WHY WOMEN LIVE LONGER THAN MEN: THE BIOLOGIC MECHANISM OF THE SEX DIFFERENTIAL IN LONGEVITY*

WILLIAM R. HAZZARD and DEBORAH APPLEBAUM-BOWDEN

WINSTON-SALEM**

The "graying of America", has captured the attention of a wide segment of society as the 20th century draws to a close. An important biological phenomenon highly relevant to the aging population as a whole, the greater longevity of women than men, will be the subject of this treatise (1). This phenomenon, which gives rise to a female:male ratio among those over age 65 of 3:2, is a by-product of the increasing survival of the species in general that has accompanied social and economic development in modern society. Thus, whereas Mexico and other developing nations in the present era still have a population distribution that is triangular or pyramidal in distribution by age, with the highest proportion in the youngest cohort and the smallest proportion in the oldest, nations such as those of Northern Europe that are now fully mature have a rectangular distribution by age, with relatively equal proportions in each 5-year segment until advanced old age. The United States is entering the final phase of this demographic shift at the present time. When the United States reaches steady state ca.2030, however, not only will its population have been rectangularized but it will also be progressively skewed toward survival of women in the older cohorts. This demographic shift has very practical and, to physicians and health care planners, alarming characteristics, since those over 65 consume, on average, over four times the health care resources per capita as those under 65. Among women, this is compounded by their greater need for long-term (i.e., nursing home) care. The special vulnerability of women to nursing home institutionalization proceeds not only from their greater longevity than men, but also the greater vulnerability of a surviving spouse to requiring extra help during periods of acute or prolonged disease and disability. Thus, since women far more commonly outlive their spouse than do men, they are in special jeopardy. Whereas fully 80% of men over 65 are married, only 40% of women over 65 are married, and the majority of women over 65 are widows. The widow:widower ratio is 4:1 (2). Therefore, if an elderly man becomes ill and in need of comfort and assistance, he is likely to be

* From The Departments of Internal Medicine and Comparative Medicine, The Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC.

** Address reprint requests to the author at: Department of Medicine, Bowman Gray School of Medicine, 300 South Hawthorne Road, Winston-Salem, NC 27103.

cared for by his wife; this is clearly not true for elderly women, who all too often wind up in long-term care.

What is the origin of this greater longevity of women? Historically, it clearly began in this country shortly after the turn of the century (Figure 1), at which time the mortality sex ratio was only 1:1. After a brief, abrupt decline coinciding with the influenza pandemic of 1918, it has risen progressively to its present level. Interestingly and importantly, however, in the 1980s, this progressive increase in mortality sex ratio appears to have slowed substantially, and, for the past two years for the first time in history, the increase in longevity enjoyed by males has actually exceeded that of females. The reasons for this most recent trend have been widely debated and boil down to a question of whether women are approaching their natural "barrier to immortality" (estimated by some at ca.85 years), whereas men have greater latitude before that barrier is reached (3, 4). Alternatively, adverse lifestyles among women may have begun to abate their progressive increase in average longevity. However, this latter appears clearly to be only conjecture, there being precious little evidence to date that changing lifestyles for women (notably increased participation in the work force) will carry health hazards heretofore not associated with the feminine gender (5).

From a different perspective, evidence from comparative zoology would suggest that greater female longevity is imbedded in the female genome. Thus female houseflies outlive their male counterparts (6), as do females

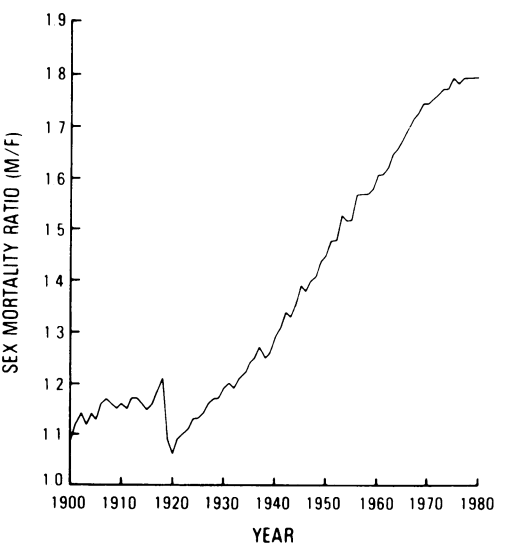

FIG. 1. Sex mortality ratio (M/F), United States 1900-1980 Based on mortality rates age-adjusted to the 1940 total US population. Wingard DL. (8)

of all mammalian species studied to date (with the exception of inbred strains which carry genes predisposing females to auto-immune diseases, such as systemic lupus erythematosus, in which case males lacking such predisposition actually outlive their female counterparts).

The inherent biological basis of the feminine survival advantage is also suggested by a plot of mortality rates from conception throughout the remainder of the human lifespan (Figure 2). This discloses that at all

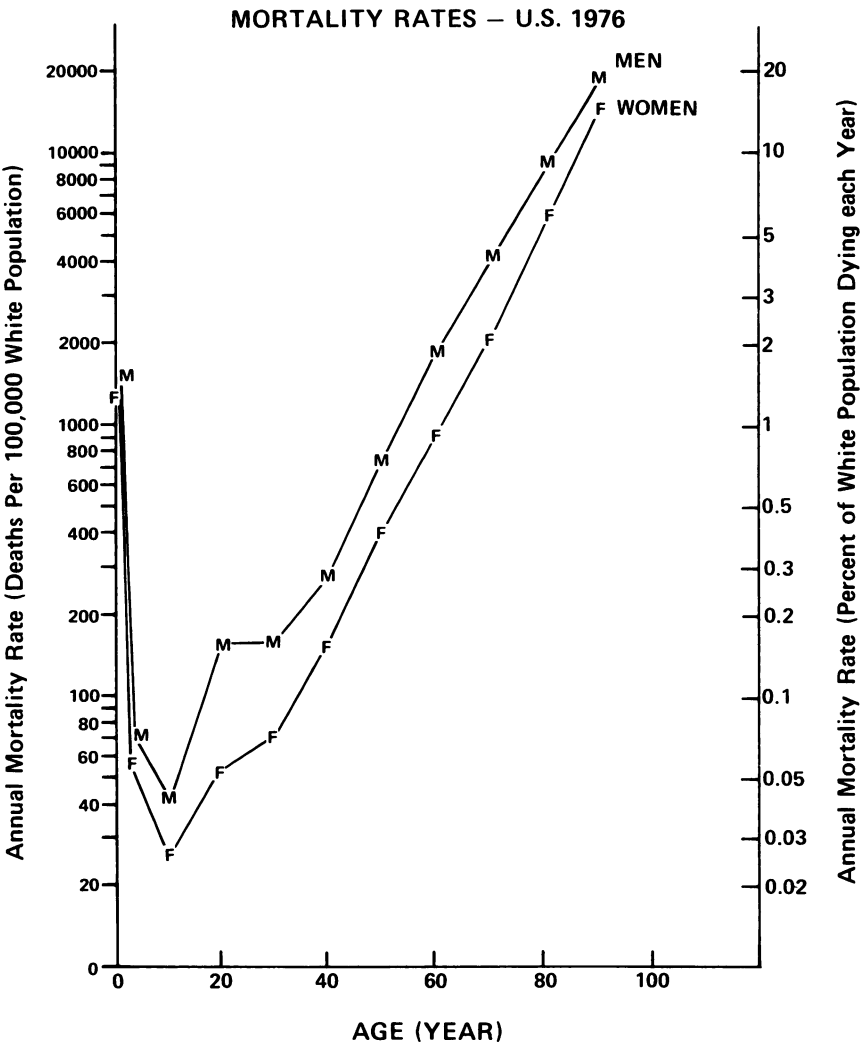

FIG. 2. Mortality rates by sex, US, 1976. Compiled with data presented in Gee EM, Veevers JE: Accelerating sex differentials in mortality: An analysis of contributing factors. *Social Biology* 1984; 30: 75.

points beyond conception the female has a lower mortality rate than the male. It is, indeed, only at the point of conception where males appear to enjoy a clear survival advantage, as many 170 male zygotes being conceived for every 100 females (7). By the time the sex ratio can be clearly determined, however, this ratio (at ca.12–16 weeks of gestation) has already declined to 130:100, and by birth it is down to 106:100. Parity between the sexes is reached during adolescence. At all points beyond childhood, however, females outnumber males. And since the sex ratio at any age reflects the cumulative effect of the sex mortality ratios at all younger ages, the gap in survival between the sexes grows progressively across the human lifespan and is greatest in advanced old age.

Insight into the mechanism of this disparity can be gained by inspecting the sex ratio in mortality rates across the human lifespan (Figure 3). This discloses a "spike and dome" configuration, the spike at age 20 and the dome in late middle age, reaching its maximum between 60 and 70. Of interest, just as this configuration has emerged in the United States

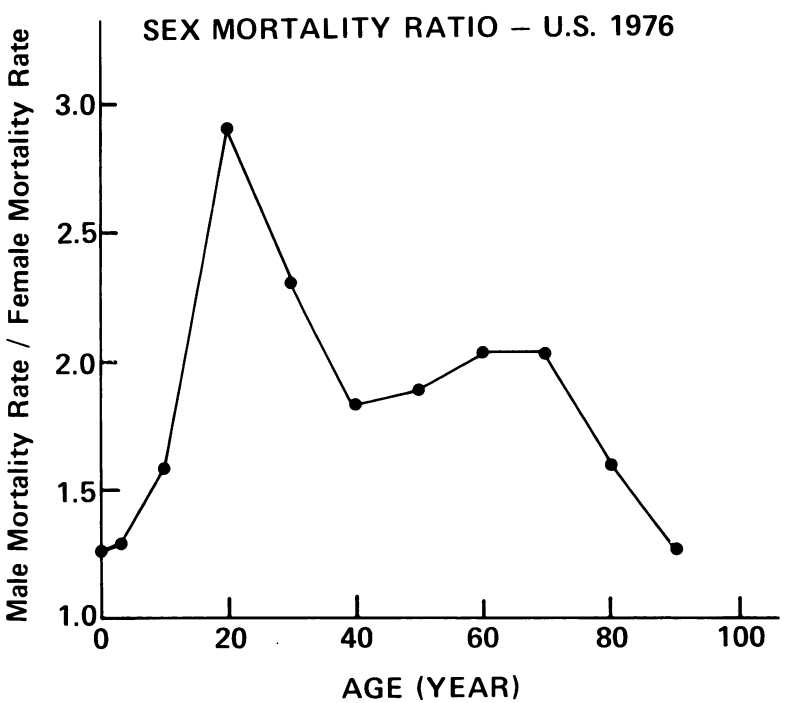

FIG. 3. Sex mortality ratio, US, 1976. Compiled from data presented in Gee EM, Veevers JE: Accelerating sex differentials in mortality: An analysis of contributing factors. *Social Biology* 1984; 30: 75.

during the present century in conjunction with the progressively increased sex ratio in mortality, this pattern is also characteristic of all industrial nations as they have undergone socioeconomic development (8).

Further insight into the genesis of this disparity can be gained by looking at sex mortality ratios for the leading causes of death (Table 1). Ranked in order or cause of death, male:female sex ratios for all leading causes of death save one exceed 100%. The notable exception is diabetes, in which the female death rate is equal to that of males (cancelling out their survival advantage from all non-diabetic causes). Inspection of this list allows the grouping of causes of death into those most likely to contribute to the spike at age 20 (e.g., accidents, homicides, and substance-abuse related deaths) and those clustering under the dome, the latter reflecting the chronic processes of atherogenesis, oncogenesis, and diseases reflecting long-term substance abuse such as chronic obstructive pulmonary disease and alcoholic cirrhosis.

Further examination permits calculation of the contribution of each

TABLE 1
Sex-specific mortality rates and sex differentials for the twelve leading causes of death,[a] United States, 1980[b] From Wingard (8).

Cause	Age-adjusted mortality rate[c]		Sex ratio (M/F)	Sex difference (M–F)
	Males	Females		
Diseases of the heart	280.4	140.3	1.99	140.1
Malignant neoplasms	165.5	109.2	1.51	56.3
Respiratory system	59.7	18.3	3.43	41.4
Cerebrovascular diseases	44.9	37.6	1.19	7.3
Accidents	64.0	21.8	2.93	42.2
Motor vehicle	34.3	11.8	2.90	22.5
Other	29.6	10.0	2.96	19.6
Chronic obstructive pulmonary disease	26.1	8.9	2.93	17.2
Pneumonia and influenza	17.4	9.8	1.77	7.6
Diabetes mellitus	10.2	10.0	1.02	0.2
Cirrhosis of the liver	17.1	7.9	2.16	9.2
Atherosclerosis	6.6	5.0	1.32	1.6
Suicide	18.0	5.4	3.33	12.6
Homicide	17.4	4.5	3.86	12.9
Certain causes in infancy	11.1	8.7	1.27	2.4
All causes	777.2	432.6	1.79	344.6

[a]Rank based on number of deaths.
[b]Calculated from data from the National Center for Health Statistics, 1983
[c]Per 100,000, direct standardization to the 1940 total US population.

major cause to the total sex differential in mortality. This points clearly to heart disease as the major basis (ca.40%) of the sex differential in longevity. However, also to be noted is the contribution of cigarette smoking to this differential via its impact on mortality from several major causes, including coronary heart disease, stroke, malignancies of many organ systems (notably the lung), chronic obstructive pulmonary disease, and lung infections in patients afflicted with this disorder. In fact, it has been estimated that the differential in cigarette smoking may account for up to 4 of the 7 year sex differential in longevity at birth in the United States (9). However, that women are as susceptible to the long-term adverse effects of cigarette smoking as men is clearly suggested by the increase in lung cancer among women that has been so dramatic within the last decade. Lung cancer is now the leading cause of cancer death among women, having outstripped breast cancer within the past several years. Although the incidence and intensity of cigarette smoking in women has declined in the United States in the last 25 years just as it has in men, the decline among men has exceeded that among women, and the historical sex ratio in cigarette smoking behavior has narrowed during this interval. Moreover, because at the peak of coronary disease in this country (in ca.1963–65), the deaths attributed to cigarette smoking were at such a high level among men, the same relative reduction in male cigarette smoking would produce a greater absolute reduction in, e.g., coronary heart disease, in men than in women. This has major implications for strategies to narrow the sex ratio in longevity, since if men can avoid the diseases associated with cigarette smoking until advanced old age, their chances of living at least nearly as long as their spouses are far greater, since the sex ratio in mortality progressively declines after the "dome" at 60–70 as the end of life approaches (Figure 3).

Regarding coronary heart disease, the sex ratio in mortality from this disorder reaches its peak in the fourth and fifth decades and declines thereafter, especially in white males versus females (Figure 4). This, too, underscores the strategy of deferring the onset of such disease until well beyond the female menopause, so that the sex ratio in mortality narrows as heart disease becomes almost as common in women as it is in men. Viewed from another perspective, the incidence of ischemic heart disease increases exponentially in both genders beyond age 30. However, there is an approximate decade lag in equivalent risk between the genders such that women at, e.g., 55 have the same incidence of coronary disease as men of 45, etc. This decade of relative immunity appears clearly related to the antecedent female hormone pattern. Thus post-menopausal women are at substantially greater risk of ischemic heart disease than are pre-menopausal women of comparable age (though they are still at less risk than men at the same age) (Figure 5).

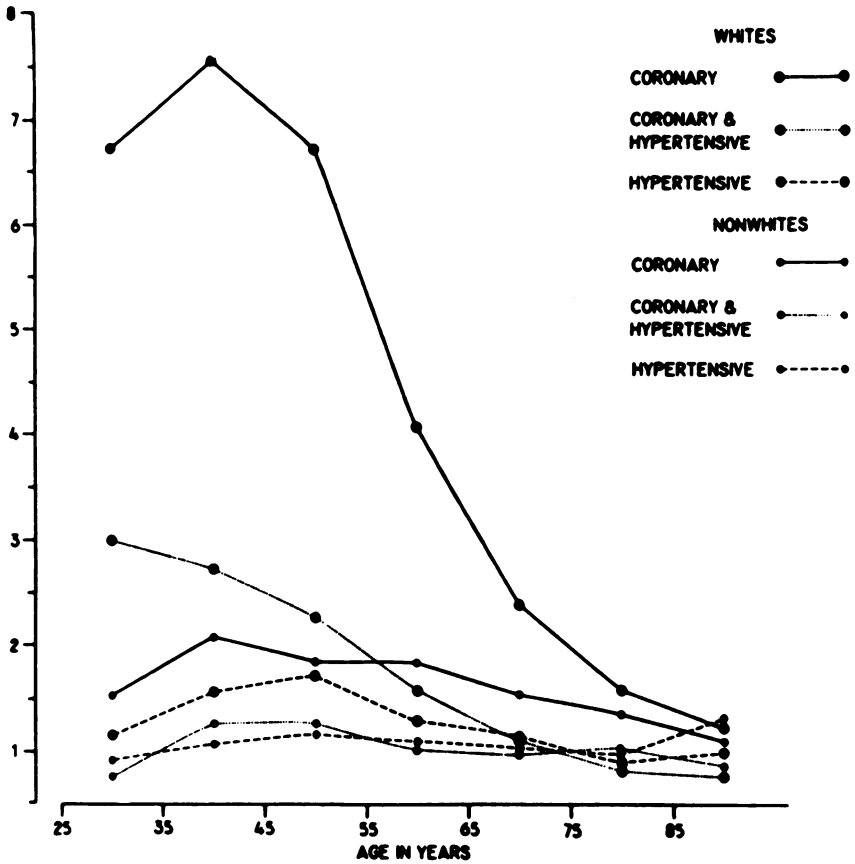

FIG. 4. Linear sex ratio (M:F) in cardiovascular mortality, coronary and hypertensive, US, by age and race, 1955. From Furman RH: Coronary heart disease and the menopause, in Ryan KJ, Gibson DC, eds: *Menopause and Aging.* US Department of HEW, DHEW Publication No. (NIH); 1973: 73.

The next level of inquiry involves analysis of the standard risk factors to coronary heart disease in women versus men (Table 2). This discloses a similar hierarchy of the major risk factors in both genders, and multivariate analysis serves to make these risk factors more clearly equivalent in men and women (note that these are in men and women beyond age 50 in the Framingham study population). This analysis clearly underscores the central roles of high density lipoproteins (HDL), which are inversely related to, and low density lipoproteins (LDL), which are positively correlated with risk of coronary disease in this population. Thus it is conceivable that the entire basis of the sex differential in cardiovascular mortality is related to a sex differential in LDL/HDL

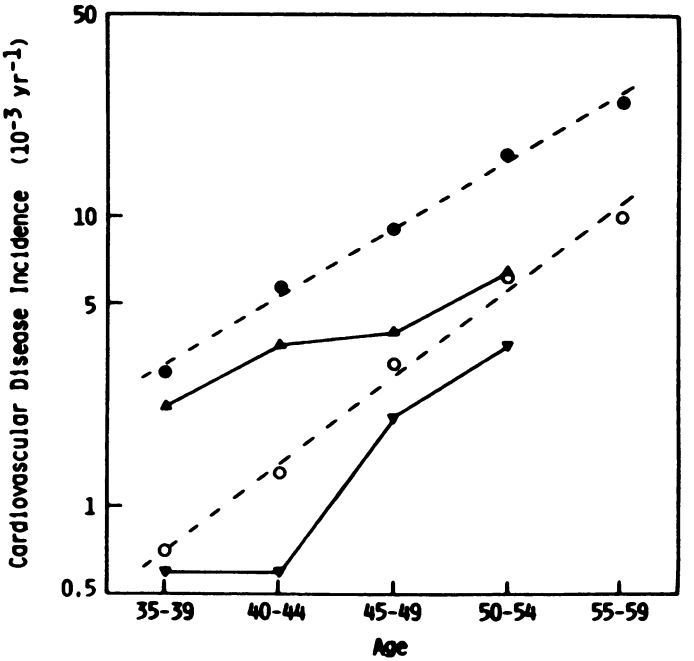

FIG. 5. Incidence of cardiovascular disease by age in years, sex, and menopausal status in the Framingham Study 20-year follow-up. Rates per 1000 per year are displayed for men (closed circles), all women (open circles), premenopausal women (downward arrowhead), and postmenopausal women (upward arrowhead). Rate for pre- and postmenopausal women "less than 40 years" are plotted with the 35 to 39 year group.

TABLE 2
Coefficient for Regression of CHD Incidence of Risk Factors Men and Women 50–82 Years Framingham Study

	Standardized logistic regression coefficients			
	Univariate		Multivariate	
Risk attributes	**Men**	**Women**	**Men**	**Women**
HDL cholesterol	−.488*	−.741	−.610*	−.650
LDL cholesterol	.288†	.303†	.332‡	.260†
Triglyceride	.048	.276‡	−.092	−.106
Systolic pressure	.323‡	.400‡	.327‡	.216
ECG-LVH	.279*	.207‡	.245‡	.159†
Relative weight	.029	.283†	−.016	.031
Diabetes	−.024	.474*	−.114	.390*

†$p = < .05$
‡$p = < .01$
*$p = < .001$

ratio as a single lipid index of atherogenic risk. This appears to be only partially true, however (Figure 6), since in the lower three quintiles of this ratio men are still at approximately twice the risk of women, though in the top two quintiles (in which the majority of events are clustered) men and women with comparable ratios are at comparable risk. Thus this single risk index appears to explain the majority but not the entirety of the sex differential in cardiovascular disease in middle and old age in this country.

How do these lipoprotein lipid levels vary by age across the human life span in North America? Analysis of the Lipid Research Clinics collaborative hyperlipidemia prevalence study data of the 1970s is useful in this regard (Figure 7). This discloses progressive increases in average cholesterol concentration in both genders beyond puberty. However, the

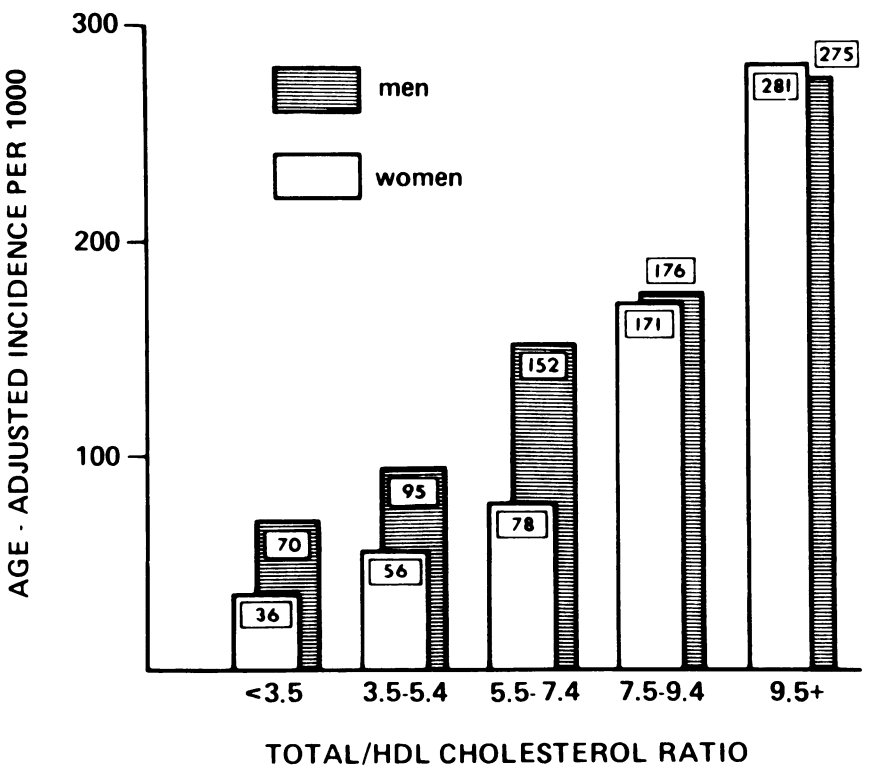

FIG. 6. Risk of coronary heart disease by total/HDL cholesterol. Framingham study: 26-year follow-up; subjects 50 to 90 years of age. Reprinted with permission from Kannel WB, Brand FN: Cardiovascular risk factors in the elderly, In: Andres R, Bierman E, Hazzard W. eds. *Principles of Geriatric Medicine.* New York, McGraw-Hill, 1984.

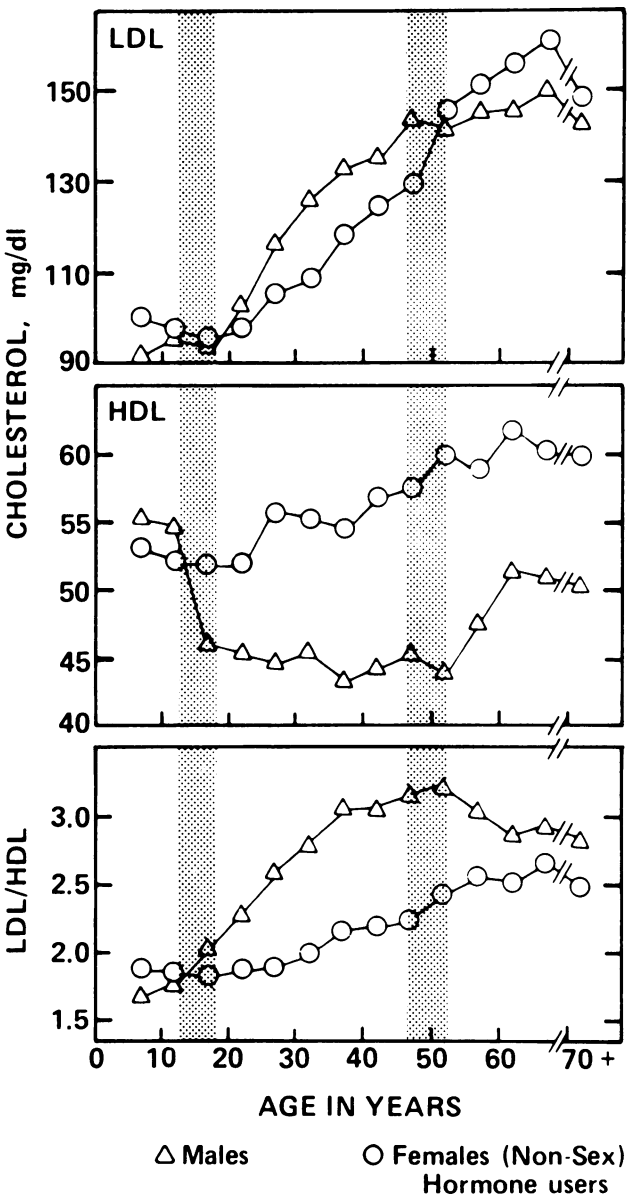

FIG. 7. Median North American population high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and the ratio between the two versus age in white subjects. Data from Lipid Research Clinics Prevalence Survey. The Lipid Research Clinics: Population Studies Data Book. Volume I. The Prevalence Study. *NIH Pub* No 80: 1527, 1980. US Dept Health and Human Services, 1980.

rise in males exceeds that in females from puberty to menopause. Beyond the menopause a reversal occurs, and the average level in women comes to exceed that of men. A different pattern is seen for HDL. Here from puberty onward the average HDL concentration in males is lower than that in females and, notably, this differential is maintained beyond the menopause. Furthermore, given that this differential exceeds that of the differential in LDL concentrations at all ages, the LDL/HDL ratio remains higher in men than women in the post-menopausal era, though the differential narrows.

Thus, to summarize to this point:

1. The male:female coronary risk ratio is greater than 1:0 at all ages (but it narrows progressively with age)
2. The male:female LDL/HDL cholesterol ratio also exceeds 1.0 at all ages (and likewise narrows progressively with age)

Therefore, given that men and women share a relatively common lifestyle, a central hypothesis emerges: The sex differential in sex hormones produces the sex differential in lipoprotein metabolism which, given the Occidental lifestyle, produces the sex differential in atherosclerosis and this in turn the sex differential in longevity.

What is the evidence for this hypothesis? This has grown progressively in recent decades. For instance, data from the same Lipid Research Clinics hyperlipidemia prevalence studies in the 1970s (10) disclose different patterns of LDL and HDL cholesterol levels in females taking versus those not taking supplemental sex steroid hormones (Figure 8). The average concentration of LDL cholesterol in the women taking post-menopausal estrogens was substantially lower than in those not taking those hormones (note that oral contraceptives, containing androgenic progestins, appear to have had the opposite effect). As to HDL, post-menopausal women taking estrogens had substantially higher levels than those not taking these hormones (once again, oral contraceptives appear to have had a different, null effect, though more detailed analysis disclosed that those preparations containing the more androgenic progestins were associated with lower average HDL and those with weaker progestins/stronger estrogens had average HDL concentrations exceeding those in the group as a whole [11]). These representative data have been widely reproduced elsewhere in both controlled and non-controlled investigations (12–17).

Lacking until recently, however, were metabolically controlled studies of the impact of supplemental estrogen upon lipoprotein lipid levels in humans. To rectify this deficiency we conducted a Clinical Research Center study to test the explicit hypothesis that estrogen replacement in post-menopausal women would reverse the hypercholesterolemia (specif-

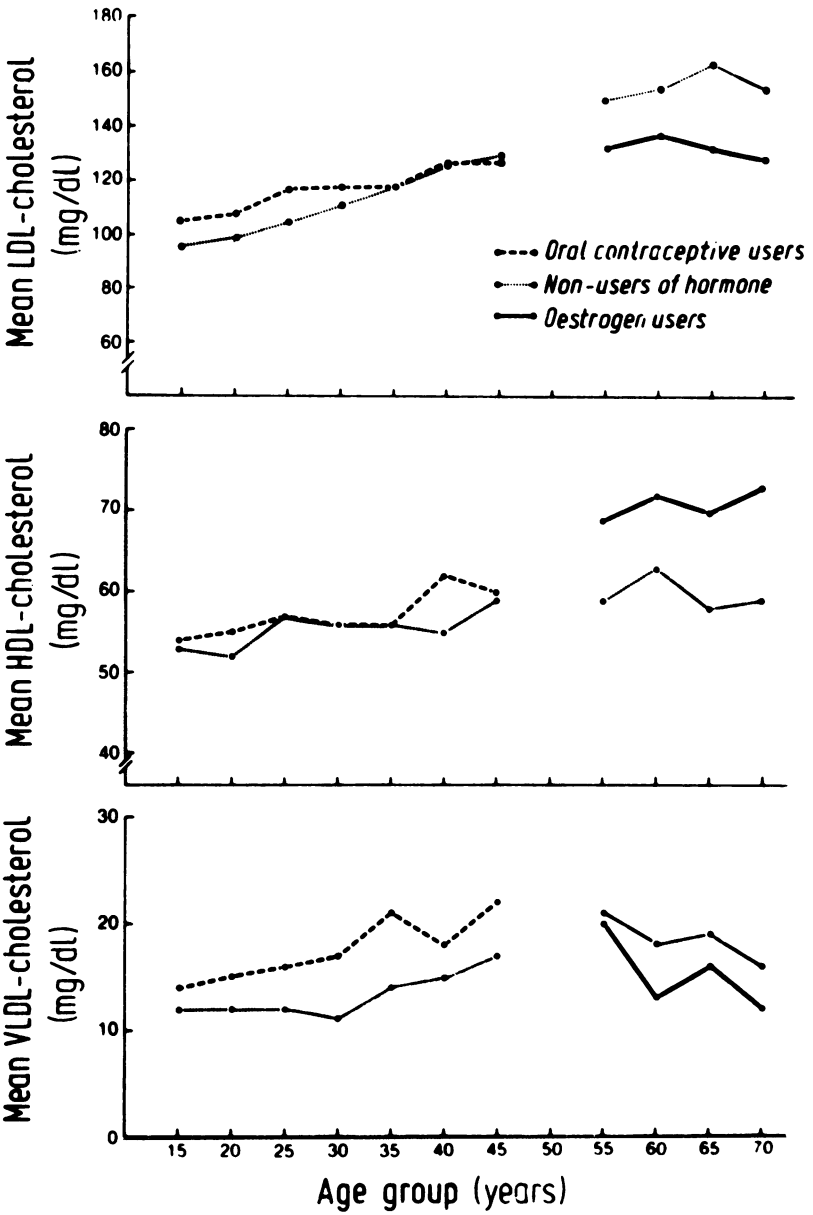

FIG. 8. Plasma lipoprotein cholesterol levels in users and nonusers of oral contraceptives and estrogens. Reprinted with permission from Wallace RB, et al. Altered plasma lipid and lipoprotein levels associated with oral contraceptive and oestrogen use. *Lancet* 1979; 2: 111.

ically, the increased LDL cholesterol levels) characteristic of the post-menopausal state (18). Moreover, given the lower LDL cholesterol levels in pre-menopausal women on the typical cholesterol-rich, saturated fat-rich Western diet, we tested the secondary hypothesis that women are able to resist the hypercholesterolemic effects of such a diet better than men because of specific cholesterol-lowering effects of estrogens. This we did by maintaining the subjects on a high cholesterol diet throughout the period of the experiment. Specifically, we recruited six menopausal women (average age 57 ± 6 years) for an 84-day study, during which they were maintained strictly on an isocaloric diet containing 1000 mg cholesterol daily (in the form of egg yolk supplements) but with an unchanging distribution of calories (protein 15%, fat 40% [polyunsaturated/saturated = 0.85], and 45% carbohydrate). They received all their meals on the Cinical Research Center and ate no other foods throughout the entire experiment. During the middle 28 days of the 84-day period, they received supplemental ethinyl estradiol ca.1mcg/kg/day (a somewhat higher than usual therapeutic estrogen replacement dose). Lipids, key apolipoproteins, and activities of post-heparin lipolytic enzymes were measured at weekly intervals during the first 28 day "run in", at daily intervals early during estrogen therapy and early after its discontinuation, and at increasing intervals for 28 days after estrogen was discontinued.

To our surprise, maintenance of the subjects on the high cholesterol diet resulted in no changes in plasma lipid levels during the first 28 days of the study (probably attributable to their relatively cholesterol- and saturated fat-rich pre-study diet) (Figure 9). With the addition of estrogen, however, certain changes, some predicted, some unpredicted, occurred. First, as anticipated, mean triglyceride levels rose abruptly and were maintained approximately 40% above baseline throughout the period of estrogen therapy, declining rapidly after its discontinuation. Second, mean total, and, specifically, LDL cholesterol levels dropped abruptly with the institution of estrogen therapy, far more rapidly and, at the time, to a greater degree than anticipated. These levels remained depressed, total cholesterol by 12%, LDL cholesterol by 25%, throughout the duration of estrogen therapy, rebounding abruptly upon its discontinuation. Third, HDL levels rose progressively (but more slowly than anticipated), reaching a plateau approximately 20% above baseline during the third week of therapy, similarly declining gradually but progressively after estrogen was discontinued. Fourth (Figure 10), apolipoprotein B (the major structural apoprotein within very low density lipoproteins [VLDL] and LDL) declined only 11% during estrogen, while apo E, an even more powerful signal for the VLDL and intermediate density lipoprotein [IDL] hepatic uptake than apo B, declined by 33%. Levels of

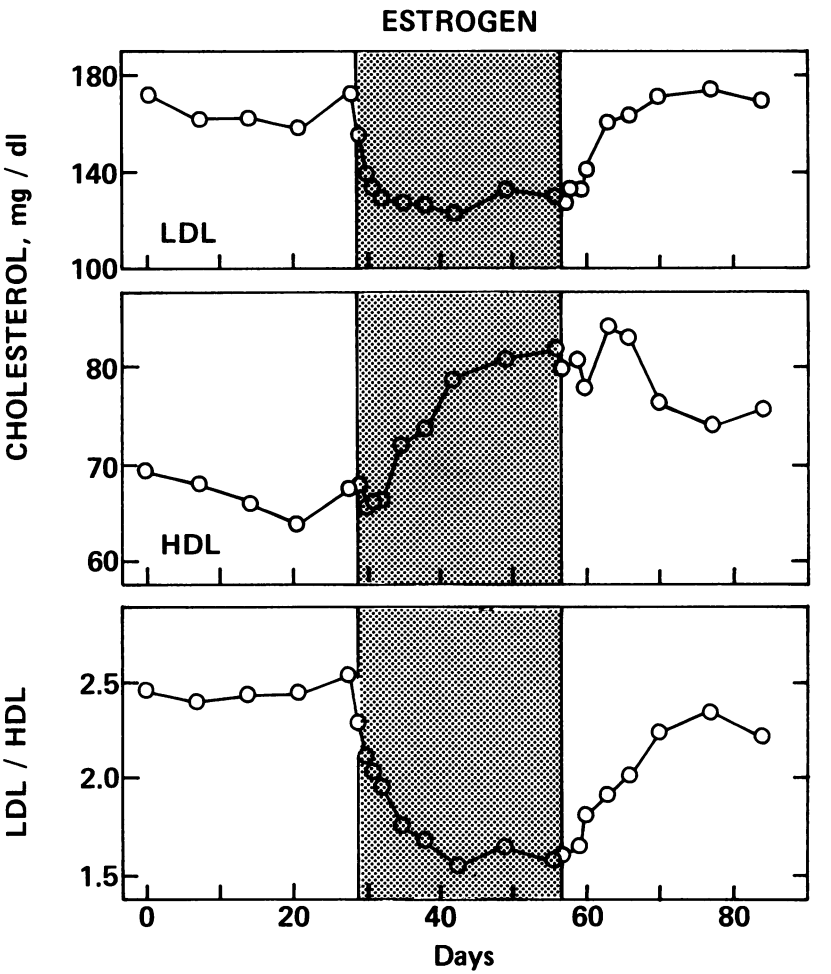

FIG. 9. Mean changes in LDL (top panel), HDL (middle panel), and LDL/HDL (lower panel) in the six postmenopausal women. The period of ethinyl estradiol administration (1 mcg/kg/d) is indicated by the shaded area (day 28–day 56). (From reference 18).

Apo A-I (the principal apolipoprotein within HDL) increased by 37%, while Apo A-II levels rose only 9%.

Several features of this modest study deserve comment. First, the average total cholesterol levels in these healthy post-menopausal women were distinctly elevated (at 256 mg/100 ml) in this small sample of healthy post-menopausal women, elevated to a level suggesting hypolipidemic intervention by current Cholesterol Education Program standards. However, it should also be noted that the average HDL cholesterol

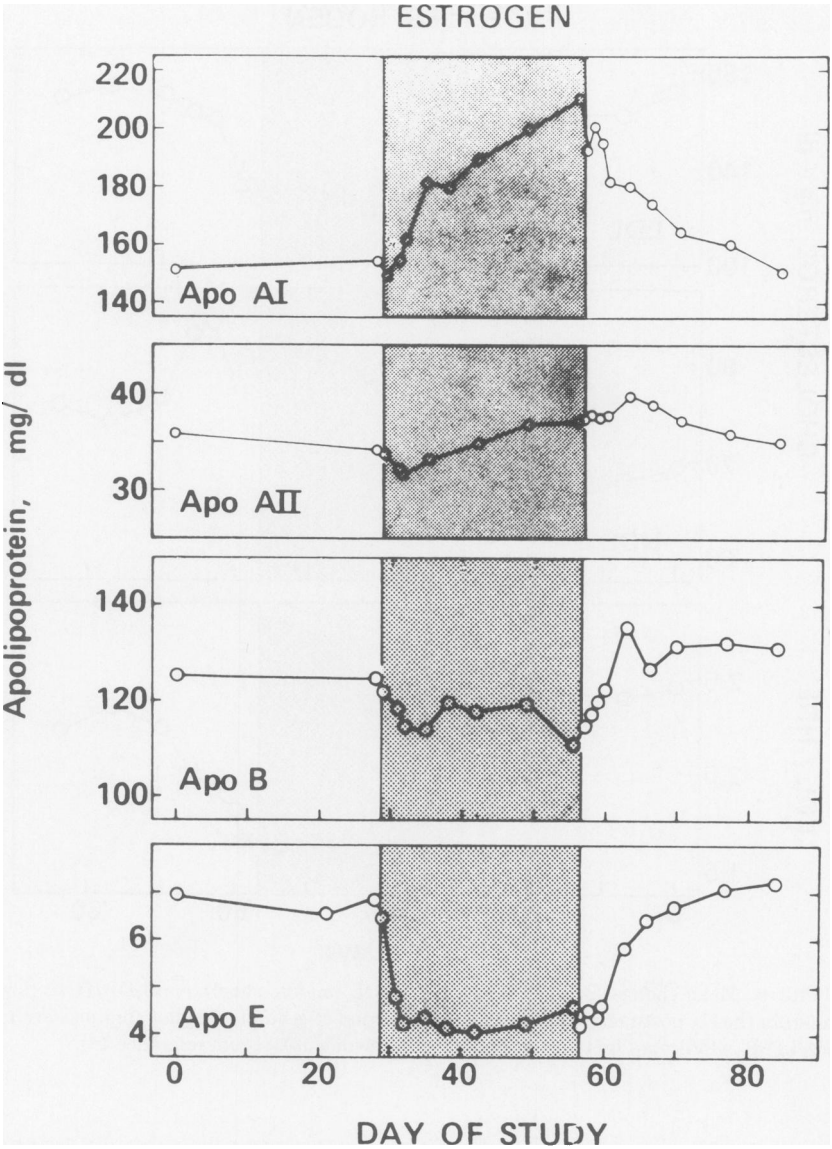

FIG. 10. Mean changes in total plasma apolipoprotein AI, AII, B and E levels in the six postmenopausal women. The ethinyl estradiol administration (1 μg/kg/d) is indicated by the shaded area from day 28 to day 56.

level was significantly elevated at 70 mg/100 ml (interestingly, HDL levels do not consistently decline during the post-menopausal era, as one might predict by the hyper HDL-emic effect of exogenous estrogen in such women, though a recent prospective study did document a statisti-

cally significant, modest fall in HDL cholesterol across the menopause [19]). Thus the average LDL/HDL ratio in these women was well within the acceptable range (at 2.5) despite their total plasma hypercholesterolemia. Second, the combined reduction in LDL and increase in HDL, affecting both the numerator and denominator of the LDL/HDL ratio, resulted in a reduction in this single most powerful index of atherogenecity of nearly 40% (to ca.1.6), a decrease equal to that of most of the newer hypocholesterolemic agents on the market (such as HMG CoA reductase inhibitors). Thus post-menopausal estrogen replacement (especially that given via the oral route) can be expected to substantially ameliorate adverse LDL/HDL ratios in post-menopausal women. This would predict that such replacement would reduce coronary heart disease in post-menopausal women, a prediction consistent with the reported reduction in cardiovascular mortality in post-menopausal women taking estrogen supplements (20–22). The population studies upon which this latter, most important conclusion were based attributed the majority of the heart disease-reducing effect of post-menopausal estrogen replacement to the dual effects on HDL and total cholesterol concentrations (20). However, though reductions in coronary disease with post-menopausal estrogen replacement have appeared to be the rule, the Framingham study represents a notable exception (23). Finally (Figure 11), the HDL_2 subfraction increased by estrogen is specifically that most associated with reduced atherogenic risk (24). Of note, there was a concomitant, uniform, abrupt, major decrease in the activity of post-heparin hepatic triglyceride lipase (HTGL). The biological function of this enigmatic enzyme remains the subject of intense speculation; however, its inverse relationship with HDL_2 levels at day 28 of estrogen therapy in this study is consistent with its purported mediation of HDL catabolism; i.e., via its phospholipase activity, it has been hypothesized to hydrolyze the surface of HDL, rendering these anti-atherogenic particles susceptible to irreversible catabolism by the liver. Thus reduction in HTGL is consistent with prolonged circulation and higher levels of HDL during estrogen, as suggested in preliminary HDL turnover studies (25–27).

What of the androgenic side of the equation? Here data are less readily available and more confusing, since testosterone levels per se do not correlate well with LDL or HDL in men of any age. However, experiments with oral androgens, specifically the widely illicitly employed anabolic steroids, suggest that androgens may exert a powerful *hyper*cholesterolemic effect, additionally adversely affecting theoretical atherogenic risk via a profound HDL-lowering effect. Relevant studies of post-menopausal osteoporotic women from this laboratory were among the first to make this dramatic point (28–30). Ten post-menopausal osteoporotic women were studied during oral stanozolol therapy (previously reported to in-

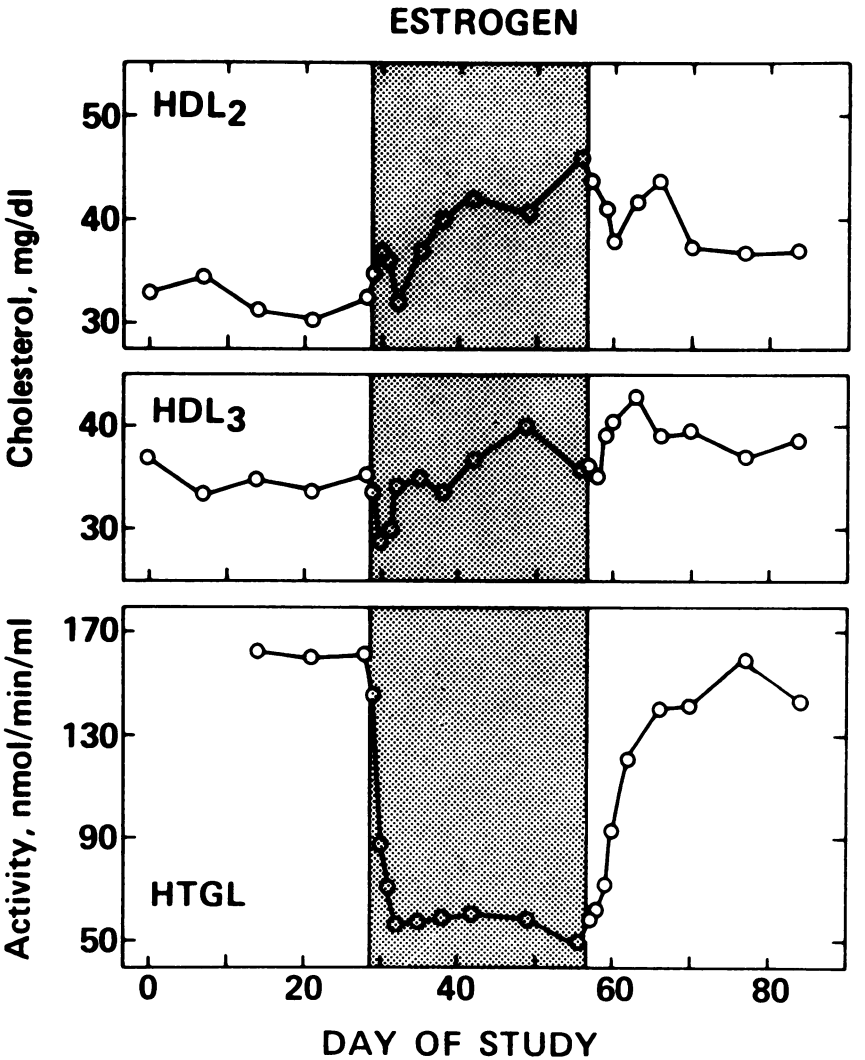

FIG. 11. Mean changes in HDL_2 and HLD_3 cholesterol levels and post-heparin plasma HTGL activity in the six postmenopausal women. The ethinyl estradiol administration (1 μg/kg/d) is indicated by the shaded area from day 28 to day 56.

crease bone mineral content in these subjects [31]). At a dosage of 6 mg of stanozolol per day for a 6-week period, these studies disclosed equal and opposite effects upon mean LDL and HDL cholesterol levels: LDL levels rose 20% while HDL levels declined 50%, raising the LDL/HDL ratio from the range of low risk (2.5) to one of high risk (6.8). Within HDL, the most dramatic effect was on HDL_2, which declined by 85%.

Finally, reciprocal effects upon post-heparin HTGL were observed: While HDL declined, HTGL increased, by an average of 300% (post-heparin lipoprotein lipase levels did not change). Consistent with these changes in post-heparin HTGL mediating the changes in HDL levels, subsequent studies disclosed that the increase in post-heparin HTGL occurred within the first day of stanozolol therapy, while levels of HDL_2 did not clearly decline until day 4 (32). Additional studies disclosed that stanozolol was associated with accelerated HDL catabolism (30).

Finally, a 15-month study in a single volunteer subject revealed that these changes in LDL and HDL concentration induced by ethinyl estradiol and stanozolol could be readily reproduced (Figure 12) (33). This

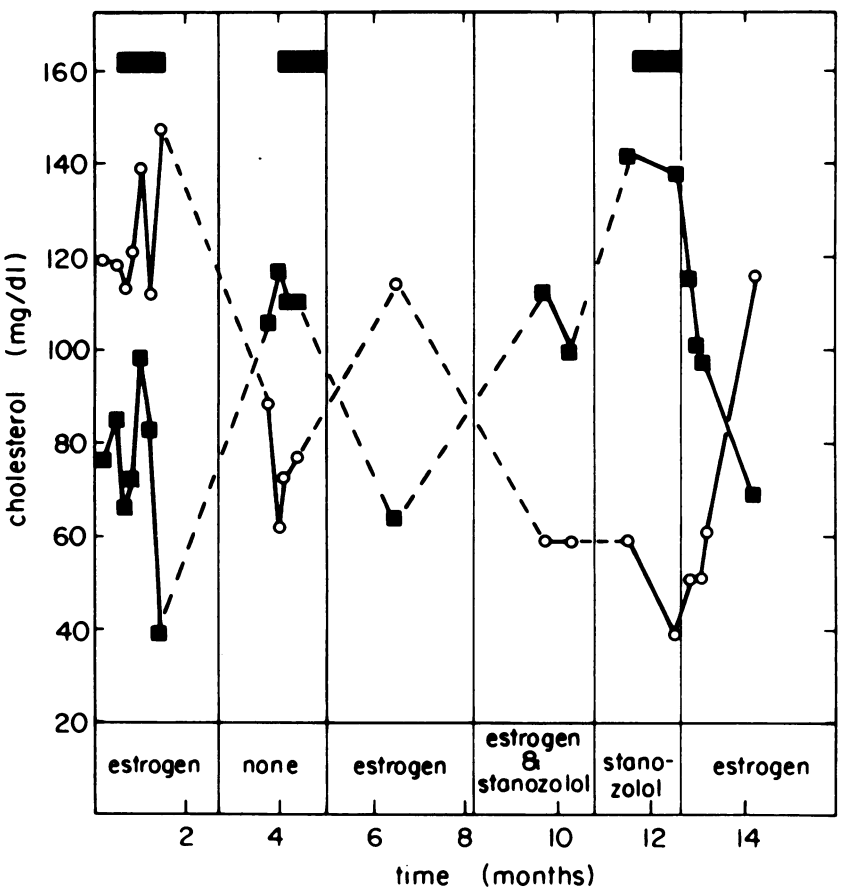

FIG. 12. High-density lipoprotein cholesterol (HDL-C, circles) and low-density lipoprotein cholesterol (LDL-C, squares) levels during treatment with estrogen (ethinyl estradiol, 0.06 mg/per day), stanozolol (6 mg/per day), both, or neither. Solid bars indicate timing of HDL turnover studies. The subject had been on cyclic estrogen therapy for several years when these studies were initiated. Reprinted with permission from Hazzard WR, et al. (33).

subject had hypercholesterolemia when referred, that due, however to elevated HDL levels (LDL levels were actually low). When her estrogen was withdrawn, LDL increased and HDL decreased; when it was restored, LDL decreased and HDL increased; when stanozolol was added, levels on both hormones were equal to where they had been off both hormones; and when stanozolol was given alone, she developed elevated levels of LDL and depressed levels of HDL, both returning to the levels existing at referral upon restoration of estrogen alone.

SUMMARY

1. Exogenous sex steroids appear to influence lipoproteins in a manner that is a *caricature* of the effects of endogenous sex steroids:
   - Estrogens raise HDL (selectively HDL_2) and lower LDL;
   - Androgens lower HDL (selectively HDL_2), while raising LDL.
2. Exogenous sex steroids are likely to affect LDL metabolism via effects on the LDL receptor
   - Estrogens increase LDL receptor activity (in non-human species at both the hepatic cellular [34] and mRNA [35] levels, though this is yet to be confirmed in humans)
   - ??Androgens decrease LDL receptor activity (yet to be tested in either human or non-human species)
3. Exogenous sex steroids appear to alter HDL levels predominantly via modulation of HDL catabolism
   - Estrogens retard HDL catabolism (33) (and may also increase apo A-I synthesis and HDL production [34])
   - Androgens accelerate HDL catabolism (30)
4. Modulation of HDL (and possibly LDL) metabolism by sex steroids may be mediated by alterations in hepatic triglyceride lipase (HTGL) activity

CONCLUSION

Sex steroids may importantly mediate the sex differential in atherogenesis (and longevity) via effects on lipoprotein metabolism.

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DISCUSSION

Schrier (Denver): I think you focused on an enormously important problem. I understand that about 37% of women over age 65 are below 150% of the poverty level, so there is not only emotional, but also financial deprivation because of this marked difference between male and female longevity. What I'd like to propose as a counterpart to your biological argument and that is a behavioral argument. First of all the data which I've heard is that in 1900 there were 102 males for every 100 females over 65. By 1980 that number had decreased to about 61 males for every 100 females over 65. This is close to the figure you quoted. The flattening of this ratio in 1980 might be due to the fact the women are smoking much more. The government's report that two-thirds of deaths below age 65 are preventable, the causes are primarily in four categories: trauma, alcohol, smoking and hypertension. Smoking causes 40% of cancers and 40% of atherosclerotic disease and the interaction between lipids and smoking is well-known. Moreover, the interaction between smoking and hypertension in causing cardiovascular disease is certainly known. Lung cancer now has passed breast cancer as the number one cause of cancer death in women. Overall, we are losing about 390,000 Americans every year from smoking related diseases. Men not only smoke more than women but also have a higher incidence of alcoholism and deaths due to trauma. All of these problems are behavioral in nature and are preventable. I would like to hear your comment about the proposal that behavioral, not biological, aspects account for the differences in male and female longevity in this century. These behavioral differences between male and females might also interact with sex hormone differences.

Hazzard: I think you have stated my position very accurately, Bob. I'd certainly agree that it is an interaction between biological and behavioral determinants and perhaps it is easier to do something about the behavioral than the biological, particularly since estrogens

don't seem to be well-tolerated by men. My own particular advice to individuals and families is that males and females need to adopt a differential strategy primarily focusing on preventing early death in men and this is in boys' driving behavior, alcohol behavior, across the entire adult life span. One of the differences that really does distinguish males and females is their attitude toward health and toward prevention and if there is one thing that we could do, it would be to inculcate in young men a preventive strategy that begins in young adulthood and doesn't wait until it's too late in their forties, fifties and beyond.

Rogers (Princeton): Bill, I much enjoyed that. This will date me, but I had thought in the 40's and 50's, that Dr. David Barr, Professor of Medicine at Cornell, had done precisely what you had suggested. He showed that estrogens did exactly what you've shown. They had to give up treating men because they were so feminized by their estrogens. I thought I heard you say that this had never been studied before. I thought it had been studied forty years ago.

Hazzard: That is, in part, true. It had never been studied in a controlled clinical research center environment, but the effects are so powerful that they can be seen even on an *ad libitum* diet, particularly in larger groups and you are absolutely right that Russ, Eder and Barr in the 1950's had demonstrated not only the powerful effects of sex steroids on lipoproteins, but also the very important role of HDL in being an anti-atherogenic mediator. What happened in the 60's is those important observations were overshadowed by perhaps an enchantment with a lipoprotein-phenotyping system and the effects of LDL, but fortunately we've come back to those pioneering studies and recognized their importance.

Gotto (Houston): Bill, how many milligrams of cholesterol a day were the subjects consuming when you added the 900 mg to their daily diet?

Hazzard: That's an important implied point. They were consuming about 250 mg in their *ad libitum* diet, so they had 750 mg added. When we've done further studies looking at a threshold for the impact of cholesterol upon lipoprotein lipid levels, essentially you are almost up at maximum by 250, and we have reduced it to 150 or less, we can start seeing an effect of added dietary cholesterol.

Gotto (Houston): One other point I wanted to mention is the ratio between male and female deaths in diabetics. It is often stated, as shown in one of your slides, that the relative female protection over the male in cardiovascular risk is abolished by diabetes. In the latest data that Jerry Stemler has presented from the Multi-Risk Factor intervention study, this does not seem to be the case. At a given age, the female diabetic is at higher risk for cardiovascular disease than is the non-diabetic female, but at a given age the male diabetic at that age is at a higher risk than the female diabetic.

Hazzard: That is very interesting. I'm not aware of those data.