. per 100 cc. in the serum phospholipid content. Glass and coworkers4 in a study of 16 men and 15 women in the age group 55 to 65 years found no evidence that estradiol in doses of 0.25 to 0.75 mg. daily for periods of from two to four months influenced the level of either the serum lipids or the low density lipoproteins. Barr,5 however, reported that the administration of 1 mg. per day of ethinyl estradiol or an equivalent amount of Premarin* to survivors of myocardial infarction was followed by decreases in the serum cholesterol level and increases in serum phospholipid levels. As a result the cholesterol—phospholipid ratio dropped from a mean value of 1.05 to 0.72. This change was shown to be due largely to changes in the concentration and composition of the beta-lipoprotein fraction. Oliver and Boyd6 found that ethinyl estradiol (0.4 mg. per day) depressed the plasma ester cholesterol in 20 hypercholesterolemic men with coronary artery disease without influencing the serum phospholipid level. Gertler and his associates7 reported that in 25 patients who received 500 mg. stilbestrol daily following bilateral orchiectomy for carcinoma of the prostate, the serum phospholipid level increased with the serum cholesterol level remaining unchanged.

The majority of these investigations indicate that estrogen therapy produces changes in the serum lipid pattern of patients with coronary heart disease generally considered to be desirable. Further study of this problem is

* Premarin was obtained from Ayerst, McKenna and Harrison, Ltd.
<table>
<thead>
<tr>
<th>Patients</th>
<th>1st Control (Neutral fat)</th>
<th>Estradiol</th>
<th>Withdrawal</th>
<th>2d Control (Neutral fat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. S. C., 40 yrs.</td>
<td>210-290</td>
<td>313*</td>
<td>240-330</td>
<td>306*</td>
</tr>
<tr>
<td>2. J. C., 52 yrs.</td>
<td>300-400</td>
<td>313*</td>
<td>240-330</td>
<td>306*</td>
</tr>
<tr>
<td>3. R. G., 54 yrs. (1st study)</td>
<td>210-290</td>
<td>313*</td>
<td>240-330</td>
<td>306*</td>
</tr>
<tr>
<td>4. S. J., 56 yrs.</td>
<td>210-290</td>
<td>313*</td>
<td>240-330</td>
<td>306*</td>
</tr>
<tr>
<td>5. G. W., 32 yrs.</td>
<td>210-290</td>
<td>313*</td>
<td>240-330</td>
<td>306*</td>
</tr>
<tr>
<td>6. A. N., 32 yrs., control</td>
<td>210-290</td>
<td>313*</td>
<td>240-330</td>
<td>306*</td>
</tr>
<tr>
<td>7. S. N., 33 yrs., control</td>
<td>210-290</td>
<td>313*</td>
<td>240-330</td>
<td>306*</td>
</tr>
<tr>
<td>8. M. W., 34 yrs., control, 1st study</td>
<td>210-290</td>
<td>313*</td>
<td>240-330</td>
<td>306*</td>
</tr>
<tr>
<td>9. M. W., 34 yrs., control, 2nd study</td>
<td>210-290</td>
<td>313*</td>
<td>240-330</td>
<td>306*</td>
</tr>
</tbody>
</table>

* Standard Error of the Mean = \( \frac{\text{Standard Deviation}}{\sqrt{N}} \)

indicated and the following observations on the effect of estrogens upon the serum lipids and the clinical state of males with significant coronary arteriosclerosis were made.

**Method**

Five male patients, aged 32 to 56, with coronary arteriosclerosis (well documented myocardial infarction) and three male patients, aged 32 to 34, with inactive multiple sclerosis, spastic paraplegia, and paralysis from old poliomyelitis, respectively, were studied. The patients were hospitalized and maintained upon a constant diet of 2000 calories containing 85 Gm. each of protein and fat. An initial control period of four weeks was followed by from 18 to 62 days of estrogen therapy* by mouth.

* Ethinyl estradiol, Estinyl (Schering).

The daily dosage varied from 0.25 to 1 mg. of ethinyl estradiol per day and was governed by the patient's ability and willingness to tolerate the medication. The four weeks period subsequent to the medication was arbitrarily designated the withdrawal period and was followed in most cases by a second control period. Two of the patients were studied through two courses of medication.

Blood was drawn in the fasting state twice weekly during the course of the experiment. Serum cholesterol was determined by the method of Schoenheimer and Sperry, a serum lipid phosphorus by the method of Fiske and Subbarow and total serum lipid by a gravimetric procedure. Serum phospholipids were calculated by multiplying the serum phosphorus by a factor of 25. The neutral fat content of the serum was estimated by sub-
tracting the sum of the phospholipids, the cholesterol and the fatty acids combined with cholesterol, from the total lipids. The estrogen therapy was considered to have produced a significant alteration of serum lipid levels only when the mean level during the treatment or withdrawal periods differed from the mean level of the control period by at least three times the standard error of the difference between the means (p < .01).

RESULTS

The results of this study are summarized in table 1 and figure 1 which give the ranges, the mean values, and the standard error of the mean values of the serum levels of neutral fat, total cholesterol and phospholipid and of the cholesterol-phospholipid ratio during the control, experimental, and withdrawal periods. The administration of ethinyl estradiol produced a fall in the serum cholesterol level in 5 of the 10 trials and an increase in concentration of phospholipid in six trials. However the changes were such as to produce a significant lowering of the cholesterol-phospholipid ratio in every case. One month later the levels had fallen toward the control range. The effect of ethinyl estradiol on the serum lipid levels of the control patients did not differ from that seen in the patients with proven coronary arteriosclerosis.

All of the patients in this study developed toxic effects from the ethinyl estradiol in the dosage given. These effects consisted of fatigue, loss of appetite, nausea, vomiting, enlargement and sensitivity of the breasts and loss of libido. In several instances the estrogen had to be reduced in dosage or discontinued because of these reactions.

There was no evidence of improvement in the clinical status of the five patients with coronary arteriosclerosis during this study. No change either in the electrocardiographic findings or in the incidence of chest pain was observed during and following the estrogen treatment.

DISCUSSION

The results of this study confirm the findings of other investigators that oral administration of ethinyl estradiol to male subjects is followed by changes in the serum lipid pattern. The serum levels of cholesterol, phospholipid, and neutral fat of all the patients used in this study were well within the range of values found for healthy adults. The only abnormality in the lipid pattern observed during the initial control period lay in the somewhat high values found for the cholesterol-phospholipid ratio. During the period of ethinyl estradiol administration the serum cholesterol level fell significantly in five cases and the phospholipid level rose significantly in six cases. These changes were distributed in such a way as to produce a lowering of the cholesterol-phospholipid ratio in all the cases.

An increase in the serum level of neutral fat has previously been reported as a result of estrogen administration in patients with biliary cirrhosis by Ahrens, Payne and Kunkel. A similar increase was observed in six instances in this study. However, the precision of determination of the serum level of neutral fat is low since the value is derived by subtracting the phospholipid, free cholesterol and cholesterol ester from the total lipids and thus includes the experimental error of four difference measurements.

During the withdrawal period the levels of cholesterol and phospholipid tended to rise to values higher than those observed during the control period. This is suggestive of the rebound seen during convalescence from a febrile illness or after withdrawal of thyroid therapy. A similar rebound is not seen when lowered serum cholesterol levels occur as a result of diets low in fat and cholesterol. After the return of the patient to a normal diet the cholesterol level rises to but not above the control value.

It should be pointed out, however, that
certain differences exist between the results obtained in this study and those recorded in the two most recent reports. Gertler and his coworkers\textsuperscript{7} found that the serum phospholipid level increased while the serum cholesterol level remained unchanged in 25 patients given 500 mg. of stilbestrol daily and who had previously been subjected to bilateral orchidectomy for carcinoma of the prostate. However, Oliver and Boyd\textsuperscript{8} reported that a fall in serum cholesterol occurred without a change in the serum phospholipid after the oral administration of 0.4 mg. estradiol daily to patients with coronary arteriosclerosis. The reports by Eilert\textsuperscript{14} and Barr\textsuperscript{5} recorded alterations in both the serum cholesterol and serum phospholipid as are reported in the present study.

Nothing can be stated with certainty about how ethinyl estradiol acts to produce these changes in the serum lipid pattern. It may have a direct effect upon the metabolism of the lipids. It may operate by disturbing the whole endocrine balance which governs these metabolic processes.

The limited data available at this time, do not indicate that estrogen therapy has a beneficial effect upon the course of coronary arteriosclerosis. It is true that during the period of estrogen administration the serum cholesterol and phospholipid levels of patients tend to approach the levels found in young healthy adults. Further work is required to show that this shift improves the prognosis of patients with coronary arteriosclerosis.

It is possible that study of the mechanisms involved in this action of estrogens may lead to the discovery of agents which can accomplish the same results without producing the distressing side effects that preclude the widespread use of this drug.

**Summary**

The oral administration of 0.25 to 1 mg. of ethinyl estradiol daily to patients with coronary arteriosclerosis and to control subjects consistently produced a significant fall in the cholesterol–phospholipid ratio. This change was due to the lowering of the serum cholesterol level without much change in the phospholipid level in 5 of the 10 experimental periods. It was due to increased phospholipid levels without significant changes in the cholesterol levels in the other five instances. Serum neutral fat levels increased in 8 of the 10 periods studied. Toxic effects of the estrogen prohibited its prolonged use, except as a tool for investigative study. There was no change in the incidence of chest pain or in the electrocardiogram in the patients with coronary arteriosclerosis during the period of observation.

**Summario in Interlingua**

Le administration oral de 0,25 a 1,0 mg ethinyl-estriol per die resultavau, tanto in patientes con arteriosclerosis coronari como etiam in subjectos de controlo, in un reduction significative del proportion de cholesterol a phospholipido. Iste cambiamento reflecteva, in 5 del 10 periodos experimental, un reduction del cholesterol seral sin grande variationes in le nivellos de phospholipido. In le caso del altere 5 periodos experimental, illo reflecteva un augmento de phospholipido sin significative variationes in le nivellos de cholesterol. Le nivellos de grassia neutre del sero accresseva in 8 del 10 periodos studiate. Le effectos toxic del estrogeno non permetiva su uso prolongate excpte como instrumento investigative. Durante le periodo de nostre observationes nulle cambiamento esseva notate in le frequentia de dolores thoracic o in le electrocardiogrammas del patientes con arteriosclerosis coronari.

**References**


5. Barr, D.: Some chemical factors in the patho-


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