[redacted]

[redacted]

ENTERED IN DATABASE

ACKNOWLEDGED

30 October 2001

The Office Administrator
ANZFA
P O Box 10559
Wellington 6036

Dear Sir,

Proposal P242 – Foods for Special Medical Purposes (Medical Foods)

It would appear that the ANZFA's preliminary safety evaluation is unwise. The World Health Organization study shows that cholesterol-lowering substances "considered to be remarkably safe" may cause excess mortality in the long term. Also as low blood cholesterol may cause an increase in violence according to the American College of Physicians, this will have a cost to Society as well as to individuals and contribute to what has been described as "a public health emergency"

See enclosed papers 1 & 2

Yours sincerely

[redacted]

D R Johnson

The Lancet · Saturday 23 August 1980

W.H.O. COOPERATIVE TRIAL ON PRIMARY PREVENTION OF ISCHÆMIC HEART DISEASE USING CLOFIBRATE TO LOWER SERUM CHOLESTEROL: MORTALITY FOLLOW-UP

Report of the Committee of Principal Investigators*

Summary This is a further report on the mortality amongst men in the W.H.O. cooperative trial of the primary prevention of ischæmic heart disease (IHD) by clofibrate. Mean observation was 9·6 years, 5·3 in the trial and 4·3 afterwards; 911 deaths are recorded in 150 000 man-years. There were 25% more deaths in the clofibrate-treated group than in the comparable high serum cholesterol, control group ($p<0·01$), and there was an excess in the treated group in all the three participating centres. Mortality from all causes was higher in the treated group than in the high cholesterol controls during the trial, equal in the first two years after leaving the trial, but higher again after that. No particular disease accounted for the overall excess: the treated group had more deaths from IHD, stroke, cancer, and other major diseases though most of the differences were not individually significant. There was no excess in deaths due to accidents and violence. There was also a significant excess in the death rate from all causes, and from causes other than IHD, in the treated group compared with the second, low cholesterol, control group. No relationship could be shown between the excess mortality and cholesterol reduction, or the length of time on clofibrate. Explanation of the excess mortality is not apparent: a long term toxic effect of clofibrate, the possible consequences of reducing body cholesterol pools and, remotely, chance have all to be considered.

Introduction

By the mid-1960s, when the trial was instituted, a high serum cholesterol concentration was accepted as a significant risk factor for ischæmic heart disease (IHD), but it was not clear whether the relationship was causal. The trial was designed to test whether reduction of raised serum cholesterol levels would reduce the incidence of IHD, so corroborating the "lipid" hypothesis —an exercise in experimental epidemiology.[2] The method selected was to lower high serum cholesterol levels by the drug clofibrate,[3] at that time considered to be remarkably safe as well as potent.[4]

The first report of the trial,[1] covering the period 1965–77, showed a reduction by 20% ($p<0·05$) in first major coronary events among healthy men given clofibrate compared with randomly selected controls. The incidence of non-fatal myocardial infarction was reduced by 25% but the rate of fatal first heart attacks showed no difference. Mortality from all causes, however, was significantly higher ($p<0·05$) in the clofibrate-treated group, and the excess was spread over a wide range of causes. The first report presented mortality in the period of the trial itself (i.e., of "treatment", 5·3 years on average) and during the first year after the end of treatment, a total period, therefore, of 6·3 years. The present report is of the mortality during and after treatment up to the end of 1978 in all the men who entered the trial, whether they attended throughout, were withdrawn for medical reasons, or left of their own choice (i.e., "lapsed").

Methods

The active phase of the trial, i.e. the period of treatment, spread over the years 1965 to 1976. Design and methods have been described earlier.[1,5,6] The volunteers, free of clinical IHD, were classified into three equal groups according to serum cholesterol. Those in the upper third of the cholesterol distribution were randomly allocated to clofibrate therapy (1·6 g daily, group I) or to an identical capsule containing olive oil (group II); the comparison between groups I and II was therefore double-blind and randomised. Half the men in the lower third constituted a second control group which also received the olive oil capsule (group III). The men in the other half of the lower third of the cholesterol distribution, and all the men in the middle third, were not studied.

The current follow-up study was implemented, early in 1979, by a questionnaire sent to all the volunteers and, if indicated, their general practitioners, asking about their current health and any illness which had required admission to hospital since they left the trial. Failure to reply to the questionnaire led to further inquiry and personal visits were made as necessary. The fact of death or survival had been established in 99·8% of subjects, and there was no statistically significant difference between groups I and II in this respect. Very few, probably less than 2% of subjects, in group I continued to take clofibrate after leaving the trial.

Hospital and general practitioner records of deceased subjects were consulted to obtain clinical information on the cause of death. This was supported by necropsy in 57% of cases (Edinburgh 27%, Budapest 76%, Prague 62%). The information was analysed by statistical techniques described in the earlier report. Age-standardisation, however, is now by the indirect rather than the direct method,[7] as being more reliable

Report prepared by: Prof. M. F. Oliver, Dr J. A. Heady, Prof. J. Morris and Ms. J. Cooper.

Principal investigators: H. Geizerova, Institute for Clinical and Experimental Medicine, Prague (J. Fodor 1966–68); I. Gyarfas, Hungarian Institute of Cardiology, Budapest (G. Lamm 1966–74); K. G. Laing, I.C.I., Macclesfield; J. A. Heady, Royal Free Hospital School of Medicine, London; J. N. Morris, London School of Hygiene and Tropical Medicine; M. F. Oliver, Royal Infirmary, Edinburgh; T. Strasser, W.H.O., Geneva (Z. Fejfar 1966–73).

Investigators and advisers: Edinburgh (W. G. Macfie, E. Scott); Budapest (M. Czukas, J. Duba, E. Östor); Prague (D. Grafnetter, Z. Hejl); London (J. Cooper); W.H.O., Geneva (Z. Pisa, K. Uemura); Copenhagen (G. Lamm [from 1974]); I.C.I. (J. M. Thorp).

for the small numbers of individual causes of death even in this large study. The "standard" rates used were the totals for all three treatment groups combined. The age used in the present report is the age at which the subjects died and not the age at entry as in the earlier report. In calculating rates, the deaths at any given age are related to the man-years of observation at that age from the time of entry to the trial until the end of 1978 or earlier death.

Results

Comparability of Groups

The clofibrate-treated group and the high cholesterol control group were closely comparable in terms of entry characteristics.[1] The men in these two groups who left the trial before it finished were also similar,[8] as were the times at which they left the study. There is thus no reason to suspect bias from these sources in comparisons of mortality between groups I and II during or after the trial.

Mortality

911 deaths are reported in 150 000 man-years of observation. The average length of follow-up is now 9·6 years, 5·3 years in the trial and 4·3 afterwards.

Table I shows numbers of deaths and age-standardised death rates for selected causes.

All causes.—The total rate for all causes is significantly greater in group I than in group II ($p<0·01$). The difference in the number of deaths has increased from 35 in our earlier report to 79 now, though the proportionate excess of group I over group II has decreased from 28% overall to 25% (23% in the new data). The survival curves (fig. 1) for the two groups are also significantly different at the 1% level. After 10 years the proportions surviving were 92·3% and 94·0% respectively. Mortality was higher in group I than in group II in each centre and in each 10-year age-group from 40 to 69.

TABLE I—CAUSES OF DEATH IN AND OUT OF TRIAL UP TO DEC. 31, 1978: NUMBERS OF DEATHS AT ALL AGES AND AGE-STANDARDISED RATES AT AGES 40–69*

Cause of death	Group I (clofibrate)		Group II (high cholesterol control)		Group III (low cholesterol control)	
	No. of deaths	Rate*	No. of deaths	Rate*	No. of deaths	Rate*
IHD:	157	3·2	138	2·9	46	1·1
Within 3 h	91		67		28	
After 3 h	66		71		18	
Stroke	30	0·6	19	0·4	12	0·3
Other circulatory diseases:	21	0·4	16	0·3	15	0·4
Subarachnoid hæmorrhage	6		3		0	
Venous thromboembolism	8		6		7	
Other†	7		7		8	
Malignant neoplasms:	125	2·6	99	2·1	82	2·0
Stomach	15		11		10	
Lung, bronchus, larynx	43		28		28	
Liver, gallbladder intestines‡	27		18		11	
Pancreas	5		9		6	
Hæmopoietic	11		6		4	
Genito-urinary	6		10		9	
Other	18		17		14	
Other medical causes:	30**	0·6**	13**	0·3**	20	0·5
Liver, gallbladder intestines‡	11**		1**		11	
Respiratory§	6		2		2	
Other	13		10		7	
Accidents and violence	31	0·6	30	0·6	21	0·5
Unknown causes	2		2	2		
All causes other than IHD¶	239**	4·9**	179**	3·7**	152	3·7
Total: all causes	396**	8·1**	3172××	6·6**	198	4·8

* Age-standardised death rate per 1000 per annum by the indirect method (age at death, ages 40–69).
† ICD (8th revision) nos. 390–404, 420–429, 440–452, 454–458.
‡ Included in previous publication under the heading "Regional Pathology".
§ ICD (8th revision) nos. 011, 460–519.
¶ Includes "unknown causes".
** Significant difference between corresponding numbers or rates in groups I and II ($p<0·01$).

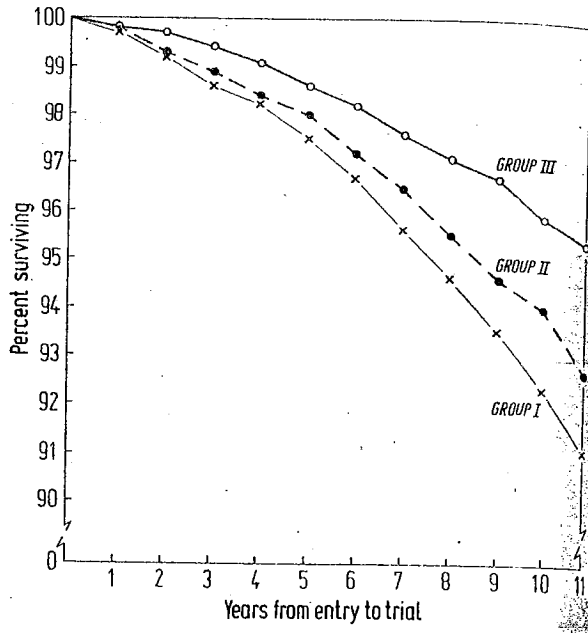


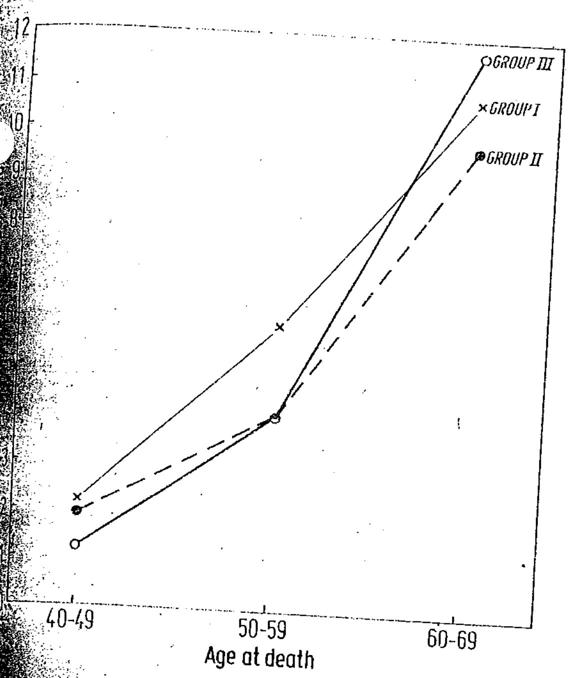
Fig. 1—Life-table analysis.

Deaths from all causes by group and time from entry. Group I v. group II, $p<0·01$.

Group	Number of men, at year from entry					
	0	2	4	6	8	10
I	5331	5288	5235	5157	4648	1559
II	5296	5261	5210	5150	4669	1613
III	5117	5100	5071	5027	4552	1599

IHD.—There is a non-significant excess overall in IHD deaths. This excess is confined to deaths within h of onset. The death rate from IHD is much lower in group III than in groups I and II, as observed in the earlier report (and as might be expected from their lower initial cholesterol levels).

All causes other than IHD.—Deaths from causes other than IHD show a significant ($p<0·01$) excess in group I compared with group II and, as with deaths from all causes, the excess is present in each centre and in each age-group (fig. 2). For deaths from causes other than IHD, since there is little evidence that increased serum cholesterol levels are related to their occurrence, the experience of the low cholesterol control group (group III) also was compared with that of group I, after correction for the differences between the two groups in entry characteristics other than cholesterol level. Of these, age is much the most important. The age-standardised death rate for group III is identical (3·7) with that of group II, and the difference between the rates for groups I and III is also significant ($p<0·01$). Age-standardised death rates in group I are also higher than



[illegible]2—Mortality from causes other than IHD per 1000 per [illegible]num, by group and age at death.

[illegible] in group III in each centre as are the rates at ages [illegible] and 50–59, though not at 60–69 (fig. 2). Adjust[illegible] for characteristics other than age, by use of the [illegible]ple logistic, makes very little difference to the [illegible] obtained by standardising for age alone. With [illegible]her variables included (smoking, father's survival, [illegible] height, and systolic blood pressure) the excess of [illegible]lity in group I over that in group II is 31%, and [illegible]at in group III is 26%.

[illegible]rate causes.—The excess of deaths in group I [illegible]ed with group II occurs in every major group of [illegible] shown in table I, though for accidents and [illegible] the difference is only 1. For *cancer* as a whole [illegible]ess is not significant, nor is it present in all three [illegible]. It is present, however, in most sites. The two [illegible] differences are in lung, bronchus, and larynx, [illegible]ver, gallbladder, and intestines.

If the deaths due to non-malignant diseases of the respiratory system, shown under "other medical causes", are added to other respiratory causes, this constitutes a group of all deaths associated with the *respiratory system*, 49 in group I and 30 in group II, a statistically significant difference ($p<0 \cdot 05$).

Malignant and non-malignant diseases associated with the liver, gallbladder, and intestines constitute the group of deaths singled out for mention in the last report under the heading "*regional pathology*", and for this combined group the excess in group I compared with group II is significant ($p<0 \cdot 05$). Compared with the last report, the proportional difference between groups I and II has diminished for malignant disease and increased for non-malignant disease of these sites, and taking the two together, and standardising for age, the rates for the three groups are 0·78, 0·40, and 0·53 per 1000 per annum, respectively.

Mortality in Trial and after Leaving it

Table II shows the number of deaths from the main causes which occurred during the trial and in various periods after leaving it. Age-standardised rates for all causes and for causes other than IHD are also shown. On average the rates for all causes ex-trial are nearly double those in the trial. Group II shows the greatest difference. The use of age-standardised rates abolishes the effect of ageing and this higher mortality after the end of the treatment period is, at least partly, due to the development of serious illness for which men were withdrawn from the trial. Table III (deaths occurring out of the trial) shows that men withdrawn for medical reasons and, to a lesser extent, men who left the trial early for other reasons, carried a higher death rate after leaving the trial than men who had remained in the trial until treatment was stopped. It also shows that there is no difference between groups I and II in the mortality of those withdrawn for medical reasons.

The increase in death rates with time out of the trial which is apparent in table II in groups I and III, and after 4 years in group I, despite the correction for the associated increase in age, is also largely explained by the

TABLE II—DEATHS IN TRIAL AND AT VARIOUS INTERVALS AFTER LEAVING TRIAL, BY MAIN CAUSE OF DEATH

[illegible]use of death	In trial	Group I (clofibrate) Out of trial (yr) 0–	2–	4+	Total	Group II (high cholesterol control) In trial	Out of trial (yr) 0–	2–	4+	Total	Group III (low cholesterol control) In trial	Out of trial (yr) 0–	2–	4+	Total
[illegible]	36	45	35	41	157	34	42	26	36	138	16	9	12	9	46
[illegible]oid hæmorrhage, [illegible]omboembolism;	7	5	10	8	30	4	5	7	3	19	3	4	1	4	12
[illegible]circulatory conditions	7	3	5	6	21	6	3	3	4	16	2	7	3	3	15
[illegible]neoplasms	42	37	28	18	125	25	42	23	9	99	30	25	15	12	82
[illegible]ical conditions	18	5	5	2	30	3	5	2	3	13	8	3	4	5	20
[illegible] and violence	18	3	3	7	31	15	7	2	6	30	14	1	3	3	21
[illegible]cept IHD ([illegible]dardised rate*)	92 (4·2)	54 (4·6)	51 (6·0)	42 (6·5)	239 (4·9)	53 (2·4)	62 (5·3)	37 (4·5)	27 (4·4)	179 (3·7)	57 (2·9)	40 (4·1)	26 (3·7)	29 (5·3)	152 (3·7)
[illegible] ([illegible]dardised rate*)	128 (5·7)	99 (8·5)	86 (10·2)	83 (12·7)	396 (8·1)	87 (4·0)	104 (8·9)	63 (7·6)	63 (10·3)	317 (6·6)	73 (3·7)	49 (5·0)	38 (5·4)	38 (7·1)	198 (4·8)
[illegible] at risk	28,197	10,304	6,831	5,248	50,580	28,118	10,323	6,893	5,291	50,625	27,204	10,023	6,757	5,324	49,308

*[illegible]dised death rate per 1000 per annum by the indirect method (age at death, ages 40–69).

TABLE III—DEATHS OUT OF TRIAL BY REASON FOR LEAVING

Reason for leaving	Group I		Group II		Group III	
	No. of deaths	Rate*	No. of deaths	Rate*	No. of deaths	Rate*
Men withdrawn from the trial for medical reasons	78	19·7	78	19·8	35	14·4
Men leaving during the trial for other reasons ("lapses")	95	13·0	71	10·4	45	7·3
Men who did not leave the trial until it was stopped	95	6·2	81	5·4	45	3·3
All men	268	10·1	230	8·9	125	5·6

* per 1000 per annum (age-standardised by the indirect method, ages at death 40–69).

high rates in men withdrawn for medical reasons. They form a relatively high proportion of men who have been out of the trial for a long time. The main interest, however, is in the difference in rates between groups I and II at equal times out of trial which is independent of this effect. For the first two years after leaving the trial the death rates from all causes, and from all causes other than IHD, are marginally lower in group I than in group II. Thereafter the difference reverts to the in-trial pattern of an excess in group I. The ratio of the age-standardised rates for all causes in groups I and II was 1·43 for deaths in the trial and 1·13 for out of trial deaths (0·96 for deaths in the first two years and 1·28 for deaths thereafter). Life table analysis confirms the lesser and non-significant difference between groups I and II ($0·10>p>0·05$) in total mortality after leaving the trial.

Mortality of Men Withdrawn from Trial because of Non-fatal Myocardial Infarction

There were 131 such men in group I and 174 in group II. 32 of the men in group I had died by the end of 1978, 23 from IHD; 39 of the group II men had died, 33 from IHD. Thus there were 10 *fewer* deaths from IHD in group I than in group II amongst these men.

Deaths in New IHD Events after End of Treatment

Among all the men who left the trial, there were 121 deaths from IHD in group I and 104 in group II (table II). It has just been shown that, of these deaths, 23 in group I and 33 in group II were in men who had an infarction in the trial. It follows that 98 in group I and 71 in group II were deaths from new infarctions arising after the end of treatment, an excess in group I of 27 or 38% ($p<0·05$).

Time in Trial (Length of Exposure to Treatment)

Table IV shows how mortality from all causes is related to time spent in the trial—a measure of the length of exposure to "treatment" in the three groups. The method of calculating this exposure is given in the footnote to the table. The mortality rates are shown for the in-trial period and the out-of-trial period separately and are adjusted for age because length of time in the trial is obviously correlated with age.

TABLE IV—DEATHS FROM ALL CAUSES IN TRIAL AND OUT OF TRIAL BY TIME IN TRIAL

Time in trial (yr)		Group I (clofibrate)			Group II (high cholesterol control)			Group III (low cholesterol control)		
		In trial	Out of trial	Total	In trial	Out of trial	Total	In trial	Out of trial	Total
0–	D	33	82	115	26	74	100	13	27	40
	R	*5·1*	*16·0*	*10·1*	*4·3*	*15·5*	*9·3*	*2·0*	*6·2*	*4·0*
2–	D	34	46	80	26	34	60	21	35	56
	R	*5·0*	*15·9*	*8·3*	*4·0*	*11·0*	*6·2*	*3·7*	*16·6*	*7·3*
4–	D	39	53	92	24	56	80	25	22	47
	R	*5·9*	*8·8*	*7·2*	*3·6*	*10·3*	*6·7*	*4·4*	*4·4*	*4·6*
6+	D	22	87	109	11	66	77	14	41	55
	R	*8·3*	*6·9*	*7·2*	*4·1*	*5·3*	*5·1*	*5·7*	*3·7*	*4·0*
Total	D	128	268	396	87	230	317	73	125	198
	R	*5·7*	*10·1*	*8·1*	*4·0*	*8·9*	*6·6*	*3·7*	*5·6*	*4·8*

D=No. of deaths. R=Death rate/1000 man-years, age-standardised by the indirect method (age at death, at ages 40–69).

Calculation of man-years at risk:

In-trial (i.e., exposure to treatment).—For example, a man who was in the trial for 5·6 years was considered to have been exposed to treatment for 2 years in the period 0–2 years, 2 years in the period 2–4 years, and 1·6 years in the period 4–6 years.

Out of the trial.—If, for example, he left the trial 3·7 years before 31.12.78 he would contribute 3·7 years to the man-years out of the trial of men who had been exposed to treatment for 4–6 years. If he died before 31.12.78 his "contribution" would be the number of years between the date he left the trial and the date of his death.

Total.—For any given time-in-trial period, the total man-years is the sum of in-trial and out of trial man-years, calculated as described above.

In groups I and III (but not in group II) the in-trial death rates increase with time in the trial. The out-of-trial rates in groups I and II (but not so uniformly in group III) decline with increasing time in the trial. The net effect, in groups I and II at any rate, is that the total rate, in and out of the trial, declines with time in the trial. This decrease is again misleading. Men who left the trial early, i.e. were withdrawn for medical reasons, or left for other reasons, provide all the man-years at risk at the short exposure times. This is because people who stayed in the trial to the end were all in the trial for more than 4 years. The higher mortality rates of those who left the trial early will therefore affect the out-of-trial rates, and hence the total rates, at the short exposure times. Once again, however, it is the difference between the rates in groups I and II which is of interest if exposure time to the drug as compared with the placebo is to be related to mortality.

Differences between total mortality rates in groups I and II are, therefore, shown in the upper part of table V, for deaths from all causes and for IHD deaths, and there is no discernible relationship between them and length of time in the trial.

For deaths from cancer and "other causes", and the combined category of all deaths other than IHD, it is perhaps permissible to compare group I with both groups II and III for the same reasons which were discussed above when comparing the overall mortality from causes other than IHD.

The lower part of table V shows these comparisons, and again no relationship can be seen between the differences and length of time in the trial.

Cholesterol Reduction

Two approaches were used to assess how much of

TABLE V—MORTALITY DIFFERENCES BETWEEN GROUPS BY TIME IN TRIAL: RATES PER 1000 PER ANNUM, AGE-STANDARDISED*

(a) Differences in mortality rates between groups I and II
(group I rate—group II rate)

Time in trial (yr)	Deaths from all causes	Deaths from IHD
0–	+0·8	−0·1
2–	+2·1	+0·1
4–	+0·5	−0·2
6+	+2·1	+0·8
Total	+1·5	+0·3

(b) Differences in mortality rates between group I and groups II and III

Time in trial (yr)	Deaths from malignant neoplasms		Deaths from other causes		Deaths from all causes except IHD	
	Gp I-II	Gp I-III	Gp I-II	Gp I-III	Gp I-II	Gp I-III
0–	+0·4	+1·8	+0·6	+0·7	+1·0	+2·5
2–	+0·9	−0·8	+1·0	+0·4	+1·9	−0·4
4–	+0·0	−0·1	+0·6	+0·7	+0·6	+0·6
6+	+0·7	+0·9	+0·6	+0·9	+1·3	+1·8
Total	+0·5	+0·6	+0·7	+0·7	+1·2	+1·3

* By the indirect method (age at death, ages 40–69).

excess mortality in the clofibrate-treated group is related to cholesterol lowering.

The first was to compare the excess mortality in those men whose serum cholesterol fell, with the excess in those whose cholesterol did not fall, or even rose (table). The excess was measured by comparing the mortality in each subset of men in group I with the expected mortality in untreated (i.e., group II) men at similar risk. This "expected" rate was derived from the multiple logistic equation for group II, including seven revelant variables measured at the start of the trial (age, smoking, father's survival, height, weight, systolic blood pressure, and serum cholesterol). The men in group I were further subdivided according to whether the level of their starting serum cholesterol was in the upper or lower half of the distribution of their cholesterol levels. They were, of course, already selected for having cholesterol levels in the top third of the distribution and thus those above the median constituted the top sixth [17%]. The mean level in the top sixth was 270 mg/dl.) In terms of rates, the excess mortality (O–E) occurred throughout. It was less in those whose cholesterol fell than in those in whom it did not fall, but this (4·7 compared with 0·3) was only marked in men with initially high levels and even this difference was not statistically significant. Numerically, the greater part of the excess of observed over expected occurred in the men whose cholesterol fell on treatment, who were, of course, the great majority (84%). Essentially the same pattern of results is true for mortality from all causes except IHD. This analysis therefore suggests, if anything, that excess mortality was greater in non-responders to treatment than in responders.

The second approach was by direct use of the multiple logistic equation calculated for all causes of death on groups I and II, and including, as well as the seven variables mentioned earlier, two others—membership of group I (i.e., treatment by clofibrate) and mean cholesterol reduction in the trial. In the resulting equation membership of group I had a significant coefficient ($p<0·05$) but cholesterol change did not. The same is true for all causes of death except IHD. This approach also gives no support to the suggestion that cholesterol reduction is an important factor in mortality.

TABLE VI—MORTALITY FROM ALL CAUSES IN CLOFIBRATE-TREATED GROUP BY CHOLESTEROL CHANGE AND PRE-TREATMENT CHOLESTEROL LEVEL: MORTALITY RATES PER 1000 PER ANNUM

Pre-treatment cholesterol*		Mean cholesterol change			
		Fall		Rise	
		Rates	No.	Rates	No.
Below median†	O	6·6	108	7·1	31
	H	5·1	83·45	5·2	22·70
	O–E	1·5	24·55	1·9	8·30
Above median†	O	7·5	143	13·1	26
	E	7·2	137·28	8·4	16·67
	O–E	0·3	5·72	4·7	9·33

* O=observed; E=expected for men in group II with similar risk factors at entry, calculated from the multiple logistic function.
† The median pre-treatment cholesterol level (corrected for differences between centres) was 247 mg/dl. The mean value above the median was 270 and below the median 231 mg/dl.
‡ Men who did not have a second visit and in whom, therefore, it was not possible to calculate a change in cholesterol level are excluded from this table as also are men in Budapest, whose initial cholesterol was determined by the Anderson method (see previous report[1]).

Men Who Showed Greatest Reduction in IHD

In the previous report a group of 6% of the men in the clofibrate-treated group was identified which showed the greatest benefit from treatment in terms of reduction of IHD. They were smokers with higher than average systolic blood pressure on entry to the trial who responded to treatment by showing some reduction of serum cholesterol levels.

This group of men, although subject to high risk, had a 31% lower mortality from IHD than corresponding men with the same disadvantages in group II (observed deaths 37, 4·3 per 1000; "expected" deaths 53, 6·2 per 1000). Mortality from causes other than IHD in these men, however, showed an excess over group II which was similar to that of the rest of the men in group I. As a result their mortality from all causes was marginally lower than for similar men in group II (10· per 1000 compared with 11·2).

Discussion

The first report, covering the period of the trial and one year after, showed that in a group of healthy men with moderately increased serum cholesterol treated with clofibrate, there was a lower incidence of non-fatal myocardial infarction than in the comparable controls, and that the difference was related to reduction of serum cholesterol. This was support for the "lipid hypothesis". But there was no reduction in *mortality* from IHD, and mortality from non-cardiovascular diseases was greater in the treated group than in the comparable control group.

The main concern arising from further follow-up is that the new data, collected since the publication of the original report, also show a higher mortality in the clofibrate-treated group, though proportionally the excess in the new data is somewhat less than before. The implica-

tumour cells, an altered cellular response to the effects of ageing, or to accelerated ageing.

It is possible that a small persistent loss of tissue cholesterol over a period of years could impair normal cell function, although the results of the present trial do not particularly suggest that the excess mortality in the clofibrate-treated group is associated with its cholesterol-lowering properties. No data yet exist which would permit assessment of the amount of cholesterol which would be removed from cells when plasma cholesterol is reduced by, say, 10% over several years. It might be assumed that synthesis of cholesterol by cells, and the lipoprotein transport system, would adjust to this, and that cell-cholesterol homœostasis would be maintained. Yet the aim of lowering course to deplete cells of some of their cholesterol, and it is too much to expect that this takes place only in those with excess cholesterol. Theoretically, reduction of cholesterol could alter cell membrane liquidity, and in ageing cells, perhaps, their biological functions. It may be recalled that there was an excess (though not significant) in non-cardiovascular mortality in the groups in which plasma cholesterol was lowered by low-saturated fat, high polyunsaturated fat diets in each of the other two substantial primary prevention trials.[14,15]

The foregoing discussion is conjectural. We do not have a plausible explanation of the findings, which of course were totally unexpected. Surveillance of the men is indeed to be continued until the situation resolves.

The present trial illustrates the kind of contribution that an epidemiological approach can make, to "completing the clinical picture",[2] seeking a comprehensive account of benefits and hazards in a large enough population to assess the overall and long-term effects, direct and indirect, of a potent drug administered over a long period. A "conventional" side effect like gallstones was indeed spotted early by investigators using clofibrate.[16,17] What we are dealing with now, however, is a suggestion of numerous undramatic increases across the range of pathology, too small in themselves to be noticed individually, but disturbing when brought together in this way. Whatever the eventual explanation of these findings, they must stimulate further thought about drug regulatory systems to protect the public health against possible adverse effects of long-term medication with healthy drugs.

The investigators are indebted once more to the individuals and institutions mentioned in the previous report[1] and also to Miss Margaret Babble, computer programmer, and Miss Jackie Harrison, secretary.

Requests for reprints should be addressed to Dr J. A. Heady, Royal Postgraduate Medical School, 21 Pond Street, London NW3 2PN.

REFERENCES

Committee of Principal Investigators. A cooperative trial in the prevention of ischæmic heart disease using clofibrate. *Br Heart J* 1978; **40**: 1069–118.

Hill AB. Principles of epidemiology, 3rd ed. Edinburgh: Churchill-Livingstone, 1971.

Oliver MF, Waring WS. Modification of metabolism and distribution of lipids by ethyl chlorophenoxyisobutyrate. *Nature* 1962; **194**: 948–49.

Committee of Principal Investigators. A cooperative trial on the primary prevention of ischæmic heart disease using clofibrate: Design, methods and progress. *Bull W.H.O.* 1973; **48**: 243–56.

References continued at foot of next column

HÆMOPOIETIC RECOVERY IN EWING'S SARCOMA AFTER INTENSIVE COMBINATION THERAPY AND AUTOLOGOUS MARROW INFUSION

ROSS A. ABRAMS DANIEL GLAUBIGER
RICHARD SIMON ALLEN LICHTER
ALBERT B. DEISSEROTH

Pediatric Oncology Branch, Experimental Hematology Section, Biometrics Research Branch and Radiation Oncology Branch, National Cancer Institute, National Institute of Health, Bethesda, Maryland, U.S.A.

Summary After the completion of combination therapy designed to achieve local control of Ewing's sarcoma, 13 patients with either truncal primary lesions or proven metastases were given 150 rad of total body irradiation over 5 weeks followed by cyclophosphamide, doxorubicin, imidazole carboxamide, and vincristine. 11 patients received autologous cryopreserved marrow infusions. In 2 patients marrow collections were not attempted. Two patterns of hæmopoietic recovery were observed: 8 patients, who had received marrow infusions, showed leucocyte, granulocyte, and platelet recovery by 27, 28, and 30 days. 5 patients, 3 of whom had also received marrow, showed more delayed recovery with leucocyte, granulocyte, and platelet recovery at 45, 53, and 77+ days. Delayed recovery in patients receiving marrow seemed to correlate with aberrations in marrow freezing-rate during phase change, and these aberrations could be shown to diminish post-freeze recovery of marrow granulocyte-monocyte precursor cells.

Introduction

HÆMOPOIETIC toxicity often limits the intensity of regimens designed to control solid tumours and hæmato-

COMMITTEE OF PRINCIPAL INVESTIGATORS:

REFERENCES—*continued*

6. Committee of Principal Investigators. Primary prevention of ischæmic heart disease: W.H.O. coordinated cooperative trial, a summary report. *Bull W.H.O.* 1979; **57**: 801–05.
7. Armitage P. Statistical methods in medical research. Oxford: Blackwell, 1971: 388–91.
8. Heady JA. A cooperative trial in the primary prevention of ischæmic heart disease using clofibrate: some statistical aspects. *Controlled Clinical Trials* (in press).
9. Rose G, Shipley MJ. Plasma lipids and mortality: a source of error. *Lancet* 1980; i: 523–26.
10. Cayen MN, Ferdinandi ES, Griselin E, Robinson WT, Dvornik D. Clofibrate and clofibric acid: Comparison of the metabolic disposition in rats and dogs. *J Pharmacol Exp Ther* 1977; **200**: 33–43.
11. Gugler R, Hartlapp J. Clofibrate kinetics after single and multiple doses. *Clin Pharmacol Ther* 1978; **24**: 432–38.
12. Reddy JK, Azarnoff DL, Hignite CE. Hypolipidæmic hepatic peroxisome proliferators form a novel class of chemical carcinogens. *Nature* 1980; **283**: 397–98.
13. Recknagel RO, Glende EA, Hruszkewycz AM. Chemical mechanisms in carbon tetrachloride toxicity. In: Pryor WA. ed. Free radicals in biology. New York: Academic Press, 1977; **3**: 97–132.
14. Dayton S, Pearce ML, Hashimoto S, Dixon WJ, Tomiyasu U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. *Circulation* 1969; **39/40**: suppl II: 1–63.
15. Miettinen M, Turpeinen O, Karvonen MJ, Elosno R, Paavilianen E. Effect of cholesterol-lowering diet on mortality from coronary heart disease and other causes: a 12 year clinical trial in men and women. *Lancet* 1972; ii: 835–38.
16. Pertsemlidis D, Panveliwalla D, Ahrens EH. Effects of clofibrate and of an estrogen-progestin combination on fasting biliary lipids and cholic acid kinetics in man. *Gastroenterology* 1974; **66**: 565–73.
17. Cooper J, Geizerova H, Oliver MF. Clofibrate and gallstones. *Lancet* 1975; i: 1083.

42

PERSPECTIVE

Cholesterol and Violence: Is There a Connection?

Beatrice A. Golomb, MD, PhD

Purpose: To determine whether the seeming relation between low or lowered cholesterol levels and violence is consistent with causality according to Hill's criteria and whether construct validity is supported by convergence of findings across different types of studies.

Data Sources: Search of the MEDLINE database for English-language articles published between 1965 and 1995 was supplemented by searches of the PsycINFO and Current Contents databases and bibliographies of relevant articles.

Study Selection: Peer-reviewed observational and experimental articles and meta-analyses that presented original research; related cholesterol levels to behaviorally defined violence; and, if experimental, had single-factor (lipid-only) intervention.

Data Extraction: Studies were grouped according to type. Data on the relation of violence to cholesterol levels from each study were recorded.

Data Synthesis: Observational studies (including cohort, case–control, and cross-sectional studies) consistently showed increased violent death and violent behaviors in persons with low cholesterol levels. Some meta-analyses of randomized trials found excess violent deaths in men without heart disease who were randomly assigned to receive cholesterol-lowering therapy. Experimental studies showed increased violent behaviors in monkeys assigned to low-cholesterol diets. Human and animal research indicates that low or lowered cholesterol levels may reduce central serotonin activity, which in turn is causally linked to violent behaviors. Many trials support a significant relation between low or lowered cholesterol levels and violence ($P < 0.001$).

Conclusions: A significant association between low or lowered cholesterol levels and violence is found across many types of studies. Data on this association conform to Hill's criteria for a causal association. Concerns about increased risk for violent outcomes should figure in risk–benefit analyses for cholesterol screening and treatment.

Ann Intern Med. 1998;128:478-487.

From the University of California, Los Angeles, Los Angeles, California. For the current author address, see end of text.

Violence, which was recently declared a public health emergency (1), is increasingly viewed as the province of the primary care practitioner (1–6). It is a substantial source of morbidity and is the leading cause of death in persons younger than 44 years of age (7) and of years of life lost for persons of all ages (8). Meanwhile, cholesterol screening and treatment remain the subject of vigorous debate (9–11), the outcome of which will influence medical care for millions of persons and annual health expenditures of billions of U.S. dollars. Arguments on both sides of the debate hinge on the costs, risks, and benefits of cholesterol level reduction (12). One possible risk stems from a putative connection between low or lowered cholesterol levels and violent death in men. However, the presence of such a connection remains controversial. In this paper, the medical literature has been systematically evaluated for evidence of this relation, including observational and experimental evidence in humans and nonhuman primates.

Methods

The MEDLINE, PsycINFO, and Current Contents databases were searched for English-language peer-reviewed articles by using the keywords *cholesterol and violence* or *cholesterol and suicide*. Bibliographies from identified articles were also searched. Articles met the inclusion criteria if they presented original research, individual-level data, and single (lipid-only) or no interventions and included persons documented to be violent or used direct measures of violence (as opposed to mood or personality indices). Psychological measures, such as depression and nonbehavioral expressions of hostility, correlate poorly with measures of violent acts (13, 14).

The neurotransmitter serotonin has been implicated in the control of violent behaviors. It is postulated that lowered cholesterol levels may lead to lowered brain serotonin activity; this may, in turn, lead to increased violence. Thus, additional searches were performed to relate brain serotonin to cholesterol and serotonin to violence.

No randomized, controlled trials have been designed to evaluate a causal connection between low or lowered cholesterol levels and violence in humans, but criteria that permit a causal connection to

41

Table 1. Association of Violent Death and Low Cholesterol Level in Cohort Studies

Study (Reference)	Violent Deaths, n*	Low Cholesterol Level†	High Cholesterol Level†	Covariates	Relative Risk for Violent Death in the Low-Cholesterol Group Compared with the High-Cholesterol Group
Jacobs et al. (16)‡	~3800	<160 mg/dL	160–190 mg/dL	Age, smoking, blood pressure, basal metabolic index, alcohol use	1.5§
Neaton et al. (17)	1277	<160 mg/dL	≥160 mg/dL	Age, smoking, blood pressure, race, socioeconomic status‖, season	1.3¶
Lindberg et al. (18)	376	<204 mg/dL	>294 mg/dL	Age	2.8**
Vartiainen et al. (19)	193	1 mmol/L change		Age, smoking, blood pressure, alcohol use	1.0
Iribarren et al. (20)	75	1 SD change		Age, blood pressure, intake of dietary cholesterol, blood glucose level, alcohol use	1.1
Pekkanen et al. (21)	47	<234 mg/dL	≥234 mg/dL	Age, smoking, blood pressure, socioeconomic status‖, basal metabolic index	1.2
Farchi et al. (22)	35	1 mg/dL change		Age, smoking, blood pressure, FEV_1, arm circumference	~1.0††
Zureik et al. (23)‡‡	32	<184 mg/dL	184–239 mg/dL	Age, mean corpuscular volume§§, smoking	3.2§
Chen et al. (24)	17	≤136 mg/dL	≥179 mg/dL	Age, sex, blood pressure, smoking, alcohol use	6.7¶

* Data shown are for men, except for the study by Chen and colleagues (24), which did not segregate data by sex.
† To convert mg/dL to mmol/L, multiply by 0.02586.
‡ Pooled analysis with data on 18 studies; 12 of 18 studies adjusted for alcohol.
§ $P < 0.01$.
‖ Income or occupation.
¶ $P < 0.05$.
** $P < 0.001$.
†† Exponential of Cox regression coefficient for cholesterol.
‡‡ Evaluated suicide outcomes only; no data on all violent death.
§§ Proxy for alcohol use.

be evaluated in the absence of direct experimental evidence have been developed. The following seven criteria, set forth by Hill (15), are used to guide presentation of the results: strength of association, consistency of association, temporality (cause precedes effect), biological gradient, biological plausibility, coherence with preexisting knowledge, and specific association.

Results

One hundred sixty-three articles that linked cholesterol and violence were identified. Of these, 32 met the inclusion criteria: 9 community cohort analyses (1 of which summarized 18 studies), 6 studies in criminal populations, 6 studies of suicide in psychiatric populations, 8 meta-analyses of randomized trials, 1 mixed-design study, and 2 controlled trials in nonhuman primates. The results of individual randomized trials reporting violent outcomes have in no case been statistically significant, and these results are not presented individually. In community cohorts and meta-analyses of randomized trials, violence was defined as death by homicide, suicide, or accident; in other types of study, violence was defined as noted in the text. Studies relating cholesterol to serotonin and serotonin to violence are briefly reviewed.

Table 2. Difference in Mean Cholesterol Level between Suicidal or Violent Group and Control Group

Study (Reference)	Patients	Sex	Study Group/Control Group	Difference in Average Cholesterol Level in Suicidal or Violent Group Compared with Control Group*
	n			mg/dL
Gallerani et al. (27)	662	Male and female	Patients admitted for parasuicide/controls	−18†
Modai et al. (28)	427	Male and female	Consecutive admissions who had attempted suicide/psychiatric and medical controls	−17‡
Virkkunen (29)	274	Male	Patients with violent antisocial personality disorder/persons with other personality disorders	−37†
Hillbrand and Foster (30)	50	Male	High-severity violent criminals/low-severity violent criminals§	−31‖
Virkkunen et al. (31)	47	Male	Patients with aggressive conduct disorder/patients with attention-deficit disorder	−44†
Gray et al. (32)	40	Male	Criminals/staff	−13

* Negative numbers signify that the average cholesterol level was lower in the suicide or violent group. To convert mg/dL to mmol/L, multiply by 0.02586.
† $P < 0.001$.
‡ $P < 0.01$.
§ According to authors' previously devised severity-of-violence scale
‖ $P < 0.05$.

Table 3. Suicide Attempts and Violence in Patients with Low Cholesterol Levels Compared with Patients with High Cholesterol Levels

Study (Reference)	Patients, *n*	Sex	Cholesterol Level		Type of Patient	Suicide or Violence Measure	Relative Risk for Parasuicide or Violence
			Low	High			
Golier et al. (34)	343	Female	Low quartile	Rest	Psychiatric inpatients	Medically serious suicide attempt*	NS†
Golier et al. (34)	307	Male	Low quartile	Rest	Psychiatric inpatients	Medically serious suicide attempt*	2.22‡
Sullivan et al. (35)	90	Male and female	Low quartile	High quartile	Outpatients with depression	Suicide ideation or attempt	5.14§
Spitz et al. (36) and Hillbrand et al. (37)	106	Male	< 200 mg/dL‖	≥ 200 mg/dL‖	Violent criminals	Number of aggressive incidents in 2 years	3.3¶

* According to the Medical Lethality Rating Scale.
† Not significant (relative risk not given).
‡ $P < 0.01$.
§ $P < 0.001$.
‖ To convert mg/dL to mmol/L, multiply by 0.02586.
¶ $P < 0.05$.

Hill's Criteria for a Causal Connection

Strength and Consistency of Association

The evidence for an association between cholesterol and violence in humans derives from community cohort studies, observational studies in violent populations, and meta-analyses of randomized trials of cholesterol-lowering therapy.

A meta-analysis of 18 community cohort studies by Jacobs and colleagues (16) (**Table 1**) found 50% more violent deaths in men with cholesterol levels less than 160 mg/dL (4.14 mmol/L) than in the group with the highest cholesterol levels. Results of 8 additional studies are also shown (17–24); 1 of these studies examined only death by suicide (23). Although the number of violent deaths in all of these studies totaled only half of that in the meta-analysis by Jacobs and colleagues (16), 4 of the 8 studies (including the 2 largest studies) independently showed a statistically significant association between low cholesterol levels and violent death. Findings presented are for men, except in the study (24) where data were not segregated by sex. Few studies reported results for women separately, and although the largest of these studies showed a trend toward increased violent death with low cholesterol levels in women (18), the increased risk was less than that in men. In no study was the association of low cholesterol levels with violence significant for women when they were studied separately. Although this may be the result of inadequate power to test the association in this group, women are at substantially lower risk for violence and violent death; therefore, even a similar relative risk would confer comparatively modest absolute risk and clinical importance.

In large community cohort analyses in which suicide was investigated separately, the relative risk for suicide with low cholesterol levels was greater than that for violence overall (17, 18), although one moderate-sized study found a significant positive association between suicide and cholesterol level (20). One meta-analysis found significantly increased violent death with low cholesterol levels only in community cohorts and not in cohorts confined to employed persons (25). However, a recent French cohort study of 6393 employed men with repeated cholesterol level measurements found that a low average cholesterol level was linked to subsequent death by suicide (relative risk, 3.16; $P = 0.007$), and the connection between a decrease in cholesterol level of more than 5 mg/dL per year and subsequent suicide was marginal (relative risk, 2.17; $P = 0.056$) (23). One study of nonhuman primates (26) noted a relation between low baseline cholesterol level and agonistic behaviors. However, multiple measures of association were examined, and the significant relation to aggression could have arisen by chance.

Because violence is rare, studies targeting populations with high rates of violence may show an association between cholesterol level and violence more efficiently. Several cross-sectional, retrospective, cohort, case–control, and mixed-design observational studies have investigated the relation between cholesterol levels and suicide attempts in psychiatric populations or between cholesterol levels and violence in criminally violent persons and controls. Substantially lower cholesterol levels were seen in the parasuicide group (suicide attempts or ideation) in 2 studies (27, 28) and in the violent group in 3 of 4 studies (29–32) (**Table 2**). Another study found that among children with psychiatric diagnoses, patients who had the diagnosis with which the most suicide attempts were associated also had the lowest average cholesterol levels (33). Two of 3 analyses reported significantly more suicide attempts among persons with low cholesterol levels (34, 35) (**Table 3**); the third analysis (34) showed a nonsignificant relation in women. One study reported a higher frequency of violence (36, 37). These psychiatric and criminal data support

Table 3. Suicide Attempts and Violence in Patients with Low Cholesterol Levels Compared with Patients with High Cholesterol Levels

Study (Reference)	Patients, *n*	Sex	Cholesterol Level		Type of Patient	Suicide or Violence Measure	Relative Risk for Parasuicide or Violence
			Low	High			
Golier et al. (34)	343	Female	Low quartile	Rest	Psychiatric inpatients	Medically serious suicide attempt*	NS†
Golier et al. (34)	307	Male	Low quartile	Rest	Psychiatric inpatients	Medically serious suicide attempt*	2.22‡
Sullivan et al. (35)	90	Male and female	Low quartile	High quartile	Outpatients with depression	Suicide ideation or attempt	5.14§
Spitz et al. (36) and Hillbrand et al. (37)	106	Male	< 200 mg/dL‖	≥200 mg/dL‖	Violent criminals	Number of aggressive incidents in 2 years	3.3¶

* According to the Medical Lethality Rating Scale.
† Not significant (relative risk not given).
‡ $P < 0.01$.
§ $P < 0.001$.
‖ To convert mg/dL to mmol/L, multiply by 0.02586.
¶ $P < 0.05$.

Hill's Criteria for a Causal Connection

Strength and Consistency of Association

The evidence for an association between cholesterol and violence in humans derives from community cohort studies, observational studies in violent populations, and meta-analyses of randomized trials of cholesterol-lowering therapy.

A meta-analysis of 18 community cohort studies by Jacobs and colleagues (16) (**Table 1**) found 50% more violent deaths in men with cholesterol levels less than 160 mg/dL (4.14 mmol/L) than in the group with the highest cholesterol levels. Results of 8 additional studies are also shown (17–24); 1 of these studies examined only death by suicide (23). Although the number of violent deaths in all of these studies totaled only half of that in the meta-analysis by Jacobs and colleagues (16), 4 of the 8 studies (including the 2 largest studies) independently showed a statistically significant association between low cholesterol levels and violent death. Findings presented are for men, except in the study (24) where data were not segregated by sex. Few studies reported results for women separately, and although the largest of these studies showed a trend toward increased violent death with low cholesterol levels in women (18), the increased risk was less than that in men. In no study was the association of low cholesterol levels with violence significant for women when they were studied separately. Although this may be the result of inadequate power to test the association in this group, women are at substantially lower risk for violence and violent death; therefore, even a similar relative risk would confer comparatively modest absolute risk and clinical importance.

In large community cohort analyses in which suicide was investigated separately, the relative risk for suicide with low cholesterol levels was greater than that for violence overall (17, 18), although one moderate-sized study found a significant positive association between suicide and cholesterol level (20). One meta-analysis found significantly increased violent death with low cholesterol levels only in community cohorts and not in cohorts confined to employed persons (25). However, a recent French cohort study of 6393 employed men with repeated cholesterol level measurements found that a low average cholesterol level was linked to subsequent death by suicide (relative risk, 3.16; $P = 0.007$), and the connection between a decrease in cholesterol level of more than 5 mg/dL per year and subsequent suicide was marginal (relative risk, 2.17; $P = 0.056$) (23). One study of nonhuman primates (26) noted a relation between low baseline cholesterol level and agonistic behaviors. However, multiple measures of association were examined, and the significant relation to aggression could have arisen by chance.

Because violence is rare, studies targeting populations with high rates of violence may show an association between cholesterol level and violence more efficiently. Several cross-sectional, retrospective, cohort, case–control, and mixed-design observational studies have investigated the relation between cholesterol levels and suicide attempts in psychiatric populations or between cholesterol levels and violence in criminally violent persons and controls. Substantially lower cholesterol levels were seen in the parasuicide group (suicide attempts or ideation) in 2 studies (27, 28) and in the violent group in 3 of 4 studies (29–32) (**Table 2**). Another study found that among children with psychiatric diagnoses, patients who had the diagnosis with which the most suicide attempts were associated also had the lowest average cholesterol levels (33). Two of 3 analyses reported significantly more suicide attempts among persons with low cholesterol levels (34, 35) (**Table 3**); the third analysis (34) showed a nonsignificant relation in women. One study reported a higher frequency of violence (36, 37). These psychiatric and criminal data support

criteria of strong association and, in conjunction with community cohort data, show consistency of effect.

An apparent increase in violent deaths was noted in several randomized, primary prevention trials of cholesterol lowering, including the well-designed Lipid Research Clinics and Helsinki Heart trials (38–40). This increase was statistically significant in one trial that included both a cholesterol and a blood pressure intervention (41), but the number of violent deaths in most studies is small, and the excess of violent deaths has not reached statistical significance in any unifactorial intervention trial. To overcome the problem of small numbers of violent deaths, several meta-analyses have been performed.

Table 4 presents results from meta-analyses of unifactorial studies, isolating primary prevention measures and men for cases in which data were separately available (25, 42–46). Overlap exists in the trials that were included; therefore, analyses are not independent. Substantially more violent deaths were found among groups randomly allocated to receive cholesterol-lowering treatment in several meta-analyses; no study found significantly fewer violent deaths. Indeed, for all meta-analyses and for all subject categories (including additional subanalyses [43, 45]), any trend was toward an increased number of violent deaths with reduction of cholesterol level, whether for men or women, primary prevention or secondary prevention, or long trials or all trials. The absolute increase in violent death was similar to the absolute reduction in cardiac death and was statistically more significant than the latter in one meta-analysis that examined both (45) for all but secondary prevention trials. For secondary prevention trials, the trend toward increase in violent death was minimal and the benefit from reduction of cardiac deaths was substantial.

More recent trials of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have also failed to show a marked increase in violent deaths associated with treatment in populations that received secondary prevention measures. The Cholesterol and Recurrent Events trial (47) and the Scandinavian Simvastatin Survival Study (48), which together contain most of the events (49), show 14 violent deaths in treated persons and 11 in controls. The West of Scotland Coronary Prevention Study (50) contains most of the events among the primary prevention trials that used HMG-CoA reductase inhibitors (49). The reported parity between benefit from reduction of cardiac deaths and harm from violent death in primary prevention (45) was not reflected in this study; moreover, violent deaths in the treatment group ($n = 5$) did not exceed those in the control group ($n = 6$), despite large reductions in cholesterol levels with treatment (50).

Temporality

Temporality requires evidence that cause precedes effect: in this case, that low or lowered cholesterol levels precede violence. Meta-analyses that find a statistically significant increase in violent death with reduction of cholesterol levels support this criterion because an increase in violent death followed random allocation to cholesterol-lowering therapy.

The studies included in meta-analyses were not designed to investigate violent outcomes; moreover, meta-analyses can be challenged on the basis of the studies they include. One blinded study performed in order to examine violent outcomes (violent behaviors rather than death) in nonhuman primates assigned to low- or high-cholesterol diets (51) (**Table 5**) showed a significant effect of cholesterol intervention on violence that indicated increased violence in the low-cholesterol diet group. A retrospectively analyzed study of nonhuman primates showed a similar effect (52). Here, data on lowered cholesterol levels provide temporal evidence for the relation of cholesterol levels to violence; however, the relation of lowered cholesterol levels to violence

Table 4. Meta-Analyses of Randomized Trials in Humans: Violent Death in Persons Who Received Cholesterol-Lowering Treatment Compared with Controls

Study (Reference)	Intervention	Sex	Violent Deaths, *n*	Odds Ratio
Muldoon et al. (42)	Primary prevention	Male	105	1.76*
Cummings and Psaty (43)	Primary prevention	Male	115	1.42
Davey Smith and Pekkanen (44)†	Primary prevention	Male	64	1.75‡
Davey Smith and Pekkanen (44)§	Primary prevention	Male	70	1.20
Muldoon et al. (45)	Primary and secondary prevention	Male	150	1.55*
Ravnskov (46)	Primary and secondary prevention	Male and female	Not stated	1.55‡
Cummings and Psaty (43)	Primary and secondary prevention	Male and female	179	1.24
Law et al. (25)	Primary and secondary prevention	Male and female	184	1.17

* $P < 0.01$.
† Group that received drug therapy.
‡ $P < 0.05$.
§ Group that received diet therapy.

Table 5. Aggression in Monkeys Assigned to Low-Cholesterol Compared with High-Cholesterol Diets

Study (Reference)	Sex	Age	Monkeys, *n*	Type of Aggression	Relative Risk for Aggression
Kaplan et al. (51)	Male and female	Juvenile	17	All aggression*	1.5†
Kaplan et al. (52)	Male	Adult	30	Contact aggression‡	2.0§

* Defined by authors to include contact aggression, threats, and displacement of other animal.
† $P < 0.01$.
‡ Defined by authors to include hitting, grabbing, pushing, grappling, and biting.
§ $P < 0.05$.

may have origins and implications that are distinct from those for low cholesterol levels and violence.

Biological Gradient

If a causal connection is present, risk for violent death might be expected to change monotonically across cholesterol quartiles, tertiles, or other groupings used in community cohort studies (although nonmonotonic relations, such as the U-shaped relation seen with cholesterol and death in men, are also possible). Data on the presence of a dose–response relation are available for community cohort analyses that show a significant link between violent death and the group with the lowest cholesterol levels. In **Table 6**, the group with the highest cholesterol levels serves as the reference and is defined as having a relative risk of 1.0. As one progresses from the group with the highest cholesterol levels through intermediate groups to the group with the lowest cholesterol levels, the risk (where it does change) increases monotonically, an effect that is consistent with a biological gradient.

Biological Plausibility

The connection between cholesterol and violence has perhaps most often been criticized on the grounds that it is biologically implausible. However, cholesterol and fats have many roles and may influence brain function and behavior through modification of membranes; myelin; enzyme function; absorption and transport of fat-soluble vitamins and toxins; and steroid hormones and through effects on production, reuptake, or metabolism of neurotransmitters.

Several studies in humans and nonhuman primates (51, 53–57) suggest a specific connection between low or lowered fats or cholesterol levels and low or lowered serotonin activity (**Table 7**). A positive relation between cholesterol and peripheral serotonin was of borderline statistical significance in one psychiatric sample (54) and was statistically significant in a nonpsychiatric analysis that included two measures of cholesterol level (55). More convincing evidence derives from studies in nonhuman primates: Monkeys assigned to diets low in fat or cholesterol showed significantly lower brain serotonin activity (as determined by hormonal measures or cerebrospinal fluid serotonin metabolites) (51, 57). The trend or effect in each study relates low or lowered fat or cholesterol levels to low or lowered serotonin measures.

Meanwhile, much of the literature supports a causal link between low or lowered brain serotonin activity and violence (58–60). Nonhuman primates and other animals with naturally low or experimentally lowered serotonin measures are more aggressive, whether serotonin is reduced by depleting the precursor tryptophan (61, 62), competitively inhibiting tryptophan hydroxylase (the rate-limiting enzyme in serotonin production) (63, 64), lesioning serotonin-producing areas (65, 66), poisoning serotonergic neurons (64, 67), or genetically engineering animals deprived of serotonin 1b receptors (68). Increasing low serotonin or restoring lowered serotonin to higher values returns violent animals to a less aggressive disposition (69–71). Similarly, in humans, low brain serotonin is linked to increased impulsive violence, including homicide, arson, and suicide (an effect that cuts across psychiatric diagnoses) and to violent and repeated suicide attempts (58, 59, 72). Administration of serotonergic drugs has reduced violent behaviors in violent persons who are institutionalized (73–78). Thus, a connection between low cholesterol levels and increased impulsive violence mediated by low serotonin activity is biologically plausible and has some experimental support.

Table 6. Risk for Violent Death by Cholesterol Group in Community Cohort Studies

Study (Reference)	Relative Risk for Violent Death			
	High Cholesterol Level	High Intermediate Cholesterol Level	Low Intermediate Cholesterol Level	Low Cholesterol Level
Jacobs et al. (16)*	1.0	1.08	1.11	1.54
Neaton et al. (17)*	1.0	1.0	1.01	1.28
Lindberg et al. (18)†	1.0	1.79	2.06	2.76‡
Chen et al. (24)§	1.0	3.70	6.26	6.74‖

* Cholesterol groups were as follows: >240 mg/dL, 200 to 239 mg/dL, 160 to 199 mg/dL, and <160 mg/dL.
† Cholesterol quartiles by 5-year age strata.
‡ $P < 0.001$.
§ Cholesterol groups were as follows: ≥179 mg/dL, 159 to 178 mg/dL, 137 to 158 mg/dL, and ≤136 mg/dL.
‖ $P < 0.05$.

Coherence and Specificity

Coherence refers to the fit of a finding with preexisting knowledge. Because a relation of cholesterol to violence dovetails with experimental evidence for a relation of serotonin to violence, the requirement for coherence is supported. Specificity of association is imperfectly satisfied by the relation of cholesterol to violence because low or lowered cholesterol levels have been linked not only to death from violence but to death from other causes, possibly including digestive disease and cancer. However, specificity should not be unduly emphasized (15) because it is routinely violated in causal relations. For example, smoking is causally related not only to lung cancer but also to emphysema and heart disease.

Convergent Validity

Meta-analysis cannot be used to pool data from studies with dissimilar methods or outcome measures. However, it is precisely the convergence of evidence in and across outcome measures and study types that supports construct validity (the ability of a measure to assess the concept of interest [79]) in the relation between low or lowered cholesterol levels and violence. Convergent validity, a form of construct validity, refers to the degree to which measures or items come together to represent the concept (79). Persons with low or lowered cholesterol levels, measured or lowered in any of several ways, score higher on average on each of several measures of violence (although the same persons are not tested in each case). These findings provide converging evidence that supports the relation between cholesterol and violence and the construct of low cholesterol–associated violence.

Convergence can be quantitatively shown by testing the null hypothesis that there is no systematic relation between low or lowered cholesterol levels and violence across studies. According to this null hypothesis, studies of all types should show statistically significant results equally in the positive and inverse directions. For this purpose, aggregation of studies across study types has advantages. Whereas bias from assorted sources may affect individual studies and some sources of bias may be preserved across studies of the same class, biases are less likely to be preserved when different study types and distinct populations and outcome measures are used. Although publication bias may disproportionately restrict the number of nonsignificant results published (80), no current evidence suggests that this type of bias will selectively affect publication of significant positive findings compared with significant inverse findings.

Because the meta-analyses considered here are not independent, all significant meta-analyses are counted as one. Five community cohort analyses examining cholesterol and all violent deaths or suicides, 10 criminal and psychiatric studies, 1 meta-analysis, and 2 experimental studies of nonhuman primates met the inclusion criteria. Across all study types, all 18 studies had statistically significant results that favored a relation between low or lowered cholesterol levels and violence (ratio, 18:0; binomial $P < 0.001$). A less unfavorable ratio (18:2; $P < 0.001$) can be achieved by including a cohort study that showed a significant association between high cholesterol level and suicide (although the association was statistically nonsignificant for violent death overall and, in fact, showed an association between low cholesterol levels and violent death for one examined subset) (20), by excluding studies of nonhuman primates, and by including published find-

Table 7. Effect of Low or Lowered Cholesterol Levels on Serotonin Measures

Study (Reference)	Design	Cohort	Method of Cholesterol Grouping	Effect of Low or Lowered Cholesterol Levels on Serotonin Measures
Ringo et al. (53)*	Observational	Sample of psychiatric patients	Serum cholesterol level	Decreased cerebrospinal fluid serotonin metabolite 5-hydroxyindolacetic acid (19% reduction)
Delva et al. (54)*	Observational	Hypercholesterolemic patients (treatment group) and controls	Serum cholesterol level	Decreased platelet serotonin†
Steegmans et al. (55)*	Observational	Community cohort	Replicated serum cholesterol level	Decreased peripheral serotonin (21% reduction)‡
Kaplan et al. (51)§	Experimental	Juvenile monkeys	High-cholesterol diet compared with low-cholesterol diet	Decreased cerebrospinal fluid serotonin metabolite 5-hydroxyindolacetic acid (43% reduction)‖
Anderson et al. (56)§	Quasi-experimental	Human dieters	Low-fat diet	Decreased tryptophan‖; altered hormonal measure of central serotonin
Muldoon et al. (57)§	Quasi-experimental	Adult monkeys	High-fat diet compared with low-fat diet	Decreased hormonal measure of central serotonin activity (24% reduction)‡

*Studies of low cholesterol levels.
†Relative risk, 0.3; $P = 0.06$.
‡$P < 0.05$.
§Studies of lowered cholesterol levels.
‖$P < 0.001$.

To put the effect of reduction of cholesterol levels on violence or cardiovascular disease into context, the overall (not just cause-specific) risks and benefits of cholesterol level reduction must be considered. No study has systematically addressed overall morbidity, only cardiovascular events. Overall mortality is reduced with cholesterol level reduction by HMG-CoA reductase inhibitors in high-risk men with existing cardiovascular disease (48). However, some studies have found increased overall mortality with cholesterol level reduction in the primary prevention population (91, 92), whereas no study has found a statistically significant reduction in mortality (one came close [50]). Meta-analysis of overall mortality as a function of baseline risk (defined by the rate of cardiac death in the control group) showed statistically significantly increased mortality in low-risk populations assigned to cholesterol reduction therapy (relative risk, 1.22 [95% CI, 1.06 to 1.42]), no effect or a trend toward benefit in moderate-risk populations (relative risk, 0.96 [CI, 0.84 to 1.09]), and statistically significantly reduced mortality in high-risk populations (relative risk, 0.74 [CI, 0.60 to 0.92]) (92). Because reduction of cholesterol level with nonstatin agents has not been shown to yield overall benefit in persons who do not have cardiovascular disease—that is, most candidates for treatment—any evidence of harm should be regarded seriously. However, statins exert benefits distinct from cholesterol reduction (89, 93–96), and the risk–benefit profile seems to be more favorable with these agents.

A recent meta-analysis of randomized trials involving HMG-CoA reductase inhibitors (49) found a reduction in cardiovascular and total mortality even for the so-called primary prevention analysis (with a combined sample of 7961 persons based largely on the West of Scotland Coronary Prevention Study [50]). This analysis failed to show an increase in noncardiovascular deaths with cholesterol reduction; indeed, a trend toward a reduction in noncardiovascular deaths was seen (49). Violent outcomes were not separately evaluated. Additional research is needed to clarify the overall mortality effect in lower-risk primary prevention populations and the effect (if any) on violence in persons with a history of or risk factors for psychiatric illness or violence.

Many vital questions remain about the relation between low or lowered cholesterol levels and violence, offering important avenues for future investigation. These include whether or the manner in which specific lipoprotein subfractions relate to violence, whether demographic, behavioral, or biochemical factors influence susceptibility to low or lowered cholesterol–associated violence and guide evaluation of risk factors (such as age, sex, alcohol use, psychiatric history, or neurochemical or personality measures), and whether serotonergic drugs attenuate an increased risk for violence in at-risk persons who are candidates for cholesterol-lowering treatment.

By showing convergence of evidence for a relation between cholesterol levels and violence and plausible causality in that relation, this analysis supports a connection between low or lowered cholesterol levels and adverse violent outcomes in certain populations and supplements existing data that show a lack of mortality benefit with reduction of cholesterol levels in persons at low or moderate risk (92). Current evidence suggests a more favorable risk–benefit profile with HMG-CoA reductase inhibitors; nonetheless, additional research is needed to clarify the effect of these agents on violence and on overall mortality in less highly selected hyperlipidemic primary prevention populations. Together, these results favor a conservative approach to cholesterol management in hypercholesterolemic persons who are at low and perhaps moderate risk for death from heart disease. Future research should focus on evaluating the association of cholesterol level reduction with illness from all causes, not just heart disease, and on establishing strategies for quantitative assessment of risks and benefits associated with treatment of hyperlipidemia on the basis of characteristics of individual patients.

Disclaimer: The views expressed here are solely those of the author and do not necessarily reflect those of the funding agencies.

Acknowledgments: The author thanks Drs. Robert Brook, Michael Criqui, Naihua Duan, Arlene Fink, Hal Morgenstern, Sally Morton, Terrence Sejnowski, and Paul Shekelle for methodologic advice and assistance and Shannon Bush for help with references.

Grant Support: By grants from the Robert Wood Johnson Clinical Scholars Program and the Harry Frank Guggenheim Foundation.

Requests for Reprints: Beatrice A. Golomb, MD, PhD, Department of Medicine, University of California San Diego/San Diego Veterans Affairs Medical Center, 3350 La Jolla Village Drive 111N-1, La Jolla, CA 92161.

References

1. **Koop CE, Lundberg GB.** Violence in America: a public health emergency. Time to bite the bullet back [Editorial]. JAMA. 1992;267:3075-6.
2. **Alpert EJ.** Violence in intimate relationships and the practicing internist: new "disease" or new agenda? Ann Intern Med. 1995;123:774-81.
3. **Drossman DA, Talley NJ, Leserman J, Olden KW, Barreiro MA.** Sexual and physical abuse and gastrointestinal illness. Review and recommendations. Ann Intern Med. 1995;123:782-94.
4. **Flitcraft A.** From public health to personal health: violence against women across the life span [Editorial]. Ann Intern Med. 1995;123:800-2.
5. **Flitcraft A.** Violence, values, and gender [Editorial]. JAMA. 1992;267:3194-5.
6. **McCauley J, Kern DE, Kolodner K, Dill L, Schroeder AF, DeChant HK, et al.** The "battering syndrome": prevalence and clinical characteristics of domestic violence in primary care internal medicine practices. Ann Intern Med. 1995;123:737-46.
7. **Martinez R.** Injury prevention. A new perspective [Editorial]. JAMA. 1994; 272:1541-2.

8. **Holinger PC, Klemen EH.** Violent deaths in the United States, 1900-75. Relationships between suicide, homicide and accidental deaths. Soc Sci Med. 1982;16:1929-38.
9. **Garber AM, Browner WS, Hulley SB.** Cholesterol screening in asymptomatic adults, revisited. Ann Intern Med. 1996;124:518-31.
10. **La Rosa JC.** Cholesterol agonistics. Ann Intern Med. 1996;124:505-8
11. **Gaziano JM, Hebert PR, Hennekens CH.** Cholesterol reduction: weighing the benefits and risks. Ann Intern Med. 1996;124:914-8.
12. **Muldoon MF, Criqui MM.** The emerging role of statins in the prevention of coronary heart disease. BMJ. 1997;315:1554-5.
13. **Leiker M, Hailey BJ.** A link between hostility and disease: poor health habits? Behav Med. 1988;14:129-33.
14. **Rochet T, Kopp N, Vedrinne J, Deluermoz S, Debilly G, Miachon S.** Benzodiazepine binding sites and their modulators in hippocampus of violent suicide victims. Biol Psychiatry. 1992;32:922-31.
15. **Hill A.** The environment and disease: association or causation. Proceedings of the Royal Society of Medicine. 1965;58:295-300.
16. **Jacobs D, Blackburn H, Higgins M, Reed D, Iso H, McMillan G, et al.** Report of the Conference on Low Blood Cholesterol: Mortality Associations. Circulation. 1992;86:1046-60.
17. **Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, et al.** Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med. 1992;152:1490-500.
18. **Lindberg G, Råstam L, Gullberg B, Eklund GA.** Low serum cholesterol concentration and short term mortality from injuries in men and women. BMJ. 1992;305:277-9.
19. **Vartiainen E, Puska P, Pekkanen J, Tuomilehto J, Lonnqvist J, Ehnholm C.** Serum cholesterol concentration and mortality from accidents, suicide, and other violent causes. BMJ. 1994;309:445-7
20. **Iribarren C, Reed DM, Wergowske G, Burchfiel CM, Dwyer JH.** Serum cholesterol level and mortality due to suicide and trauma in the Honolulu Heart Program. Arch Intern Med. 1995;155:695-700.
21. **Pekkanen J, Nissinen A, Punsar S, Karvonen MJ.** Serum cholesterol and risk of accidental or violent death in a 25-year follow-up. The Finnish cohorts of the Seven Countries Study. Arch Intern Med. 1989;149:1589-91.
22. **Farchi G, Menotti A, Conti S.** Coronary risk factors and survival probability from coronary and other causes of death. Am J Epidemiol. 1987;126:400-8.
23. **Zureik M, Courbon D, Ducimetière P.** Serum cholesterol concentration and death from suicide in men: Paris prospective study I. BMJ. 1996;313:649-51.
24. **Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W.** Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. BMJ. 1991;303:276-82.
25. **Law MR, Thompson SG, Wald NJ.** Assessing possible hazards of reducing serum cholesterol. BMJ. 1994;308:373-9.
26. **Bramblett C, Coelho AM, Mott GE.** Behavior and serum cholesterol in a social group of *Cercopithecus aethiops*. Primates. 1981;22:96-102.
27. **Gallerani M, Manfredini R, Caracciolo S, Scapoli C, Molinari S, Fersini C.** Serum cholesterol concentrations in parasuicide. BMJ. 1995;310:1632-6.
28. **Modai I, Valevski A, Dror S, Weizman A.** Serum cholesterol levels and suicidal tendencies in psychiatric inpatients. J Clin Psychiatry. 1994;55:252-4.
29. **Virkkunen M.** Serum cholesterol in antisocial personality. Neuropsychobiology. 1979;5:27-30.
30. **Hillbrand M, Foster HG.** Serum cholesterol levels and severity of aggression. Psychol Rep. 1993;72:270.
31. **Virkkunen M, Penttinen H.** Serum cholesterol in aggressive conduct disorder: a preliminary study. Biol Psychiatry. 1984;19:435-9.
32. **Gray RF, Corrigan FM, Strathdee A, Skinner ER, van Rhijn AG, Horrobin DF.** Cholesterol metabolism and violence: a study of individuals convicted of violent crimes. Neuroreport. 1993;4:754-6.
33. **Glueck CJ, Kuller FE, Hamer T, Rodriguez R, Sosa F, Sieve-Smith L, et al.** Hypocholesterolemia, hypertriglyceridemia, suicide, and suicide ideation in children hospitalized for psychiatric diseases. Pediatric Res. 1994;35:602-10.
34. **Golier JA, Marzuk PM, Leon AC, Weiner C, Tardiff K.** Low serum cholesterol level and attempted suicide. Am J Psychiatry. 1995;152:419-23.
35. **Sullivan PF, Joyce PR, Bulik CM, Mulder RT, Oakley-Browne M.** Total cholesterol and suicidality in depression. Biol Psychiatry 1994;36:472-7.
36. **Spitz RT, Hillbrand M, Foster HJ Jr.** Serum cholesterol levels and frequency of aggression. Psychol Rep. 1994;74:622.
37. **Hillbrand M, Spitz RT, Foster HG.** Serum cholesterol and aggression in hospitalized male forensic patients. J Behav Med. 1995;18:33-43.
38. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA. 1984;251:365-74.
39. **Frick MH, Elo M, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al.** Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987;317:1237-45.
40. **Dayton S, Pearce ML, Hashimoto S, Dixon W, Tamiyasu U.** Controlled trial of a diet high in unsaturated fat for prevention of atherosclerotic complications. Circulation. 1969;40(Suppl 2):1-63.
41. **Strandberg TE, Salomaa VV, Naukkarinen VA, Vanhanen HT, Sarna SJ, Miettinen TA.** Long-term mortality after 5-year multifactorial primary prevention of cardiovascular diseases in middle-aged men. JAMA. 1991;266:1225-9.
42. **Muldoon MF, Manuck SB, Matthews KA.** Lowering cholesterol concentrations and mortality: a review of primary prevention trials. BMJ. 1990;301:309-14.
43. **Cummings P, Psaty BM.** The association between cholesterol and death from injury. Ann Intern Med. 1994;120:848-55.
44. **Davey Smith G, Pekkanen J.** Should there be a moratorium on the use of cholesterol-lowering drugs? BMJ. 1992;304:431-4.
45. **Muldoon M, Rossouw JE, Manuck SB, Glueck CJ, Kaplan JR, Kaufmann PG.** Low or lowered cholesterol and risk of death from suicide and trauma. Metabolism 1993;42(9 Suppl 1):45-56.
46. **Ravnskov U.** Cholesterol lowering trials in coronary heart disease: frequency of citation and outcome. BMJ. 1992;305:15-9.
47. **Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al.** The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. N Engl J Med. 1996;335:1001-9.
48. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383-9.
49. **Hebert PR, Gaziano JM, Chan KS, Hennekens CH.** Cholesterol lowering with statin drugs, risk of stroke, and total mortality. JAMA. 1997;278:313-21.
50. **Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al.** Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333:1301-7.
51. **Kaplan JR, Shively CA, Fontenot MB, Morgan TM, Howell SM, Manuck SB, et al.** Demonstration of an association among dietary cholesterol, central serotonergic activity, and social behavior in monkeys. Psychosom Med. 1994;56:479-84.
52. Kaplan JR, Manuck SB, Shively C. The effects of fat and cholesterol on social behavior in monkeys. Psychosom Med. 1991;53:634-42.
53. **Ringo DL, Lindley SE, Faull KF, Faustman WO.** Cholesterol and serotonin: seeking a possible link between blood cholesterol and CSF 5-HIAA. Biol Psychiatry. 1994;35:957-9.
54. **Delva NJ, Matthews DR, Cowen PJ.** Brain serotonin (5-HT) neuroendocrine function in patients taking cholesterol-lowering drugs. Biol Psychiatry. 1996;39:100-6.
55. **Steegmans PH, Fekkes D, Hoes AW, Bak AA, van der Does E, Grobbee DE.** Low serum cholesterol concentration and serotonin metabolism in men. BMJ. 1996;312:221.
56. **Anderson IM, Parry-Billings M, Newsholme EA, Fairburn CG, Cowen PJ.** Dieting reduces plasma tryptophan and alters brain 5-HT function in women. Psychol Med. 1990;20:785-91.
57. **Muldoon MF, Kaplan JR, Manuck SB, Mann JJ.** Effects of a low-fat diet on brain serotonergic responsivity in cynomolgus monkeys. Biol Psychiatry. 1992;31:739-42.
58. **Åsberg M.** Monoamine neurotransmitters in human aggressiveness and violence: a selective review. Criminal Behaviour and Mental Health. 1994;4:303-327.
59. **Brown GL, Linnoila MI.** CSF serotonin metabolite (5-HIAA) studies in depression, impulsivity, and violence. J Clin Psychiat. 1990;51(Suppl):31-41.
60. **Coccaro EF.** Central serotonin and impulsive aggression. Br J Psychiatry Suppl. 1989;155:52-62.
61. **Gibbons JL, Barr GA, Bridger WH, Leibowitz SF.** Manipulations of dietary tryptophan: effects on mouse killing and brain serotonin in the rat. Brain Res. 1979;169:139-53.
62. **Kantak KM, Hegstrand LR, Eichelman B.** Dietary tryptophan modulation and aggressive behavior in mice. Pharmacol Biochem Behav. 1980;12:675-9.
63. **Sheard M, Davis M.** p-Chloroamphetamine: short and long term effects upon shock-elicited aggression. Eur J Pharmacol. 1976;40:295-302.
64. **Gibbons JL, Barr GA, Bridger WH, Leibowitz SF.** Effects of para-chlorophenylalanine and 5-hydroxytryptophan on mouse killing behavior in killer rats. Pharmacol Biochem Behav. 1978;9:91-8.
65. **Grant LD, Coscina DV, Grossman SP, Freedman DX.** Muricide after serotonin-depleting lesions of midbrain raphe nuclei. Pharmacol Biochem Behav. 1973;1:77-80.
66. **Yamamoto T, Ueki S.** Characteristics in aggressive behavior induced by midbrain raphe lesions in rats. Physiol Behav. 1977;19:105-10.
67. **Paxinos G, Atrens D.** 5,7 Dihydroxytryptamine lesions: effects on body weight, irritability and muricide. Aggressive Behavior. 1977;3:107-18.
68. **Saudou F, Amara DA, Dierich A, LeMeur M, Ramboz S, Segu L, et al.** Enhanced aggressive behavior in mice lacking 5-HT1B receptor. Science. 1994;265:1875-8.
69. **Miczek KA, Weerts E, Haney M, Tidey J.** Neurobiological mechanisms controlling aggression: preclinical developments for pharmacotherapeutic interventions. Neurosci Biobehav Rev. 1994;18:97-110.
70. **Blanchard DC, Rodgers RJ, Hendrie CA, Hori K.** "Taming" of wild rats *(Rattus rattus)* by 5HT1A agonists buspirone and gepirone. Pharmacol Biochem Behav. 1988;31:269-78.
71. **Berzsenyi P, Galateo E, Valzelli L.** Fluoxetine activity of muricidal aggression induced in rats by p-chlorophenylalanine. Aggressive Behavior. 1983;9:333-8.
72. **Mann JJ, Marzuk PM, Arango V, McBride PA, Leon AC, Tierney H.** Neurochemical studies of violent and nonviolent suicide. Psychopharmacol Bull. 1989;25:407-13.
73. **Gedye A.** Buspirone alone or with serotonergic diet reduced aggression in a developmentally disabled adult. Biol Psychiatry. 1991;30:88-91.
74. **Ratey J, Sovner R, Parks A, Rogentine K.** Buspirone treatment of aggression and anxiety in mentally retarded patients: a multiple-baseline, placebo lead-in study. J Clin Psychiatry. 1991;52:159-62.
75. **Morand C, Young SN, Ervin FR.** Clinical response of aggressive schizophrenics to oral tryptophan. Biol Psychiatry. 1983;18:575-8.
76. **Bioulac B, Benezech M, Renaud B, Roche D, Noel B.** Biogenic amines in 47, XYY syndrome. Neuropsychobiology. 1978;4:366-70.

77. **Bioulac B, Benezech M, Renaud B, Noel B, Roche D.** Serotonergic dysfunction in the 47, XYY syndrome. Biol Psychiatry. 1980;15:917-23.
78. **Sheard MH, Marini JL, Bridges CI, Wagner E.** The effect of lithium on impulsive aggression behavior in man. Am J Psychiatry. 1976;133:1409-13.
79. **Lareau SC, Breslin EH, Meek PM.** Functional status instruments: outcome measure in the evaluation of patients with chronic obstructive pulmonary disease. Heart Lung. 1996;25:212-24.
80. **Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR.** Publication bias in clinical research. Lancet. 1991;337:867-72.
81. **Schuit AJ, Dekker JM, Schouten EG, Kok FJ.** Low serum cholesterol and death due to accidents, violence, or suicide [Letter]. Lancet. 1993;341:827.
82. **Takei N, Kunugi H, Nanko S, Aoki H, Iyo R, Kazamatsuri H.** Low serum cholesterol and suicide attempts [Letter]. Br J Psychiatry. 1994;164:702-3.
83. **Ryan M, Murray FE.** Serum cholesterol concentrations in parasuicide. Scottish study does not replicate findings [Letter]. BMJ. 1995;311:807.
84. **Siguel EN, Lerman RH.** Altered fatty acid metabolism in patients with angiographically documented coronary artery disease. Metabolism. 1994;43:982-93.
85. **Ericsson CG, Hamsten A, Nilsson J, Grip L, Svane B, de Faire U.** Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. Lancet. 1996;347:849-53.
86. **Wannamethee G, Shaper AG.** Blood lipids: the relationship with alcohol intake, smoking, and body weight. J Epidemiol Community Health. 1992;46:197-202.
87. **Suh I, Shaten BJ, Cutler JA, Kuller LH.** Alcohol use and mortality from coronary heart disease: the role of high-density lipoprotein cholesterol. The Multiple Risk Factor Intervention Trial Research Group. Ann Intern Med. 1992;116:881-7.
88. **Gordon T, Doyle JT.** Alcohol consumption and its relationship to smoking, weight, blood pressure, and blood lipids. The Albany Study. Arch Intern Med. 1986;146:262-5.
89. **Massy ZA, Keane WF, Kasiske BL.** Inhibition of the mevalonate pathway: benefits beyond cholesterol reduction? Lancet. 1996;347:102-3.
90. **Pfeffer MA, Sacks FM, Moye LA, Brown L, Rouleau JL, Hartley LH, et al.** Cholesterol and Recurrent Events: a secondary prevention trial for normolipidemic patients. Am J Cardiol. 1995;76:98C-106C.
91. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Report from the Committee of Principal Investigators. Br Heart J. 1978;40:1069-118.
92. **Smith GD, Song F, Sheldon TA.** Cholesterol lowering and mortality: the importance of considering initial level of risk. BMJ. 1993;306:1367-73.
93. **Corsini A, Bernini F, Quarato P, Donetti E, Bellosta S, Fumagelli R, et al.** Non-lipid-related effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Cardiology. 1996;87:458-68.
94. **Harper CM, Fyfe AI.** HMG-CoA reductase inhibitors block multiple events in atherogenesis. Circulation. 1997;96:I677.
95. **Laufs U, Plutzky J, Liao JK.** Upregulation of endothelial nitric oxide synthase by HMG-CoA reductase inhibitors. Circulation. 1997;96:I677.
96. **Williams K, Sukhova GH, Anthony MS, Libby P.** The cholesterol-lowering independent effects of pravastatin on the artery wall of monkeys. Circulation. 1997;96:I607.

And my body which took for food only a single berry became extremely thin and weak. O monks, like the knots of the asitaki plant or the knots of the kalika plant were my limbs and their joints. Like the sides of the crab, so also were my sides. My rib cage was like an old stable with its sides caved in, so that light shines through—so likewise, you could see light shine through my body. The vertebrae of my spine were like the uneven contours of a braid of hair—high and low, uneven. So were the vertebrae of my spine. Like a gourd cut too young which has withered and finally dried up completely, my head withered until it looked old and wrinkled and dry. Like the reflections of the stars in a well during the last month of summer when the water is so low the reflections are difficult to see, so also my eyeballs sank in, becoming difficult to see. Like the foot of the goat or the hoof of the camel were my shoulders, my stomach, my chest, and the rest.

And, monks, when I thought I was touching my stomach with my hands, it was my spine that I was feeling. When I tried to get up, I was so bent over that I fell backwards. When with difficulty I again got up, and rubbed my limbs with dust, all the hairs came away from my body. Through the rough self-abasement I was undertaking, my former beautiful and delicate complexion disappeared. And the people who dwelt in the neighboring village thought: "Ah, truly, he is black, the Sramana Gautama! Ah, truly, he is dark blue, the Sramana Gautama! Ah, truly, the Sramana Gautama is the color of the madgura fish! His former beautiful and clear complexion has disappeared!"

The Lalitavistara Sutra
The Voice of the Buddha: The Beauty of Compassion, volume II
Berkeley, CA: Dharma Publishing; 1983

Submitted by:
Nayan Kothari, MD
New Brunswick, NJ 08903

Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation, as done for any reference.—*The Editor*