Seasonal Variation of Cholesterol in Serum of Men and Women

ROBERTA E. BLEILER, PH.D.,* ELISABETH S. YEARICK, PH.D.,† SANDRA S. SCHNUR, M.S.,‡ IMELDA L. SINGSON, M.S.§ AND MARGARET A. OHLSON, PH.D.¶

IT HAS been suggested that in estimating the chances for coronary heart disease developing in a person, the variability of his serum cholesterol concentration may be more important than its mean value.[1-6] Few data on variability are available, particularly for healthy persons, and these data do not include healthy women.

METHODS

White men and women, twenty to sixty-nine years of age, participated in this study. Two studies were made as outlined in Table I. In study 1 samples of venous blood were obtained from each subject in the postabsorptive state on four different days, approximately one week apart, and three, five and seven hours after the ingestion of one of four test meals. (These subjects were participating concurrently in a lipid clearance study; they did not receive other food until after blood was drawn at the seventh hour.)

In study 2 all subjects participated in period A; whereas only the older persons completed periods B and C. One period consisted of two test days approximately one week apart. Blood was drawn four times each day from each subject in the postabsorptive state and at irregular intervals from 10 A.M. to 9 P.M. The subjects followed their ordinary daily routines and meal schedules. One young woman, three young men and four older women from study 1 also participated in study 2, which was conducted one to two years later.

In both studies, serum concentrations of total and free cholesterol were measured by a modification of the Sperry-Webb revision[7] of the Schoenheimer-Sperry method.[8] All sample measurements were replicated, and standards, treated in the same manner as samples, were determined simultaneously.

RESULTS AND COMMENTS

In Table I is a summary of determinations of total and free cholesterol concentrations in 1,336 blood samples. The fasting cholesterol concentration, which is generally indistinguishable from the mean of all tests, has been included, since many reports in literature specifically designate their values as fasting. Free cholesterol is the mean of all tests and is reported in the table only. In the discussion, the cholesterol concentration referred to is total.

The fasting mean values for serum cholesterol in our young men and women in studies 1 and 2 are within the range reported in the literature for subjects of the same sex and similar age.[3,9-13] Even though all subjects were apparently healthy and were taken at random, the mean concentration for young men in study 2 was significantly higher than that for young men in study 1 ($P \leq 0.01$); the means for young women also differed. Changes in serum cholesterol concentrations of the one young woman and three young men who participated in study 1 and then study 2 accounted for increases in the respective means of only 3.5 and 2.3 mg. per cent. All young men were tested in winter months; for young women, study 1 was completed in the spring and study 2 in the summer.

From the Department of Internal Medicine, Nutrition Section, State University of Iowa, College of Medicine, Iowa City, Iowa.

* Assistant Professor, Nutrition Section, Present address: Animal Nutrition, University of Illinois, Urbana, Illinois; † Public Health Research Fellow of the National Heart Institute, Present address: University of West Virginia, Morgantown, West Virginia; ‡ Present address: Iowa City, Iowa. § Present address: St. Scholastica's College, Manila, The Philippines; ¶ Professor, Nutrition, State University of Iowa, Iowa City, Iowa.

This work was supported by a grant from the Life Insurance Medical Research Fund.

TABLE I
Serum Cholesterol Concentrations and Standard Deviations for All Subjects

Subjects	No.	Age (yr.)	Total Cholesterol (mg. %)		Free Cholesterol
			Fasting Mean	Over-all Mean	
Study 1					
Young men	10	20–24	185 ± 19.8	183 ± 26.2	54 ± 6.1
Young women	10	21–23	193 ± 39.5	193 ± 40.0	53 ± 13.6
Pregnant women*	10	22–27	315 ± 97.0	319 ± 88.4	85 ± 26.1
Older women	10	49–69	315 ± 57.3	316 ± 56.6	81 ± 14.5
Study 2					
Period A (March 3 to May 24)					
Young men	10	20–24	214 ± 22.9	221 ± 23.8	59 ± 8.5
Young women	11	20–26	212 ± 36.1	218 ± 34.7	60 ± 9.7
Older women	11	40–59	284 ± 49.8	283 ± 38.8	71 ± 11.8
Older men	11	39–59	279 ± 31.5	284 ± 38.2	76 ± 12.9
Period B (June 20 to August 25)					
Older women	11	40–59	314 ± 36.8	314 ± 44.4	85 ± 13.9
Older men	11	39–59	269 ± 37.8	266 ± 38.5	74 ± 12.8
Period C (October 20 to December 10)					
Older women	11	40–59	272 ± 39.7	267 ± 31.5	79 ± 13.0
Older men	11	39–59	266 ± 24.4	266 ± 27.1	77 ± 10.2

* Twenty-eighth to thirty-second weeks.

The fasting mean for nonpregnant women was significantly lower than that measured for the pregnant group which for one subject included the average of 540 mg. per cent. Exclusion of this individual average would cause the group mean to decrease to 294 mg. per cent, which approaches the mean value of 282 mg. per cent reported by Russ et al.[14] for twenty-seven women at term. However, there was no valid clinical reason for excluding her from the group.

The group of older men averaged fifty years in age, and the fasting mean cholesterol concentrations were 284 mg. per cent in period A and 266 mg. per cent in periods B and C. Fasting means for this series of older women, who averaged fifty-eight years of age in study 1 and fifty-four years in study 2, ranged from 272 to 315 mg. per cent, depending upon the period of the study. In these older subjects the serum cholesterol concentrations are comparable to those reported by other investigators for subjects of the same sex and similar age ranges.[3,10–12,15,16]

Neither the problems of sampling nor of local environment have been studied extensively for their effect on serum cholesterol. The problem of sampling is well illustrated by the results for the older women. The mean value of 315 mg. per cent for study 1 was significantly higher than the 272 mg. per cent for study 2 in period C ($P \leq 0.01$), even though both groups were studied during the same season of the year. Furthermore, the serum concentrations for the four older women who participated in both studies only increased an average of 2.5 mg. per cent per person from study 1 to study 2. However, the mean age for those in study 1 was fifty-eight years, compared with fifty-three years for those in study 2. Several investigators have indicated that the serum cholesterol concentration of older women in the age group of fifty to sixty years is, on the average, definitely higher than for those in the forty to fifty year age group.[10–12]

In study 2, the same subjects participated for three periods. During period B, seasonal differences in cholesterol concentrations were

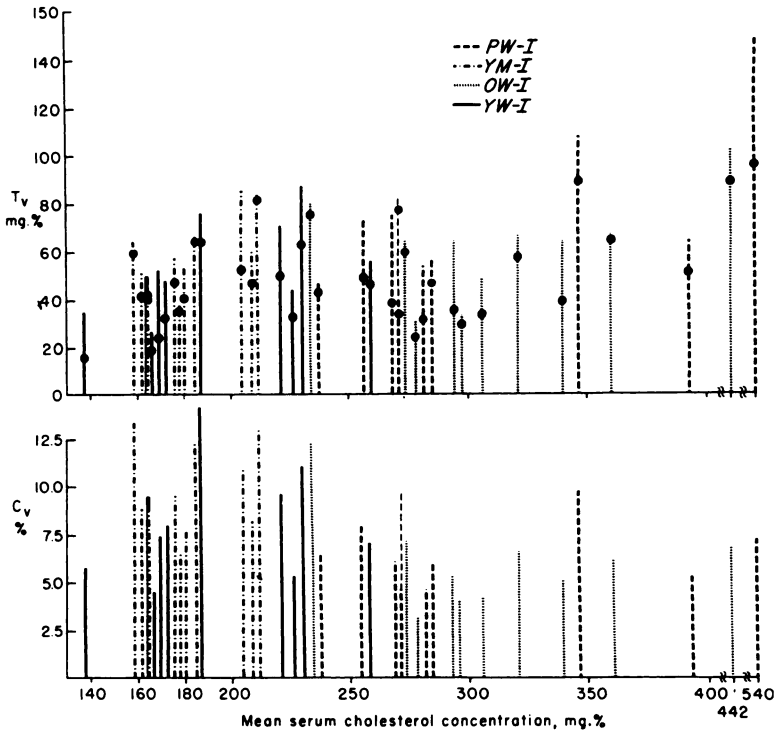

FIG. 1. Individual variability of serum cholesterol concentrations. *Tv* is the total variation, i.e., the difference between the highest and lowest recorded values graphed against the mean value for that individual. *Cv* is the coefficient of variation (mean × 100/standard deviation).

seen, especially in the data for the women. Not only did the mean serum concentration of older women in period B increase over the averages in periods A and C, but all the individual means of the women in each period followed the pattern of the respective group mean; the mean for period B was significantly higher than that for period C ($P \leq 0.02$). The means for older men were lower during summer and fall than in the spring, but the decrease was not typical of each member of the male group as was the increase for the women. In the group of younger women tested during the early summer the mean serum cholesterol concentrations were higher than in those tested during the spring. In contrast, seasonal changes similar to those for older men may not explain the differences in means for younger men in study 1, which was completed during the winter months, and study 2, which was carried out in the spring.

The elevation of serum cholesterol values for women in the summer months, compared with the apparent decrease in the mean for men of similar ages, is an observation which has not been reported previously. Seasonal variations in the serum cholesterol concentrations of men have been reported from several areas having distinctive weather patterns for summer and winter.[17–20] It is interesting that Thompson et al.[21] in Arizona, in a fifteen month study of twelve postmen, found no correlation between mean cholesterol concentration and season. Arizona is comparatively hot and dry, and temperature and humidity changes are small throughout a year. This supports the concept of variation in serum cholesterol in response to stress—in this instance, to the stimuli of naturally changing environment within a specific locale. We have observed, however, that alterations in environment did not elicit similar responses in serum cholesterol concentrations of our older men and women. It can be concluded that seasonal variations in serum cho-

lesterol concentrations of our subjects were sex-related, but as is frequently the case when sex differences are shown, there is no immediate explanation of why middle-aged men and women react differently to season.

The subjects of study 1 were selected for evaluation of individual variability during a period of approximately a month. The fasting concentration of cholesterol was no more characteristic of the subject than that determined at any other hour of the day. In Figure 1, the coefficient of variation C_v = mean $\times$ 100/standard deviation and the total variation (T_r), i.e., the difference between the highest and lowest value, were graphed for sixteen values for each subject against his mean. The circle on each T_r line represents the range of fourteen determinations, omitting the highest and lowest result from the sixteen values for each subject. If the same amount of variability was apparent in all subjects, the C_v would be expected to decrease uniformly as the mean concentration of serum cholesterol increased; in the case of T_r, the tips of the perpendiculars would lay on an arbitrary horizontal line. If degree of variation increased proportionately with the magnitude of the mean, the C_v perpendiculars would be the same length, but the T_r would increase uniformly.

There was no apparent consistency in the individual trends per group or for the over-all range of mean concentrations (Fig. 1); this was true for both C_v and T_r. The possibility of an uncharacteristically extreme concentration for a person does exist. However, the center fourteen of the sixteen values for T_r (marked by the circle in Figure 1) did not depict a trend of change more strikingly than when variability was expressed as T_r of sixteen values.

Watkin et al.[22] found that variability did not increase with the magnitude of the mean for sixty-eight men, aged twenty-six to ninety-two. In our study, the two groups with mean cholesterol values greater than 300 mg. per cent were the pregnant and the older women. There did not appear to be differences in variation despite dissimilarity of ages. For young subjects, Thomas and Eisenberg[9] reported increased variability when the cholesterol concentrations were high or low. This evaluation was based on the difference between two samples from twenty or more persons obtained over a five month period. A similar pattern was not observed in our study.

It also has been suggested that the spread of values around a higher group mean is greater than that around a lower group mean.[9,23] The general trend of values for subjects in study 1 (Table 1 and Fig. 1) appears to support this hypothesis, whereas that for subjects in study 2 shows exceptions. The over-all mean for older men in study 2 was the same from period B to C, but the standard deviations differed markedly. The results of the present studies include season of the year as an environmental factor in determining the magnitude of the individual mean, and hence should be considered in evaluating the spread of individual means around a group mean.

SUMMARY

Serum cholesterol concentrations of younger men and women, older men and women and pregnant women were determined at various intervals. Within hours, days or weeks, fluctuation in individual values appeared to be random and was not influenced markedly by the magnitude of the mean. The mean serum cholesterol concentration of every older woman increased during the warmest season of the year in comparison with the cooler seasons, whereas the group mean for the older men was greatest during the late winter and early spring months. It is suggested from these results that seasonal variation in serum cholesterol concentration may be sex-related.

ACKNOWLEDGMENT

We are grateful to Dr. Robert E. Hodges and the residents and interns who drew blood for these studies.

REFERENCES

1. Steiner, A. and Domanski, B. Serum cholesterol level in coronary arteriosclerosis. *Arch. Int. Med.*, 71: 397, 1943.
2. Morrison, L. M., Gonzales, W. T. and Hall, L. The significance of cholesterol variations in human blood serum. *J. Lab. & Clin. Med.*, 34: 1473, 1949.

3. Gertler, M. M., Garn, S. M. and Bland, E. F. Age, serum cholesterol and coronary artery disease. *Circulation*, 2: 517, 1950.
4. Groover, M. E., Jr., Jernigan, J. A. and Martin, C. D. Variations in serum lipid concentration and clinical coronary disease. *Am. J. M. Sc.*, 239: 133, 1960.
5. Peterson, J. E., Wilcox, A. A., Haley, M. I. and Keith, R. A. Hourly variation in total serum cholesterol. *Circulation*, 22: 247, 1960.
6. Segall, S. and Neufeld, A. H. Blood lipid variations in patients with hypercholesterolaemia and coronary artery disease. I. *Canad. M. A. J.*, 83: 521, 1960.
7. Sperry, W. M. and Webb, M. A revision of the Schoenheimer-Sperry method for cholesterol determination. *J. Biol. Chem.*, 187: 97, 1950.
8. Schoenheimer, R. and Sperry, W. M. A micromethod for the determination of free and combined cholesterol. *J. Biol. Chem.*, 106: 745, 1934.
9. Thomas, C. B. and Eisenberg, F. F. Observations on the variability of total serum cholesterol in Johns Hopkins medical students. *J. Chron. Dis.*, 6: 1, 1957.
10. Gram, M. R. and Leverton, R. M. Interrelation of age, serum cholesterol and basal metabolism of women. *Fed. Proc.*, 8: 384, 1949.
11. Lawry, E. Y., Mann, G. V., Peterson, A., Wysocki, A. P., O'Connell, R. and Stare, F. J. Cholesterol and beta lipoproteins in the serums of Americans. *Am. J. Med.*, 22: 605, 1957.
12. Adlersberg, D., Schaefer, L. E., Steinberg, A. G. and Wang, C. Age, sex, serum lipids and coronary atherosclerosis. *J. A. M. A.*, 162: 619, 1956.
13. Keys, A., Fidanza, F., Scardi, V. and Bergami, C. The trend of serum-cholesterol levels with age. *Lancet*, 2: 209, 1952.
14. Russ, E. M., Eder, H. A. and Barr, D. P., with the technical assistance of Raymunt, J. Protein-lipid relationships in human plasma. III. In pregnancy and the newborn. *J. Clin. Invest.*, 33: 1662, 1954.
15. Gofman, J. W., Jones, H. B., Lyon, T. P., Lindgren, F., Strisower, B., Colman, D. and Herring, V. Blood lipids in human atherosclerosis. *Circulation*, 5: 119, 1952.
16. Garcia, P., Roderuck, C. and Swanson, P. The relation of age to fat absorption in adult women together with observations on concentration of serum cholesterol. *J. Nutrition*, 55: 601, 1955.
17. Currie, A. N. The cholesterol of blood in malignant disease. *Brit. J. Exper. Path.*, 5: 293, 1924.
18. Man, E. B. and Gildea, E. F. Variation in lipemia of normal subjects. *J. Biol. Chem.*, 119: 769, 1937.
19. McEachern, J. M. and Gilmour, C. R. Studies in cholesterol metabolism. II. Blood cholesterol in various conditions. *Canad. M. A. J.*, 26: 158, 1932.
20. Thomas, C. B., Holljes, H. W. D. and Eisenberg, F. F. Observations on seasonal variations in total serum cholesterol level among healthy young prisoners. *Ann. Int. Med.*, 54: 413, 1961.
21. Thompson, E. M. and Kight, M. A. Serum cholesterol and thyroid activity as affected by high environmental temperature. *Fed. Proc.*, 20: 282, 1961.
22. Watkin, D. M., Lawry, E. Y., Mann, G. V. and Halperin, M. A study of serum beta lipoprotein and total cholesterol variability and its relation to age and serum level in adult human subjects. *J. Clin. Invest.*, 33: 874, 1954.
23. Keys, A., Mickelsen, O., Miller, E. v. O., Hayes, E. R. and Todd, R. L. The concentration of cholesterol in the blood serum of normal man and its relation to age. *J. Clin. Invest.*, 29: 1347, 1950.