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Influence of Sex and Sex Hormones on Lipoproteins and the Pathogenesis of Atherosclerosis

By **David P. Barr**

Clinical experience indicates that women, and particularly young women, possess a notable degree of protection from the more serious consequences of coronary atherosclerosis. In men angina is much more frequent, and myocardial infarction occurs five to ten times as often. Among one hundred patients under the age of 40 with coronary heart disease, *Glendy*, *Levine*, and *White* (1) saw only four in women. By dissections and injections of coronary arteries, *Schlesinger* and *Zoll* (2) showed occlusions to be more frequent in men at every age and, in the decades from 40 to 59, six times as great as in women. Mortality statistics (3, 4) reflect the same trend.

Susceptibility of men and relative immunity of women to serious complications of coronary artery disease are not readily explained on the sole basis of lipid deposits in arterial walls, since atherosclerosis is prevalent and extensive in both sexes. Meticulous study by *Sjövall* and *Wihman* (5) of the aorta and its branches showed that in Stockholm total deposit of lipid was slightly greater in men, while among the hard-working, well-nourished farm population of Lund the women were slightly more atherosclerotic. More significant sex differences were detected in coronary arteries. Women in the sixth decade had about the same degree of involvement as men in the fourth; in the seventh decade the degree of atherosclerosis corresponded to that of men in the fifth. It must be noted, however, that even in the fourth decade the women had more than 70 per cent as much coronary involvement as the men. Similar incidence was found by *Ackerman*, *Dry*, and *Edwards* (6). The conclusion seems justified that factors other than mere deposit of lipid must contribute to morbidity and mortality from coronary heart disease.

Efforts to explain more precisely the vulnerability of human males have been numerous. Concentration of cholesterol, phospholipids, and total lipids is almost identical in the sexes. Cholesterol content in different age groups in men and women is shown in Table 1. It will be seen that in later decades the concentration increases in both sexes; but the average increment with age is not greater in men.

Table 1
Distribution of Cholesterol
Age and Sex

Subjects	Age	Total Cholesterol Mg./100 Ml.	Percentage of Total Cholesterol in α-Lipoprotein	Percentage of Total Cholesterol in β-Lipoprotein
Normal women	18–35	187	34.3	61.8
Normal men	18–35	197	25.2	72.0
Normal women	45–65	252	23.4	75.0
Normal men	45–65	239	22.9	75.3

Distribution of cholesterol, also shown in Table 1, exhibits significant sex-linked differences. The percentage of total cholesterol in α-lipoprotein is higher, and in β-lipoprotein is lower, in young women. After the menopause, averages for the two sexes are approximately the same. In this study (7) and in others (8, 9, 10), it has been shown that plasma of young men contains more β-lipoprotein, a higher ratio of β-lipoprotein to α-lipoprotein, and more S_f 10–20 lipoproteins in the ultracentrifuge.

Table 2
Distribution of Cholesterol in Survivors of Myocardial Infarction

Subjects	Age	Total Cholesterol Mg./100 Ml.	Percentage of Total Cholesterol in α-Lipoprotein	Percentage of Total Cholesterol in β-Lipoprotein
Normal men and women	18–35	190	29.3	67.5
Normal men and women	45–65	245	23.1	75.2
Myocardial Infarction	18–64	259	13.6	83.9

In survivors of myocardial infarction all of these properties are exaggerated (11). In Table 2 comparison is made of concentrations and distribution of total cholesterol in normal men and women at different ages and of male survivors of myocardial infarction. Although cholesterol concentration in the men with coronary heart disease is only a little greater than in men and women of comparable age, there are great

differences in its distribution. The amount in β-lipoprotein is much increased, and in α-lipoprotein is relatively diminished.

Table 3

Calculated β-Lipoprotein/α-Lipoprotein Ratios in Healthy Young Men and in Survivors of Myocardial Infarction

(*Russ, Eder* and *Barr/Barr, Russ* and *Eder:* Amer. J. Med. **11,** 468 (1951)

Subjects	Total Cholesterol Mg./100 Ml.	Cholesterol in VI+V+VI Mg./100 Ml.	α* Lipoprotein Mg./100 Ml.	Cholesterol in I+II+III Mg./100 Ml.	β** Lipoprotein Mg./100 Ml.	$\frac{\beta}{\alpha}$ Ratio
Healthy women (aged 18–35)	187	66	533	123	399	0.75
Healthy men (aged 18–35)	197	50	417	147	477	1.15
Survivors of Myocardial Infarction	239	55	467	184	595	1.26

* Values for α-lipoprotein are obtained by dividing cholesterol concentration in Fraction IV + V + VI by 0.12.

** Values for β-lipoprotein are obtained by dividing cholesterol concentration in Fraction I + II + III by 0.309.

In Table 3 the same relationships are expressed in terms of concentrations of the two main forms of lipoprotein and as ratios of β-lipoprotein to α-lipoprotein. It can be seen that the chief difference is in the increased concentration of β-lipoprotein. Similarly, *Jones* and his associates (10) have shown increments in the concentration of S_f 10–20 lipoproteins of normal males and survivors of myocardial infarction.

Other possibly relevant differences in composition of plasma of males and females have been demonstrated. *Block, Barker,* and *Mann* (12) discovered that, after ingestion of a fat meal, parenteral administration of heparin cleared plasma of fat at variable rates in the several groups.

Table 4

Percentage Clearing of Plasma following Injection of Heparin *

Group	Number	Percentage Clearing			Number clearing less than 40 per cent
		Highest	Lowest	Average	
Normal women	20	100	62	84	0
Normal men	23	100	28	74	2
Atherosclerotic	27	100	0	38	16

* *Block, Barker* and *Mann:* Circulation **4,** 674 (1951).

It developed most promptly in normal women, less rapidly in normal men, and most slowly in atherosclerotic males. Differences are indicated in Table 4.

Observations have been made in heart muscle by *Cairns* and *Constantinides* (12) on mast cells, which are thought to be functionally implicated in production of heparin-like substances. Their number was greatest in young women and least in atherosclerotic men and women during the later decades of life. Counts of mast cells are shown in Table V.

Table 5

Heart Mast Cells *

Number of Subjects	Group	Number of Mast Cells/cm²
23	Normal young women	351 ± 30.1
23	Normal young men	239 ± 33.1
24	Non-atherosclerotic old women	276 ± 33.5
24	Non-atherosclerotic old men	270 ± 30.7
24	Atherosclerotic old women	193 ± 28.5
24	Atherosclerotic old men	201 ± 30.7

* *Cairns* and *Constantinides:* Science **120,** 31 (1954)

Another intriguing sex-linked difference has been noted by *Wintrobe* and his group (14, 15) in the content of total copper and caeruloplasmin. In Table 6 it may be seen that copper concentration is higher in normal women than in normal men and that it is notably increased in pregnancy.

Table 6

Concentration of Total Copper and Caeruloplasmin

Subjects		Total Copper	Indirect (Caeruloplasmin) Copper
23	Normal women *	116 ± 17	
40	Normal men *	105 ± 16	
10	Normal pregnant women **	257 ± 38	228 ± 35

* *Lahey, Gubler, Cartwright* and *Wintrobe:* J. clin. Invest. **32,** 322 (1953).

** *Markowitz, Gubler, Mahoney, Cartwright* and *Wintrobe:* J. clin. Invest. **34,** 1498 (1955).

Although it is reasonable to think that hormonal influences account for chemical differences of the sexes, it is not known at present whether estrogens or androgens are responsible. It is also not known whether

women are protected by estrogen from the complications of atherosclerosis or whether men are made more susceptible because of the influence of testosterone.

Table 7

Effect of Administration and Withdrawal of Estrogen in 20 Survivors of Myocardial Infarction *

Stage of Treatment	Total Cholesterol (Mg. per 100 Ml.)	Cholesterol in α-Lipoproteins		Cholesterol in β-Lipoproteins (Mg. per 100 Ml.)	β/α-Ratio
		Per Cent of Total	(Mg. per 100 Ml.)		
Before estrogen	282	11.3	32	250	3.12
After 9 weeks of estrogen	210	27.1	57	153	1.04
Two weeks after discontinuing estrogen	285	18.5	53	220	1.61

* *Barr, Russ* and *Eder:* Amer. J. Med. **11,** 480 (1951).

In Table 7 are shown effects of administration and withdrawal of estrogen in twenty survivors of myocardial infarction (16). It may be seen that the hormone tends to restore to normal both concentration and distribution of cholesterol with consequent reduction of the ratios of β-lipoprotein to α-lipoprotein. Withdrawal of hormone permits prompt return to the previous pathological state.

Estrogen also causes a reduction in the cholesterol/phospholipid ratio of the total plasma, which is attributable to changes in composition or distribution of β-lipoproteins. This is shown in Table 8.

Table 8

Effect of Estrogens on Cholesterol/Phospholipid Ratio
Average of 14 Subjects *

	Without Estrogen	With Estrogen
Plasma	1.05	0.72
Fraction IV + V + VI (α-Lipoprotein)	0.47	0.44
Fraction I + III (β-Lipoprotein)	1.32	0.97

* *Russ, Eder* and *Barr:* Amer. J. Med., **19,** 4 (1955)

Table 9

Effect of Estrogen Therapy in Myocardial Infarction of Women

Patient	Age	Conditions	Total Cholesterol Mg./100 Ml.	Percentage of Total Cholesterol in α-Lipoprotein	Cholesterol in β-Lipoprotein Mg./100 Ml.	Cholesterol-Phospholipid Ratio	
						Plasma	β-Lipoprotein
Bie	46	Before estrogen	342	12.4	297	1.03	1.26
		After 84 days 10 000 r. u. Estinyl o. d.	211	36.6	132	0.67	0.94
Cha	59	Before estrogen	368	20.3	288	0.93	1.29
		After 41 days 10 000 r. u. Estinyl o. d.	313	29.8	213	0.82	1.27
Coh	44	Before estrogen	358	10.2	316	1.19	1.34
		After 54 days 10 000 r. u. Estinyl o. d.	313	22.7	234	0.91	1.33
Wol	48	Before estrogen	411	8.5	369		
		After 5 month 10 000 r. u. Estinyl o. d.	337	19.8	265		
		2 months after withdrawal	441	9.8	362		

Table 10

Effect of Estrogen on Lipids of Xanthomatous Women

Patient	Age	Conditions	Total Cholesterol Mg./100 Ml.	Percentage of Total Cholesterol in α-Lipoprotein	Cholesterol in β-Lipoprotein Mg./100 Ml.	Cholesterol-Phospholipid Ratio	
						Plasma	β-Lipoprotein
Ha	56	Before estrogen	557	7.3	510	1.26	1.51
		After 8 weeks of estrogen *	**365**	**16.3**	**300**	**0.89**	**1.17**
		14 weeks after withdrawal	520	11.5	439	1.15	1.43
Co	39	Before estrogen *	444	7.2	415	1.26	1.51
		After 15 weeks of estrogen *	**350**	**15.8**	**283**	**0.94**	**1.20**
St	49	Before estrogen	466	6.5	425	1.22	1.45
		After 4 weeks of estrogen *	**340**	**18.2**	**259**	**0.96**	**1.23**
		After 11 weeks of estrogen *	**304**	**17.6**	**245**	**0.92**	**1.23**
Le	49	Before estrogen	426	12.6	367	1.08	1.33
		After 3 weeks of estrogen **	**393**	**14.7**	**330**	**1.00**	**1.30**

* Estrogen was given in form of *Estinyl* (ethinyl estradiol) 1.0 mg o. d.

** *Estinyl* dosage only 0.5 mg o. d.

Effects of similar character can be produced in women both before and after the menopause (17) as is shown in Table 9.

Even in xanthomatous women with maximum disturbances in lipid relationships, administration of estrogen reduces concentration of cholesterol and β-lipoprotein and lowers cholesterol/phospholipid ratios of the plasma and of β-lipoprotein.

Table 11

Effect of Estrogen Therapy in Cretinism

Patient	Age	Conditions	Total Cholesterol Mg./100 Ml.	Percentage of Total Cholesterol in α-Lipoprotein	Cholesterol in β-Lipoprotein Mg./100 Ml.	Cholesterol-Phospholipid Ratio	
						Plasma	β-Lipoprotein
Laz	58	Before estrogen	374	11.3	330	1.10	1.40
		After 22 days 10 000 r. u. Estinyl o. d	301	21.3	232	0.91	1.20
		2 months after withdrawal	391	10.8	343	1.17	1.35
		After 27 days 10 000 r u. Estinyl o. d.	260	25.4	189	0.68	0.97

Table 12

Effect of Estrogen on Lipids in Myxedema *

Patient	Sex	Age	Conditions	Total Cholesterol Mg./100 Ml.	Percentage of Total Cholesterol in α-Lipoprotein	Cholesterol in β-Lipoprotein Mg./100 Ml.	Cholesterol-Phospholipid Ratio	
							Plasma	β-Lipoprotein
Bo	♀	72	Before estrogen	571	11.4	475	1.28	1.53
			After 14 days of estrogen	**397**	**17.6**	**322**	**0.95**	**1.30**
			14 days after withdrawal	523	14.0	440	1.05	1.41
Un	♀	45	Before estrogen	427	12.2	368	1.03	1.29
			After 21 days of estrogen	**240**	**32.9**	**156**	**0.56**	**0.80**
Ci	♀	59	Before estrogen	334	19.4	255	1.05	1.36
			After 28 days	**292**	**30.7**	**196**	**0.88**	**1.27**
Ei	♀	67	Before estrogen	277	9.7	249	1.03	1.27
			After 14 days of estrogen	**285**	**23.0**	**211**	**0.76**	**0.91**
O'B	♀	63	Before estrogen	339	21.2	262	1.07	1.39
			After 14 days of estrogen	**260**	**26.6**	**186**	**0.86**	**1.23**

* Estrogen was given in form of *Estinyl* (ethinyl estradiol) 1.0 mg o. d.

Administration of estrogen causes similar changes in cretinism and in myxedema (17). Effects on lipid content and distribution are almost as marked as those following treatment with thyroid but are accomplished without other notable changes in the hypothyroid state.

In Table 11 is shown the effect of estrogen in a cretin woman aged 58.

Action of the hormone in five cases of adult myxedema is shown in Table 12.

Table 13
Effect of Estrogen on Concentration of Total Copper and Caeruloplasmin *

Patient	Diagnosis	Relation to Estrogen * Treatment	Total Copper	Indirect (Caerulo-plasmin) Copper
Bea	Myocardial Infarction	Before	157	132
		After 4 weeks	**334**	**382**
Adi	Myocardial Infarction	Before	153	138
		After 4 weeks	**356**	**322**
Unr	Myxedema	Before	131	117
		After 3 weeks	**340**	**304**
Cit	Myxedema	Before	254	220
		After 4 weeks	**374**	**356**
Bor	Myxedema	Before	150	137
		After 2 weeks	**202**	**195**
Cop	Myxedema	Before	152	146
		After 2 weeks	**325**	**256**
Sta	Xanthomatosis	Before	175	151
		After 4 weeks	**328**	**299**
Has	Xanthomatosis	Before	169	169
		After 8 weeks	**360**	**321**
Average		Before estrogen	168	151
		After estrogen	**327**	**304**

**Russ* and *Raymunt* (in press).
** Estrogen given as *Estinyl* (ethinyl estradiol) 1 mg o. d.

Recent observations by *Russ* and *Raymunt* (18) in our laboratory have shown an extraordinary effect of estrogen on the concentration of total copper and caeruloplasmin. In Table 13 it may be seen that the caeruloplasmin, which accounts for almost all of the total copper, is approximately doubled in most of the cases. Values after estrogen are greater than those previously observed in any clinical condition.

The action of methyl testosterone on lipid concentration and distribution is opposite to that of estrogen (18). In Table 14 averages of various lipid relationships are presented. Not only is the concentration of cholesterol increased but there is also a marked augmentation of the concentration of β-lipoprotein and a large increase in the β-lipoprotein/

α-lipoprotein ratios. These changes occur both in pathological states and in normal men and women.

Table 14

Effects of Methyl-Testosterone on Concentration and Distribution of Lipids
Averages of 21 Patients *

	Before Testosterone	After Testosterone	After Withdrawal of Testosterone
Total Cholesterol (mg/100 ml)	170	220	205
% Total Cholesterol in IV + V + VI	24.9	14.4	21.0
Cholesterol in IV + V + VI (mg/100 ml)	46	27	41
α-Lipoprotein (mg/100 ml) **	383	225	342
Cholesterol in I + II + III (mg/100 ml)	154	194	160
β-Lipoprotein (mg/100 ml) ***	498	634	518
$\frac{\beta\text{-Lipoprotein}}{\alpha\text{-Lipoprotein}}$ Ratio	1.30	2.82	1.52

* *Russ, Eder* and *Barr:* Amer. J. Med. **19,** 4 (1955).

** α-lipoprotein is obtained by dividing cholesterol concentration in Fraction IV + V + VI by 0.12.

*** β-lipoprotein is obtained by dividing cholesterol concentration in Fraction I + II + III by 0.309.

Some experiments have been performed to test the combined effect of estrogen and methyl-testosterone when given simultaneously (16). These are presented in Table 15. It was originally hoped that the administration of methyl-testosterone might counteract some of the unfavorable side actions that develop when estrogens are given to men. Although

Table 15
Influence of Combined Estrogen and Methyl-Testosterone

Conditions	Total Cholesterol Mg./100 Ml.	Percentage of Cholesterol in Form of α-Lipoproteins	Cholesterol in Form of β-Lipoproteins Mg./100 Ml.
Before use of hormone	202	9.7	171
After 5 days 10 000 r. u. Estinyl o. d.	173	29.6	120
After 69 days 5 000 r. u. Estinyl o. d.	194	33.1	130
After 56 days 2 500 r. u. Estinyl o. d.	217	31.2	148
After 28 days combined dosage of 2 500 r. u. Estinyl and 50 mg of methyl-testosterone o. d	351	3.2	338
After 50 days 2 500 r. u. Estinyl o. d. without methyl-testosterone	226	27.6	161

this hope was not realized, the male sex hormone in every instance reversed the effects of estrogen on lipid relationships. In some instances the simultaneous administration of estrogen appeared to augment the action of methyl testosterone.

Summary

Complications of coronary atherosclerosis rarely occur in young women but are not infrequent in young men. The difference in susceptibility is attributable only in part to the degree of coronary atherosclerosis in the sexes. Chemical factors may contribute not only to the deposit of lipid in arteries but also to development of coronary thrombosis and myocardial infarction. There are sex-linked differences in concentration and distribution of lipoproteins; in the response to heparin after fat ingestion; in the abundance of mast cells; and in the concentration of caeruloplasmin. Many of the qualities that distinguish young men are exaggerated in survivors of myocardial infarction.

Administration of estrogen corrects some of the abnormalities found in the plasma of survivors of myocardial infarction and tends to establish a pattern like that found in plasma of young women. It accomplishes similar effects in older women as well as in cretinism and myxedema.

Administration of testosterone exaggerates abnormalities in survivors of myocardial infarction and produces them in normal men and women.

It is not yet known whether estrogen or testosterone is responsible for differences in susceptibility to complications of coronary atherosclerosis.

Zusammenfassung

Komplikationen bei Atherosklerose der Coronarien treten selten bei jungen Frauen auf, sind aber nicht selten bei jungen Männern. Das ist nicht allein dem unterschiedlichen Grad der Atherosklerose bei beiden Geschlechtern zuzuschreiben. Chemische Faktoren tragen möglicherweise nicht nur zur Ablagerung von Lipiden in den Arterien bei, sondern auch zur Entwicklung von Coronarthrombosen und Myokardinfarkten. Es bestehen geschlechtsgebundene Unterschiede in der Konzentration und Verteilung der Lipoproteide, und zwar sowohl in der Reaktion auf Heparin nach Fettverdauung als auch in der Häufigkeit von Mastzellen sowie in der Konzentration von Caeruloplasmin. Viele der Befunde, die für den jungen Mann charakteristisch sind, sind gerade bei solchen, die einen Myokardinfarkt überstanden haben, stark übertrieben nachweisbar.

Gaben von Oestrogen korrigieren einige der abnormen Befunde, die bei Überlebenden nach Myokardinfarkten vorhanden sind, und neigen dazu, ein Bild hervorzurufen, wie es das Plasma junger Frauen zeigt. Das Oestrogen führt zu gleichen Wirkungen bei älteren Frauen sowie beim Kretinismus und beim Myxödem.

Testosterongaben dagegen steigern die abnormen Befunde bei Überlebenden nach Myokardinfarkten und verursachen sie sogar bei normalen Männern und Frauen.

Es ist aber noch nicht bekannt, ob Oestrogen oder Testosteron für die unterschiedliche Anfälligkeit für Komplikationen bei koronarer Atherosklerose verantwortlich zu machen sind.

Résumé

Alors que les complications des coronaires se rencontrent rarement chez les jeunes femmes, elles sont plus fréquentes chez les hommes jeunes. Cette différence de prédisposition n'est attribuable qu'en partie à la proportion relative de l'athérosclérose des coronaires dans les deux sexes. Des facteurs chimiques peuvent non seulement contribuer au dépôt de lipides dans les artères, mais aussi à la formation de thromboses des coronaires et à la provocation d'infarctus du myocarde. Il existe des différences liées au sexe dans la concentration et la distribution des lipoprotéines, dans la réaction à l'héparine après ingestion de graisses, dans l'abondance de mastocytes et dans la concentration en caeruloplasmine. Beaucoup de facteurs, qui caractérisent les hommes jeunes, sont amplifiés chez les hommes, qui survivent à un infarctus du myocarde.

L'administration d'œstrogènes corrige certaines anomalies que l'on trouve dans le plasma des survivants à un infarctus du myocarde; elle tend à donner au plasma les caractères que l'on trouve dans celui des jeunes femmes. Les mêmes effets s'obtiennent chez les vieilles femmes, ainsi que chez les crétins et les myxœdémateux.

L'administration de testostérone accentue les anomalies que l'on trouve chez les survivants à un infarctus du myocarde et les crée chez des hommes et des femmes normaux.

On ne sait pas encore si les œstrogènes ou la testostérone sont responsables des différences de prédisposition dans les complications de l'athérosclérose des coronaires.

1. *Glendy, R. E., Levine, S. A.*, and *White, P. D.:* J. Amer. med. Ass. **109,** 1775 (1937). – 2. *Schlesinger, M. J.*, and *Zoll, P. M.:* Arch. Path. (Chicago) **32,** 178 (1941). – 3. *Gover, M.*, and *Pennell, M. Y.:* Publ. Hlth Rep. (Wash.) **65,** 819 (1950). – 4. *Moriyama, I. M.*, and *Woolsey, T. D.:* Publ. Hlth Rep. (Wash.) **66,** 355 (1951). – 5. *Sjövall, H.*, and *Wihman, G.:* Acta path. microbiol. scand., Supp. 20, 1 (1934). – 6. *Ackerman, R. F., Dry,*

T. J., and *Edwards, J. E.:* Circulation **1,** 1345 (1950). – 7. *Russ, E. M., Eder, H. A.*, and *Barr, D. P.:* Amer. J. Med. **11,** 468 (1951). – 8. *Swahn, B.:* Scand. J. clin. Lab. Invest. **5,** supp. 9, 1 (1953). – 9. *Nikkilä, E.:* Scand. J. clin. Lab. Invest. **5,** supp. 8 (1953). – 10. *Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B.*, and *Nichols, A. V.:* Amer. J. Med. **11,** 358 (1951). – 11. *Barr, D. P., Russ, E. M.*, and *Eder, H. A.:* Amer. J. Med. **11,** 480 (1951). – 12. *Block, W. J., Barker, N. W.*, and *Mann, F. D.:* Circulation **4,** 674 (1951). – 13. *Cairns, A.*, and *Constantinides, P.:* Science **120,** 31 (1954).– 14. *Lahey, M. E., Gubler, C. J., Cartwright, G. E.*, and *Wintrobe, M. M.:* J. clin. Invest. **32,** 322 (1953). – 15. *Markowitz, H., Gubler, C. J., Mahoney, J. P., Cartwright, G. E.*, and *Wintrobe, M. M.:* J. clin. Invest. **34,** 1498 (1955). – 16. *Russ, E. M., Eder, H. A.*, and *Barr, D. P.:* Amer. J. Med. **19,** 4 (1955). – 17. *Barr, D. P., Russ, E. M.*, and *Raymunt, J.:* Unpublished Observations. – 18. *Russ, E. M.*, and *Raymunt, J.:* Proc. Soc. exp. Biol. (N. Y.) (in press).