The Influence of the Sex Hormones on the Circulating Lipids and Lipoproteins in Coronary Sclerosis

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During the fourth and fifth decades of life, the clinical manifestations of coronary sclerosis are impressively more frequent in men than in women. So long as their reproductive physiology is maintained, women apparently enjoy some protection from the development of clinical coronary disease. There are abnormalities of the circulating lipids and lipoproteins in association with clinical coronary disease, and during the menstrual cycle there are cyclical variations in the circulating lipids and lipoproteins. It has been suggested that the physiologic depression at ovulation of plasma total cholesterol and the plasma total-cholesterol:phospholipid ratio (the C/P ratio) might be due to endogenous estrogen secretion. Corresponding fluctuations occur in the distribution of cholesterol between the alpha and beta lipoprotein fractions during the menstrual cycle. The administration of an oral estrogen to subjects with clinical coronary disease has resulted in considerable rectification of the abnormalities in the circulating lipid and lipoprotein patterns.

This report, which elaborates this effect of the estrogenic hormones and describes the influences of androgens and progestins, is part of a comprehensive study of the hormonal factors which may be involved in the homeostasis of the circulating lipids and lipoproteins, and of lipid metabolism.

Methods and Results

All the subjects were men whose ages ranged from 32 to 64 years, and all had electrocardiographic proof of myocardial infarction. A large majority of the men were in full employment and visited the Department of Cardiology in the Edinburgh Royal Infirmary during their working day. They attended at the same time at each visit and were not fasting or subject to any dietary restrictions, unless there was associated obesity. With the exception of the long-term ethinyl estradiol study, for which the selection of cases followed a separate pattern, all the subjects were hypercholesterolemic and at least three months had elapsed between the time of the infarct and the start of the investigation. Plasma total cholesterol was estimated by the Schoenheimer-Sperry procedure as modified by Sperry and Webb. Plasma lipid phosphorus was estimated by the molybdenum blue method of Allen. The distribution of cholesterol between the lipoprotein fractions was estimated by the zone electrophoresis method of Boyd, the percentage distribution of cholesterol between the alpha and beta lipoprotein fractions was expressed as a ratio, the \( \alpha: \beta \) lipoprotein ratio.

The investigations have been divided into five groups.
(1) Ethinyl Estradiol

(a) Graduated Study. Fifteen men received daily 200 μg. of ethinyl estradiol (British Schering) for two weeks, then 300 μg. for the next two weeks and then 400 μg. for the next two weeks. The daily dose was then increased by 200 μg. every two weeks until the men had received 1 mg. daily for a period of two weeks after which ethinyl estradiol was withdrawn.

This study was continued for six more weeks after ethinyl estradiol was withdrawn. The results of this study are shown in figure 1. The plasma total cholesterol fell from 300 mg. per 100 cc. to 230 mg. per 100 cc. after 12 weeks, a fall of 23 per cent (p < 0.01) and the total-cholesterol:phospholipid ratio from 1.12 to 0.75, a fall of 33 per cent (p < 0.01). The serum alpha:beta lipoprotein ratio rose from 7:93 to 15:85 (table 1). Following the withdrawal of ethinyl estradiol these values rapidly returned to their pretreatment levels, and not infrequently there occurred a rebound above the values prevailing during the control period.

(b) Large Dose Study. Thirty men received 1 mg. of ethinyl estradiol daily for six weeks and were followed for a further six weeks after this had been withdrawn. The results of this study are shown in figure 2. The plasma cholesterol fell from 268 mg. per 100 cc. to 225 mg. per 100 cc. after six weeks, a fall of 16 per cent (p < 0.02), and the total-cholesterol:phospholipid ratio fell from 1.00 to 0.77, a fall of 23 per cent (p < 0.01). The serum alpha:beta lipoprotein ratio rose from 9:91 to 14:86 (table 1).

(c) Long-Term Study. This investigation differed from the others in that the principal object was an attempt to assess the effect of ethinyl estradiol on the morbidity and mortality rates in men who were admitted to hospital following their first myocardial infarct; the results of this aspect of this long-term study will be reported in full when the series is larger and more time has elapsed. Between four and six weeks after discharge from hospital, alternate cases received either tablets containing 200 μg. of ethinyl estradiol or identical inert tablets. In each group 25 men have been followed for 3 months, 20 men for 6 months, 16 men for 9 months, 10 men for 12 months and 6 men for 15 months. As the subjects were consecutive admissions, not all were hypercholesterolemic, although they all showed some abnormality of their circulating lipids or lipoproteins.

The results of this study are shown in figure 3. In the group receiving ethinyl estradiol, the plasma total cholesterol fell from 255 mg. per 100 cc. to 222 mg. per 100 cc. 15 months later, a fall of 13 per cent; the total-cholesterol:phospholipid ratio fell from 0.97 to 0.68 15 months later, a fall of 30 per cent and the alpha:beta lipoprotein ratio rose from 9:91 to 18:82 after six months (table 1). In the group receiving inert tablets, the plasma total cholesterol fell from 239 mg. per 100 cc. to 224
mg. per 100 cc. 15 months later, a fall of 6 per cent; the total-cholesterol:phospholipid ratio fell from 0.95 to 0.90 after 15 months later, a fall of 5 per cent, and the alpha:beta lipoprotein ratio changed from 10:90 to 9:91 after six months (table 1).

**TABLE 1.**—The Changes in the Percentage Distribution of Cholesterol Between the Alpha and Beta Lipoprotein Fractions Produced By Various Sex Hormones

<table>
<thead>
<tr>
<th>No. of Men</th>
<th>α:β Lipoprotein Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethinyl estradiol</td>
<td></td>
</tr>
<tr>
<td>(a) Graduated study</td>
<td>15</td>
</tr>
<tr>
<td>(b) Large dose study</td>
<td>30</td>
</tr>
<tr>
<td>(c) Long-term study</td>
<td></td>
</tr>
<tr>
<td>Active preparation</td>
<td>20</td>
</tr>
<tr>
<td>Inert preparation</td>
<td>20</td>
</tr>
<tr>
<td>Estradiol</td>
<td></td>
</tr>
<tr>
<td>(a) 12 mg. daily</td>
<td>3</td>
</tr>
<tr>
<td>(b) 24 mg. daily</td>
<td>3</td>
</tr>
<tr>
<td>Estrone</td>
<td></td>
</tr>
<tr>
<td>(a) 30 mg. daily</td>
<td>3</td>
</tr>
<tr>
<td>(b) 50 mg. daily</td>
<td>3</td>
</tr>
<tr>
<td>Hexestrol</td>
<td>6</td>
</tr>
<tr>
<td>Progesterone</td>
<td>6</td>
</tr>
</tbody>
</table>

The majority of the 100 men who have received ethinyl estradiol experienced gynecomastia, which at first caused some concern to a few but was generally very well tolerated. Depression or loss of libido was not uncommon, but caused acute distress in only one case. Nausea occurred occasionally and caused the withdrawal of the estrogen in two cases; these subjects were excluded from the studies. Angina occurred more readily and more severely in two men and ethinyl estradiol was withdrawn from them both, and they were also excluded from these studies.

(2) The Naturally Occurring Estrogens

Although the potency of these estrogens is comparatively low when administered orally, this route was chosen for the convenience of the subjects.

(a) Estradiol. Three men received 12 mg. of estradiol (Ciba) orally each day for 14 days. The results of this study are shown in figure 4. The plasma total cholesterol fell from 259 mg. per 100 cc. to 237 mg. per 100 cc. after 14 days, a fall of 8 per cent, and the total-cholesterol:phospholipid ratio fell from 0.95 to 0.87, a fall of 8 per cent. The alpha:beta lipoprotein ratio rose from 12:88 to 19:81 (table 1).

Three men received 24 mg. of estradiol orally each day for 14 days. The results of this study are shown in figure 5. The plasma total cholesterol fell from 260 mg. per 100 cc. to 228 mg. per 100 cc. after 14 days, a fall of 12 per...
cent, and the total-cholesterol:phospholipid ratio fell from 0.96 to 0.88, a fall of 8 per cent. The alpha:beta lipoprotein ratio rose from 10:90 to 14:86 (table 1).

(b) Estrone. Three men received 30 mg. of estrone (Organon) orally each day for 14 days. The results of this study are shown in figure 6. The plasma total cholesterol fell from 312 mg. per 100 cc. to 300 mg. per 100 cc. after 14 days, a fall of 3 per cent, and the total-cholesterol:phospholipid ratio fell from 0.99 to 0.96, a fall of 3 per cent. The alpha:beta lipoprotein ratio fell from 14:86 to 12:88 (table 1).

Three men received 50 mg. of estrone orally each day for 14 days. The results of this study are shown in figure 7. The plasma total cholesterol fell from 286 mg. per 100 cc. to 261 mg. per 100 cc. after 14 days, a fall of 9 per cent, and the total-cholesterol:phospholipid ratio remained constant at 0.94. The alpha:beta lipoprotein ratio fell from 13:87 to 11:89 (table 1). Despite the lack of response to estrone while it was being administered, a slight rebound occurred in the plasma total cholesterol which rose to 300 mg. per 100 cc. two weeks after estrone was withdrawn; the total-cholesterol:phospholipid ratio rose to 1.03 at that time, but there was no rebound in the alpha:beta lipoprotein ratio.

(3) Hexestrol

Six men received 60 mg. of hexestrol (British Drug Houses) orally each day for 14 days. The results of this study are shown in figure 8. The plasma total cholesterol fell from 272 mg. per 100 cc. to 247 mg. per 100 cc. after 14 days, a fall of 9 per cent ($p > 0.5$), and the total-cholesterol:phospholipid ratio fell from 1.01 to 0.85, a fall of 16 per cent ($p < 0.05$). The alpha:beta lipoprotein ratio rose from 10:90 to 14:86 (table 1).

(4) Methyl Testosterone

(a) Methyl Testosterone + Ethinyl Estradiol. Twelve men were studied for 68 weeks. Five mg. of methyl testosterone (Ciba) were administered daily sublingually for four weeks and 10 mg. for a further four weeks. During these eight weeks the men also received inert
Tablets similar in size and shape to ethinyl estradiol. At the end of eight weeks tablets containing 400 μg. of ethinyl estradiol were substituted for the inert tablets, and for the next 14 weeks the men received the estrogen and 10 mg. of methyl testosterone daily; after the first two weeks 600 μg. of ethinyl estradiol were administered, and after two more weeks 800 μg. and after two further weeks 1 mg. of ethinyl estradiol was administered daily. At the end of 14 weeks combined therapy, inert linguets identical to the androgen were substituted, and the men received 1 mg. of ethinyl estradiol daily for four more weeks when identical inert tablets were again substituted for the estrogen; the men then received two groups of inert tablets for a further 12 weeks.

The results of this study are shown in figure 9. The plasma total cholesterol did not undergo any appreciable fall when ethinyl estradiol was administered in conjunction with methyl testosterone until 1 mg. of ethinyl estradiol was being received daily. When methyl testosterone was withdrawn, the plasma total cholesterol fell from a control value of 284 mg. per 100 cc. to 255 mg. per 100 cc., a fall of 21 per cent. Until 800 μg. of ethinyl estradiol was being received daily the total cholesterol:phospholipid ratio did not undergo any appreciable fall, but when methyl testosterone was withdrawn, the total-cholesterol:phospho-

FIG. 9. The effect of the administration of methyl testosterone, and subsequently also ethinyl estradiol, on the plasma lipids of 12 hypercholesterolemic men with coronary disease.

(b) Ethinyl Estradiol + Methyl Testosterone. Twelve men were studied for 30 weeks. Two hundred μg. of ethinyl estradiol were administered daily for two weeks and thereafter up to the end of the tenth week the daily dose was increased by 200 μg. every two weeks. During these 10 weeks the men also received inert linguets similar in size, shape and taste to methyl testosterone linguets. At the end of 10 weeks linguets containing 20 mg. of methyl testosterone were substituted for the inert linguets, and for the next four weeks the men received the androgen and 1 mg. of ethinyl estradiol daily. At the end of four weeks of combined therapy, inert tablet, identical to

FIG. 10. The effect of the administration of ethinyl estradiol, and subsequently also methyl testosterone, on the plasma lipids of 12 hypercholesterolemic men with coronary disease.
The estrogen were substituted, and the men received 20 mg. of methyl testosterone daily for four more weeks when inert linguets were again substituted for the androgen; the men then received two groups of inert tablets for a further four weeks.

The results of this study are shown in figure 10. The plasma total cholesterol fell from 278 mg. per 100 cc. to 209 mg. per 100 cc. after 10 weeks of ethinyl estradiol, a fall of 25 per cent. When methyl testosterone was administered in conjunction with ethinyl estradiol, the plasma total cholesterol rose to 279 mg. per 100 cc., and when ethinyl estradiol was withdrawn, the plasma total cholesterol rose still further to 312 mg. per 100 cc. The total-cholesterol:phospholipid ratio fell from 0.99 to 0.74 after 10 weeks of ethinyl estradiol, a fall of 25 per cent. When methyl testosterone was administered in conjunction with ethinyl estradiol, the total-cholesterol:phospholipid ratio rose to 0.89, and when ethinyl estradiol was withdrawn, the total-cholesterol:phospholipid ratio rose still further to 1.06.

The administration of methyl testosterone in these two studies did not modify or prevent any of the side effects of ethinyl estradiol, but its administration was associated with the development of clinical jaundice in four men who were consequently excluded from the study.

(c) Methyl Testosterone. Six men received 50 mg. linguets of methyl testosterone daily for 10 days. The results of this study are shown in figure 11. The plasma total cholesterol remained at 274 mg. per 100 cc. while methyl testosterone was being administered but rose slightly one week later to 282 mg. per 100 cc. The total-cholesterol:phospholipid ratio fell from 1.04 to 1.00 while methyl testosterone was being administered. These changes were not statistically significant. The alpha:beta lipoprotein ratio fell from 13:87 to 6:94 ($p < 0.05$) (table 1).

(5) Progestins

(a) Ethinyl Testosterone + Ethinyl Estradiol. Twelve men were studied for 26 weeks. Twenty mg. of ethinyl testosterone (anhydrohydroxyprogestosterone, Ciba) were administered daily sublingually for two weeks, 40 mg. daily for two more weeks and then 60 mg. daily for the next two weeks. During these six weeks the men also received inert tablets similar in size and shape to ethinyl estradiol. At the end of six weeks tablets containing ethinyl estradiol 500 µg. daily were substituted for the inert tablets, and for the next four weeks the men received the estrogen and 60 mg. of the progesterone analogue daily; after two weeks 1 mg. of ethinyl estradiol was administered daily. At the end of four weeks of combined therapy inert linguets identical to the progesterone analogue were substituted, and the men received 1 mg. of ethinyl estradiol daily for two more weeks when identical inert tablets were again substituted for the estrogen; the men then received two groups of inert tablets for a further eight weeks.

The results of this study are shown in figure 12. The plasma total cholesterol fell from 256 mg. per 100 cc. to 225 mg. per 100 cc. after six weeks of ethinyl testosterone, a fall of 12 per cent; it fell further to 208 mg. per 100 cc. when 1 mg. of ethinyl estradiol was administered at the same time. There was a rise in plasma total cholesterol to 242 mg. per 100 cc. when ethinyl testosterone was withdrawn even although the men were still receiving 1 mg. of ethinyl estradiol daily; there was a further rise on withdrawal of ethinyl estradiol to 271 mg. per 100 cc. The total-cholesterol:phospholipid ratio did not alter appreciably after six weeks of ethinyl testosterone; it fell from the control.
value of 0.93 to 0.80 when ethinyl estradiol was introduced, and subsequently rose to 1.03 following withdrawal of ethinyl estradiol.

(b) Progesterone. Six men received 100 mg. of progesterone (British Drug Houses) intramuscularly daily for five days. The results of this study are shown in figure 13. The plasma total cholesterol and the total-cholesterol: phospholipid ratio did not undergo any significant change during or after the course. Similarly the alpha:beta lipoprotein ratio failed to show significant change (table 1). The packed cell volumes and the weights of these men did not alter.

When the concentration of cholesterol on the alpha and beta lipoprotein fractions was expressed in mg. per 100 cc., the cholesterol on the beta lipoprotein fraction decreased absolutely and the cholesterol on the alpha lipoprotein fraction increased absolutely during the administration of ethinyl estradiol and, conversely, during the administration of methyl testosterone.

**FIG. 12**. The effect of the administration of anhydrohydroxy-progesterone (ethinyl testosterone), and subsequently also ethinyl estradiol, on the plasma lipids of 12 hypercholesterolemic men with coronary disease.

**FIG. 13**. The effect of progesterone on the plasma lipids of six hypercholesterolemic men with coronary disease. One hundred mg. were administered intramuscularly each day for five days.

Discussion

There can be no doubt from our studies on 100 survivors of myocardial infarction that ethinyl estradiol caused uniform depression of the plasma total cholesterol, the total-cholesterol: phospholipid ratio and the concentration of cholesterol attached to the beta lipoprotein fraction, and therefore a rise in the serum alpha:beta ratio. These results confirm our previous observation and those of Barr, Russ and Eder, and Steiner, Payson and Kendall. The percentage fall in the total-cholesterol: phospholipid ratio was greater than the percentage fall in the plasma total cholesterol whether ethinyl estradiol was administered at a low dose over a long period, in increasing doses over a moderate period or at a high dose over a short period. In these studies, ethinyl estradiol caused elevation of the plasma phospholipids as well as depression of the total cholesterol. This observation agrees with the findings of Eilert, Barr and associates, and Steiner and co-workers and contrasts with our previous observation that the phospholipids remained more or less constant. There was no significant alteration in body weight or in plasma volume, as judged by hematocrit determinations, in these men who were not subject to any dietetic restrictions. There was no significant difference in the degree or rate of the depression of plasma total cholesterol and the total cholesterol-phospho-
lipid ratio at the end of six weeks whether ethinyl estradiol was administered at a level of 1 mg. daily, at a level of 200 μg. daily or was increased gradually from 200 μg. to 1 mg. daily. This comparative study of the dosage of ethinyl estradiol was not possible beyond six weeks as some of the men who received 1 mg. of ethinyl estradiol complained of side effects, but it suggests that a dose larger than 200 μg. daily is not more effective in depressing the circulating lipids and may even be a disadvantage as side effects are more readily encountered. Generally, the higher the plasma total cholesterol, the total-cholesterol:phospholipid ratio and the concentration of cholesterol attached to the beta lipoprotein fraction the greater the response to the administration of ethinyl estradiol.

Ethinyl estradiol was the only estrogen preparation which produced highly significant depression of the circulating lipids and of the concentration of cholesterol attached to the beta lipoprotein fraction although hexestrol and estradiol administration resulted in a similar trend. The two principal side effects of ethinyl estradiol administration, gynecomastia and depression of libido, were remarkably well tolerated and were not regarded as major obstacles to the administration of estrogens to men. However, an attempt was made to minimize these side effects by the combination of an androgen or a progestin with ethinyl estradiol.

The simultaneous administration of methyl testosterone and ethinyl estradiol resulted in partial inhibition of the depressant action of the estrogen on the circulating lipids and lipoproteins. This inhibition was apparent when ethinyl estradiol was introduced in the course of the administration of methyl testosterone and in the converse study. Moreover, continued administration of methyl testosterone following withdrawal of ethinyl estradiol resulted in further elevation of the plasma total cholesterol and the total-cholesterol:phospholipid ratio and this elevation may partly be due to the rebound sometimes seen after withdrawal of ethinyl estradiol. When methyl testosterone was given alone there was no significant elevation in the plasma total-cholesterol or the total-cholesterol:phospholipid ratio but the alpha:beta lipoprotein ratio fell significantly. The effect of methyl testosterone on the plasma total cholesterol and on the total cholesterol:phospholipid ratio was more striking when ethinyl estradiol had been administered and its action was being antagonized. These observations are in agreement with those of Barr.11, 13 In our experience, methyl testosterone failed to ameliorate any of the side effects produced by ethinyl estradiol. The development of clinical jaundice in four men is in accord with the experiences of Werner who attributes to methyl testosterone a hepatotoxic action manifested by biliary stasis.19, 20

Progestosterone administered intramuscularly failed to elicit any response in the circulating lipids and lipoproteins, although a progestosterone analogue (ethinyl testosterone) administered sublingually produced some depression of the plasma total cholesterol and the plasma phospholipids. In our experience the administration of this progestosterone analogue also failed to ameliorate any of the side effects produced by ethinyl estradiol.

The mechanism by which ethinyl estradiol ameliorates the abnormal circulating lipid and lipoprotein patterns in coronary disease is at present obscure. The liver is probably the principal site of biosynthesis and catabolism of the circulating cholesterol, the quantity of which is largely dependent on the net result of these opposing dynamic processes; either or both of these processes may be influenced directly or indirectly by ethinyl estradiol. It is important to determine whether control of the circulating lipids and lipoproteins is associated with inhibition or even regression of atherosclerotic lesions. It is encouraging that less coronary atherosclerosis has been reported in men with carcinoma of the prostate, treated with large doses of stilbestrol, compared with similar men treated with small doses or none at all.21 Inhibition of the atherosclerotic process may not necessarily prolong life, once a myocardial infarct has occurred, and it is, therefore, essential to assess the effect of estrogens by a controlled clinical and, ultimately, pathologic study of subjects with coronary disease treated in this way.
There is considerable evidence that human coronary atherogenesis is influenced by sex. There is a striking sex difference in the incidence of the clinical manifestations of coronary sclerosis during the fourth and fifth decades. An analysis of 1000 consecutive patients with clinical coronary disease indicated that it was 19 times more common in men than in women under the age of 35 and 15 times more common under the age of 40.27 Young men have lower alpha:beta lipoprotein ratios4, 22-24 and a higher concentration of S1 12–20 low density lipoproteins25 than young women; it is probable that this sex difference in lipoprotein concentrations depends to some extent on cyclical variations which occur during the menstrual cycle and may be related to endogenous estrogen secretion.5, 9 Morphologic studies indicate that the physical characteristics of the very masculine and robust male are just those most commonly found to exceed in subjects of coronary disease.26 The estrogenic and androgenic sex hormones seem to be mutually antagonistic so far as the circulating lipids and lipoproteins are concerned and the estrogen-androgen balance may be of considerable importance in the development of clinical coronary disease. Whether alteration of this balance by estrogens will result in retardation of the atherosclerotic process and, if so, whether belated control of this process is of any value once it has become manifest clinically, can only be determined by further investigation and assessment in terms of morbidity and mortality.

SUMMARY

(1) The administration of ethinyl estradiol to men with myocardial infarction decreased the plasma total cholesterol, elevated the plasma phospholipids thereby depressing the total cholesterol-phospholipid ratio and decreased the concentration of cholesterol attached to the beta lipoprotein fraction.

(2) A daily dose of more than 200 μg. of ethinyl estradiol was no more effective in its influence on the circulating lipids and lipoproteins and was regarded as a disadvantage, as it was more readily associated with feminizing side effects.

(3) Hexestrol and estradiol had a similar but less marked effect.

(4) Ethinyl estradiol and methyl testosterone had a mutually antagonistic action on the circulating lipids and lipoproteins.

(5) Progesterone had no significant action on the circulating lipids and lipoproteins.

(6) Methyl testosterone and ethinyl testosterone failed to relieve the side effects of ethinyl estradiol administration.

(7) The efficacy of ethinyl estradiol administration in coronary disease must await assessment in terms of morbidity and mortality rates, rather than in its ability to correct the abnormal circulating lipid and lipoprotein concentrations.

ACKNOWLEDGMENT

We wish to thank Dr. Rae Gilchrist and Professor G. F. Marrian, F.R.S., of our respective departments, for their advice and encouragement, and Mr. Fraser Syme and Mr. William Cooper for their technical assistance.

SUMMARIO IN INTERLINGUA

Le administracion de ethinyl-estradiol a 100 superviventives de infarcimento myocardico resultava uniformemente in le correction del anormal concentrationes de circulate lipidos e liproteinas. Gynecomastia e depression del libido esseva ben tolerate per le patientes sed non esseva meliorate per un preparato androgenic o un analogo de progesterona. Methylo-testosterona, que effectuava un inhibition partial del efecto de estrogeno, augmentava le concentration de cholesterol del fraction lipoproteineic beta. Progesterona non havela un efecto significative super le circulate lipidos e liproteinas. Le determinacion del effecto de ethinyl-estradiol super le atherogenese human debe depender de un evalutation a longe durantia de su influenta super morbiditate e mortalitate.

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_Circulation_. 1956;13:82-91
doi: 10.1161/01.CIR.13.1.82

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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