CHOLESTEROL, CORONARY HEART DISEASE AND OESTROGENS*

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SUMMARY

Present concepts of the interrelationship between oestrogens, endogenous and exogenous, and the development of atheromatosis and coronary heart disease in the human female are reviewed. Aspects of research conducted by me at Groote Schuur Hospital, Cape Town, are incorporated in the discussion. The current role of oestrogen replacement therapy in the prevention of coronary heart disease in postmenopausal females is presented. It is concluded that although this role at present is limited, there is hope for the development of new oestrogenic steroids with a more specific effect on cholesterol metabolism. Finally, a plea is made for conservatism with ovaries during gynaecological operations on young females.

Some investigators have noted that the premenopausal female, compared with the human male, is protected against coronary accidents.[1-4] The sex difference is alleged to be due to oestrogens.

The purpose of this paper is to review present concepts of the inter-relationship between oestrogens, endogenous and exogenous, and the development of atheromatosis and coronary heart disease. Aspects of research conducted at a Menopause Clinic, Groote Schuur Hospital, will be incorporated in the discussion.[5] Finally, some conclusions as to the current role of oestrogen therapy in the prevention of coronary heart disease in postmenopausal females will be presented.

Normal Cholesterol Balance

The circulating cholesterol is largely synthesized in the liver and discharged into plasma bound to lipoproteins. The plasma cholesterol pool reflects the net result of a series of reactions which are donating sterol to the pool while others are removing sterol.[6]

Among western populations and the prosperous moiety of non-White populations serum cholesterol and other blood lipids rise with age.[7,8] Serum cholesterol is thought to increase from about 180 mg/100 ml between the ages of 20 and 30 years to about 220[10-12] between the ages of 50 and 60 years.[9] The levels vary, however, in different population groups. For example, Barr[1] recorded mean levels of 197 in normal women aged 18 - 35 and 252 in normal women aged 45 - 65 years. Oliver and Boyd[13] reported mean levels of 217 for women aged 40 - 49 years, 240 for those aged 50 - 54 years and 259 for those aged 55 - 59 years. The risks of coronary thrombosis are said to be seriously increased if serum cholesterol levels exceed 250.[9,14]

Cholesterol is a precursor of oestrogenic hormones.[15,16] Endogenous oestrogens appear to influence cholesterol metabolism in at least two ways. There is an effect on the biosynthetic mechanism and also an influence on the rate of degradation or excretion.[6] Thus these oestrogens appear to exert an effect on human plasma cholesterol and lipid - lipoprotein levels.[1,2,17,18]

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Coronary Risk Factors

Atheromatosis is a metabolic disease that is influenced by many factors.[18-23] The development of atheromatous lesions does not lend itself to precise measurement in the living. However, the extent and severity of coronary atheromatosis determines the risk of ischaemic heart disease in a given population.[24] This presentation is concerned with only one phase of atheromatosis, namely, its relation to ovarian function and plasma cholesterol.

Coronary risk factors are those abnormalities demonstrable in persons free of coronary heart disease (CHD) and known to be associated with significantly increased risk of developing the disease in subsequent years. Numerous prospective studies on western populations have indicated a close correlation between the moiety with elevated cholesterol levels and their proness to ischaemic heart disease.[14,18,25-29] Population groups with hypercholesterolaemia experience four times as many heart attacks as those with low serum cholesterol levels.[28] This strong relationship is well shown in the Framingham study[14,26,30] and in the Los Angeles heart study.[20] Katz and Stamler[17] have demonstrated experimentally a similar relationship. They noted that feeding cholesterol to cockerels produced coronary atherosclerosis.

In western populations a similarity exists in the proportions of the leading causes of death.[31] Thus CHD accounts for about one-third, cancer one-quarter or less and 'strokes' 10% - 15% of total mortality. An important question, therefore, in improving mortality statistics is whether long-term reduction of hypercholesterolaemia will in turn reduce the incidence of atheromatosis and subsequent ischaemic heart disease. In this direction it is important to determine factors responsible for increasing and for decreasing plasma cholesterol levels.[11]

Oophorectomy and Coronary Heart Disease

Considerable evidence, experimental and clinical, is available indicating that endogenous ovarian oestrogen secretion plays a key role in protecting women against clinical atheromatous (atherosclerotic), coronary heart disease. This evidence is well reviewed by Berkson *et al.*[32] and key references only will be discussed below.

Numerous studies have been done on the effects of castration or premature menopause on the occurrence of both clinical heart disease and autopsy evidence of atherosclerosis in women.[13,33-36] Wuest *et al.*[36] compared the degree of sclerosis in hearts of bilaterally oophorectomized women with hearts of men and women of comparable ages. They found that the degree of coronary sclerosis in oophorectomized women was greater than in control women but less than in control men. Oliver and Boyd[13] reported that bilateral oophorectomy was followed by the premature development of clinical coronary artery disease; similar findings were found by Robinson *et al.*[35] Higano and Cohen[33] reported the risk to be 4-fold. Novak and Williams[34] stated that the data of Robinson *et al.*[35] and Oliver and Boyd,[13] being clinical in nature, could not be as

objective and precise as data obtained at autopsy. Regardless of initial age at operation or years intervening before death, they could find no significant differences in the incidence of atherosclerosis in statistically comparable groups of castrated and control patients at autopsy. A follow-up study[37] suggested that operation before the age of 40 years might be of significance. Parrish *et al.*[38] suspected that an important factor overlooked by previous writers was the time interval between castration and the 'expected date' of the normal menopause. From a study of autopsy records they found that castrated patients did have an excess of coronary atherosclerosis and myocardial infarcts, but this was directly related to the time interval from castration to 'expected menopause' and the time interval from castration to death. No excessive coronary atherosclerosis was found in women castrated after the age of 41 years in contrast to those castrated when younger; excessive coronary atherosclerosis became apparent about 14 years after castration. They concluded that women castrated before the age of 40 who were expected to survive more than 14 years were at high risk of developing coronary heart disease. Finally, in a 6 - 20-year follow-up study of 35 women who had undergone spontaneous premature menopause, Sznajderman and Oliver[39] further supported the view that cessation of ovarian activity, whether premature or at the time of a normal menopause, leads to an increase in the incidence of ischaemic heart disease and in serum lipid levels in later life.

Thus the evidence as to the protective effect of the functioning ovary is convincing. Unfortunately, as yet the supporting evidence for the next logical step in this argument is not as sound, namely the effect of replacement exogenous oestrogen on the female cardiovascular system.

Exogenous Oestrogens and Coronary Heart Disease

A wide range of oestrogenic substances has been studied for their effects on cholesterol metabolism in experimental animals and to a lesser extent in humans.[21,40] Oestradiol, oestradiol benzoate and diethylstilboestrol are more potent than oestrone as regards both lipid effects and oestrogenic activity. Ethinyl oestradiol has less effects on lipids and is more potent as an oestrogen than oestrone.[21,41] Table I gives a summary from Boyd[6] of a few of the oestrogens studied for their effect on cholesterol metabolism.

TABLE I. DOSES OF OESTROGENS STUDIED WITH REGARD TO EFFECT ON CHOLESTEROL METABOLISM*

Trivial name	*Approximate oestrogenic dose* (μg)	*Approximate dose affecting plasma cholesterol concentration* (μg)
Oestradiol-17 β	200 - 500	25 000
Ethinyl oestradiol	10 - 50	100 - 200
Oestrone	1 000 - 5 000	50 000
Oestriol	100 - 500	100 000
Stilboestrol	100 - 1 000	40 000

*From Boyd.[6]

Thus, in the human, the administration of oestrogenic substances at certain dosages produces a depression in the plasma cholesterol concentration and the dosage necessary to produce this effect on the plasma cholesterol level is in excess of the threshold oestrogenic dose.[6] However, there are insufficient data at this stage to allow more than speculation on the possible mode of action of the oestrogens in cholesterol metabolism.

Experimentally, Pick *et al.*[42] have shown that administration of oestrogens inhibits coronary atherogenesis in cockerels fed a cholesterol-supplemented diet. There are no comparable studies in man. Oliver and Boyd[43] administered oestrogen to survivors of myocardial infarction. They found that, although significant reduction of the serum cholesterol was evident throughout the 5 years of treatment, the continued reduction of serum lipids did not improve prognosis once myocardial infarction had occurred. Similar findings were reported by Marmorston *et al.*[2] Other studies have shown the effects of oestrogens on serum lipid patterns in postmenopausal women.[44,45] In most cases 1·25 mg of mixed conjugated equine oestrogens daily was adequate to produce a fall in serum cholesterol.

Numerous workers have attempted to prove that exogenous oestrogen therapy decreases the incidence of coronary heart diseases, but there is no conclusive proof to date.[2,3,43,46] Despite the above lack of definite evidence there is a growing tendency towards the empirical use of long-term exogenous oestrogen therapy in the postmenopausal woman to prevent ischaemic heart disease.[47-50]

GROOTE SCHUUR SERIES

The discussion presented thus far illustrates that there are still many aspects of this complex inter-relationship requiring further elucidation or confirmation. The Groote Schuur study[5] was planned to evaluate just two of these aspects, namely the effect of oophorectomy on plasma cholesterol levels and whether exogenous oestrogen administration to identical and statistically comparable groups of patients could cause a lowering of these values. It is not the purpose of this paper to present the detailed results, which are reported elsewhere,[5] but to summarize the more important and pertinent findings.

Several selected groups of females were investigated through a Menopause Research Clinic established for the purpose, at Groote Schuur Hospital, Cape Town. These groups included normal premenopausal females and patients who had undergone hysterectomy with and without bilateral oophorectomy. A group of 50 oophorectomized female volunteers were further observed for a period of 1 year, during which time control observations preceded single-blind cross-over administration of two forms of oestrogen and a placebo.

In brief, there was considerable overlap in values between the various groups investigated. Oophorectomy was not shown in the short term (less than 2 years) to increase significantly the serum cholesterol value. However, oestradiol valerate (Progynova, Schering) administration to oophorectomized females was of some benefit in reducing the value of serum cholesterol ($p<0{\cdot}05$). In this respect mixed conjugated equine oestrogens (Premarin, Ayerst) were non-effective.

GENERAL DISCUSSION AND CONCLUSIONS

The results of the Groote Schuur Study do not agree with the findings of Oliver and Boyd[43] who reported oophorectomy to produce an increase in the plasma cholesterol concentration of about 15% to 30% of the pre-operative value; nor with Sznajderman and Oliver[39] who showed spontaneous premature menopause to result in elevation of these levels later in life.

Despite the limitations of direct comparison, the summary in Table II is of interest. Thus the oophorectomized

TABLE II. SERUM CHOLESTEROL LEVELS

Author	*Description*	*Age range (years)*	*Mean serum cholesterol (SD in brackets) mg/100 ml*
Oliver & Boyd[13]	Bilateral oophorectomy 15 - 20 years previously	37 - 56	251 (43)
Sznajderman & Oliver[39]	Spontaneous premature menopause 6 - 20 years previously	45 - 49	299
	Healthy women	45 - 49	217
Barr[1]	Normal women	45 - 65	252
Groote Schuur study[5]	Normal premenopausal	45 - 55	268 (43)
	Premenopausal immediately after oophorectomy	45 - 55	250 (54)
	2 years after oophorectomy	45 - 55	265 (41)
	2 years after hysterectomy with conserved ovaries	45 - 55	260 (41)

groups of Oliver and Boyd[13] and the Groote Schuur Study[5] and the normal women of Barr's study[1] and the Groote Schuur group[5] demonstrate remarkably similar results. It is therefore concluded that bilateral oophorectomy in the premenopausal female does not result in an increase in the serum cholesterol for at least 2 years. This lack of early direct response to endogenous oestrogen withdrawal would therefore suggest oestrogens to be of no more than secondary importance in the known relationship of increasing blood cholesterol with age.[7,8] Speculation as to what the primary factor or factors that are responsible for differences in cholesterol with age and between the sexes may be is beyond the scope of the present article.

The potential ability of exogenous oestrogen therapy to reduce serum cholesterol values appears well documented.[43,44,45] In the Groote Schuur study,[5] administration of oestradiol valerate (Progynova) continuously for 6 months to 50 oophorectomized females resulted in a decrease of the total serum cholesterol value of possible significance only ($p<0{\cdot}05$). Moreover, mixed conjugated equine oestrogen (Premarin) administration had little or no effect on the cholesterol values. Robinson *et al.*[44] reported a significant serum cholesterol lowering effect at 1 month, 3 months, 6 months and 12 months when administering conjugated oestrogens to oophorectomized females. There is no obvious explanation for the failure of the Groote Schuur study to confirm these findings. It certainly would appear that different exogenous oestrogens have different effects and the hope for the future is the synthesis of an oestrogen with a more potent effect on serum cholesterol levels.

None the less, the negative findings of the Groote Schuur investigation in relation to the effect of oophorectomy on serum cholesterol and the minimal short-term value of subsequent exogenous oestrogen therapy to oophorectomized females are considered sufficient evidence for questioning the empirical use of such hormones for the prevention of ischaemic heart disease in postmenopausal women.[48,50,51]

The conclusion is that despite the relatively small depressive effect of presently available exogenous oestrogens on blood cholesterol values, the role of such therapy in the prevention of coronary heart disease is no more than a minor one. Finally it is emphasized that the effects of endogenous and exogenous oestrogens are by no means the same. The convincing direct evidence of the protective role of endogenous oestrogens in the development of coronary atheromatosis is a sound argument against the pernicious operation of bilateral oophorectomy in young females. A plea is therefore made for conservatism with ovaries during gynaecological operations on young females.[52] The hope for the future is the isolation and synthesis of all the natural endogenous ovarian oestrogens and their ultimate availability for true oestrogen replacement therapy in the postmenopausal female.

REFERENCES

1. Barr, D. P. (1953): Circulation, **8**, 641.
2. Marmorston, J., Moore, F. J., Hopkins, C. E., Kuzma, O. T. and Weiner, J. (1962): Proc. Soc. Exp. Biol (N.Y.), **110**, 400.
3. Stamler, J., Pick, R., Katz, L. N., Pick, A., Kaplan, D. B., Berkson, D. M. and Century, D. (1963): J. Amer. Med. Assoc., **183**, 632
4. Schlesinger, M. L. and Zoll, P. M. (1941): Arch. Path., **32**, 198.
5. Utian, W. H. (1970): 'Clinical and metabolic effects of the menopause and the role of replacement oestrogen therapy', Ph.D. thesis, University of Cape Town.
6. Boyd, G. S. (1963): Biochemical Society Symposium, **24**, 79.
7. Keys, A. *in* Sandler, M. and Bourne, G. H., eds. (1963): *Atherosclerosis and its Origin*, p. 263. New York: Academic Press.
8. National Centre for Health Statistics (1966): *Serum Cholesterol Level of Adults, United States 1960 - 1962*. Series II, No. 23. Washington, DC: Department of Health, Education and Welfare.
9. Wyndham, C. H. (1969): S. Afr. Med. J., **43**, 720.
10. Gram, M. R. and Leverton, R. M. (1949): Fed. Proc., **8**, 384.
11. Walker, A. R. P. (1968): S. Afr. J. Nutr., **4**, 50.
12. Wessel, J. A., Ufer, A., Van Huss, W. D. and Cederquist, D. (1963): Ann. N.Y. Acad. Sci., **110**, 608.
13. Oliver, M. F. and Boyd, G. S. (1959): Lancet, **2**, 690.
14. Kannel, W. B., Dawber, T. R., Kagan, A., Revotskie, N. and Stokes, J. (1961): Arn. Intern. Med., **55**, 33.
15. Gual, C., Morato, T., Hayano, M., Gut, M. and Dorfman, R. I. (1962): Endocrinology, **71**, 920.
16. Ryan, K. J. and Smith, O. W. (1961): J. Biol. Chem., **236**, 2204.
17. Katz, L. N. and Stamler, J. (1953): *Experimental Atherosclerosis*, p. 291. Springfield, Ill.: Charles C. Thomas.
18. Katz, L. N., Stamler, J. and Pick, R. (1958): *Nutrition and Atherosclerosis*. Philadelphia: Lea & Febiger.
19. Bleyl, U. and Wegener, K. (1969): Triangle (En.) **9**, 9.
20. Chapman, J. M. and Massey, F. J. (1964): J. Chron. Dis., **17**, 933.
21. Drill, V. A. and Riegel, B. (1958): Recent Progr. Hormone Res., **14**, 29.
22. Doyle, J. T., Dawber, T. R., Kannel, W. B., Kinch, S. H. and Kahn, H. A. (1964): J. Amer. Med. Assoc., **190**, 886.
23. Kurland, G. S. and Freedberg, A. S. (1960): Circulation, **22**, 464.
24. McGill, H. C., Geer, J. C. and Strong, J. P. (1963): *Natural History of Human Atherosclerotic Lesions*, p. 39. New York: Academic Press.
25. Epstein, F. H. (1965): J. Chron. Dis., **18**, 735.
26. Kannel, W. B., Dawber, T. R., Friedman, G. D., Glennon, W. E. and McNamara, P. M. (1964): Ann Intern. Med., **61**, suppl., 888.
27. Morris, J. N., Pattison, D. C., Kagan, A. and Gardner, M. J. (1966): Lancet, **2**, 553.
28. Stamler, J. (1964): Conn. Med., **28**, 675.
29. Stamler, J., Berkson, D. M., Lindberg, H. A., Hall, Y., Miller, W., Mojonnier, L., Levinson, M., Cohen, D. B. and Young, Q. D. (1966): Med. Clin. N. Amer., **50**, 229.
30. Thomas, H. E., Kannel, W. B., Dawber, T. R. and McNamara, P. M. (1966): New Engl. J. Med., **274**, 701.
31. Mortality Statistics (1967): Epidem. Vital Statist. Rep., **20**, 401 and 535.
32. Berkson, M. D., Stamler, J. and Cohen, D. B. (1964): Clin. Obstet. Gynec., **7**, 504.
33. Higano, R. W. and Cohen, W. D. (1963): Med. Intell., **268**, 1123.
34. Novak, E. R. and Williams, T. J. (1960): Amer. J. Obstet. Gynec., **80**, 863.
35. Robinson, R. W., Higano, N. and Cohen, W. D. (1959): Arch. Intern. Med., **104**, 908.
36. Wuest, J. H., Dry, T. J. and Edwards, J. E. (1953): Circulation, **7**, 807.
37. Williams, T. J. and Novak, E. R. (1963): Geriatrics, **18**, 852.
38. Parrish, H. M., Carr, C. A., Hall, D. G. and King, T. M. (1967): Amer. J. Obstet. Gynec., **99**, 155.
39. Sznajderman, M. and Oliver, M. F. (1963): Lancet, **1**, 962.
40. Nestel, P. J., Hirsch, E. Z. and Couzens, E. A. (1965): J. Clin. Invest., **44**, 891.
41. Rubin, B. L., Dorfman, A. S., Black, L. and Dorfman, R. K. (1951): Endocrinology, **49**, 429.
42. Pick, R., Stamler, J., Rodbard, S. and Katz, L. M. (1952): Circulation, **6**, 276.
43. Oliver, M. F. and Boyd, G. S. (1961): Lancet, **2**, 499.
44. Robinson, R. W., Higano, N. and Cohen, W. D. (1960): New Engl. J. Med., **263**, 828.
45. Barr, D. P., Russ, E. M. and Edar, H. A. (1952): Trans. Assoc. Amer. Phycns., **65**, 102.
46. Spritz, N. (1968): Mod. Treat., **5**, 581.
47. Davis, M. E. (1964): Clin. Obstet. Gynec., **7**, 558.
48. Davis, M. E., Jones, R. J. and Jarolim, C. (1961): Amer. J. Obstet. Gynec., **82**, 1003.
49. McEwen, D. C. (1965): Canad. Med. Assoc. J., **92**, 962.
50. Wilson, R. A., Brevetti, R. E. and Wilson, T. A. (1963): West. J. Surg., **71**, 110.
51. Wilson, R. A. and Wilson, T. A. (1963): J. Amer. Geriat. Soc., **11**, 347.
52. Van der Wat, J. J. (1970): S. Afr. Med. J., **44**, 687.