If High Blood Cholesterol Is Bad — Is Low Good?

E. Cheraskin, M.D., D.M.D.[1]

Today, by act if not by word, you either have a high blood cholesterol or you don't. In other words, if your cholesterol is high, that's bad; if it isn't high — that's good. Implied, if not so stated, in all of these discussions is that there is some kind of a linear, some sort of a straight-line relationship. Since *high* blood cholesterol seems to be bad for us, and the *higher* it is the worse it is, it logically follows that low blood cholesterol must be good — and the lower the better.

What we haven't considered, at least so far (and very few of the so-called experts ever do) is the common sense of the problem. No one — but no one, for example, will argue with the point that it's surely bad to be too tall — as it is to be too short. There is, likewise, no disagreement that there is abundant corroborative evidence that it's not a good idea to be too fat — or too thin. Who'll question that pathologic consequences are observed when we're too hot — or too cold. The point of these, and almost countless other, such common sense examples is that there is a plethora of hard data in the scientific pool which underlines that all, yes all, physiologic (like height and weight and temperature) and biochemical (such as blood glucose and uric acid) parameters are parabolically (a fancy word for curvilinear) distributed, and not linear. Common sense would, therefore, suggest that hypercholesterolemia (the high-falutin designation for low blood cholesterol) must be just as clinically important, just as dangerous, just as diagnostic and predictive as hypercholesterolemia (high blood cholesterol).
The logic is there — but are the facts?

The simplest and the most convincing as well as the most incontestable proof was observed in the inmates of concentration camps during World War II. As a matter of fact, hypercholesterolemia was reported with regularity in all cachectic states such as with starvation and consuming diseases like cancer and tuberculosis. Blood cholesterol concentrations as low as 100 mg per cent or even less are the rule. While the complete mechanism is still not entirely clear, it is surely more-or-less related to the diminished total food and fat intake. But even in these dramatic instances, increased loss of cholesterol by diminished reabsorption cannot be discounted. Whatever the sequence-of-events, here is an undeniable demonstration of an undesirably low blood cholesterol level.

It has also long been known (and this can be confirmed by checking any standard medical textbook) that there is a significant correlation between the level of blood cholesterol and certain hormonal states. The most glaring examples are the hypercholesterolemia found with hypothyroidism (low thyroid state) and the hypercholesterolemia associated with hyperthyroidism (hyperactive thyroid state). A less common but more graphic example of blood cholesterol may be found with Addison's Disease. This syndrome is characterized by chronic adrenocortical insufficiency (in the old days most often due to tuberculosis).

Also well-known in traditional medical circles is the fact that specific as well as generalized disorders which distort liver metabolism may interfere with the synthesis of cholesterol in the liver, producing blood cholesterol levels under 100 mg per cent. Hence, one notes hypercholesterolemia with infections, for instance, and acute exacerbations (flare-ups) of chronic syndromes such as alcoholism.

Two points must be underlined. First, many well-established syndromes may be accompanied by hypercholesterolemia. Second, this information has been known for a long time and is readily available in the standard and traditional textbooks.

1. Box 20287 Vestavia Hills, Alabama 35216-0287

But is there more and better "new" proof?

Within the past few decades, there's been increasing information along five different but interdependent directions, all with the same thrust — that low blood cholesterol is not a desirable biochemical state. First, we'll look at the work which demonstrates that hypercholesterolemia parallels nonspecific disease states in general as expressed by mortality (death) figures. Secondly, there's some evidence that hypercholesterolemia is, in some still-to-be-established way, in parallel with nonspecific pathologic states as judged by morbidity (sickness) data. Thirdly, there is a considerable body of fact with regard to specific medical problems, notably cancer and hypercholesterolemia. Fourth, one can't dismiss the possibility of both hyper- and hypercholesterolemia being associated with the same or similar problems. Fifth, there's some scientific support to suggest that low as well as high blood cholesterol may, in fact, be associated with cardiovascular pathosis. Finally, there's exciting data about low cholesterol and general behavior and specific mental problems.

Now back to square one — what do we know to suggest a relationship between low blood cholesterol and general well-being and disease? Doctor Robert Beagle-hole and his colleagues reported in 1980 in the *British Medical Journal* a prospective study of over 600 persons with at least half Maori ancestry living in New Zealand. They collected several health characteristics of this group in 1962-1963 and compared mortality data for the intervening years. It was discovered that low blood cholesterol levels (specifically less 200 mg per cent) was paralleled by greater than expected mortality due to cancer and other causes of death even when data were corrected for poor initial health, blood pressure, and excessive weight for height. While these researchers were careful not to overextend these observations to the general population, they did recommend that attempts to decrease blood cholesterol in this population were contraindicated.

Just one year later, Doctor P. Oster and his cohorts at the Klinisches Institut fur Herzinfarktforschung an der Medizin-ischen Universitatsklinik Heidelberg studied hypercholesterolemia (less than 120 mg per cent) in 200 out of 3700 patients admitted consecutively to the University Department of Internal Medicine. Mortality in this group was 32%. When diagnosis was grouped in 5 categories, prognosis was particularly poor in heart problems (36%), liver disease (31%), and with malignant states (33%). They concluded "... it appears that in our population severe hypercholesterolemia usually is a sign of severe and possibly life-threatening disease." And so, within the limits of this and similar studies, there's some evidence that there's a positive correlation between low blood cholesterol levels and mortality state even though the mechanism is still open to argument.

Now to the second point — what about low blood cholesterol and morbidity (sickness) figures? The Director of the Clinical Laboratories at the University of Utah, Dewitt T. Hunter, M.D. attempted to answer this question in the October 1966 issue of *Minnesota Medicine.* He examined over 750 consecutive low (less than 150 mg per cent) blood cholesterol levels. This represented about 3.4% of the total choles-terols assayed. He concluded that thyroid hyperactivity, certain liver diseases, patients on profoundly low-fat diets, hypo-functioning of the pituitary and adrenal glands, and collagen vascular disorders were the principal groups of problems most often associated with low blood cholesterol.

Doctor Grace Oladunni Taylor, Senior Lecturer in the Department of Chemical Pathology at the University of Ibadan in Nigeria and Afolabi E. Bamboye, a Lecturer in the Department of Preventive and Social Medicine did a retrospective study of 3451 serum cholesterol determinations in the light of their medical problems. While there are some differences between their observations and those of Doctor Hunter, there are more agreements as judged by their conclusion, "It is worthy of note that most disease states caused either a decrease in serum cholesterol or no significant change." And so, within the limits of available reporting, we can conclude that hypercholesterolemia and a sizable number of varied and diverse disease states are related — precisely how is still

in most cases to be unravelled.

Number three. Aside from the nonspecific mortality and morbidity figures already cited, have there been any efforts to relate low blood cholesterol to any specific disease state or cluster of syndromes? The quick answer is a resounding yes! The more detailed and accurate response is that the principal thrust has been to study hypercholesterolemia and cancer. More papers have appeared, more arguments have been held, more conclusions have been made than time and space will allow.

An editorial from the National Institutes of Health (NIH) appeared in the 4 July 1980 issue of the *Journal of the American Medical Association* entitled "Cholesterol and Non-cardiovascular Mortality". The release stemmed from a meeting held at the National Institutes of Health under the auspices of the National Heart, Lung, and Blood Institute (NHLBI) to review data from eight epidemiologic studies relating serum cholesterol levels and mortality from non-cardiovascular causes. Data from four of these studies suggested that very low blood cholesterol levels (below 180 mg per cent), while paralleling very low mortality from coronary heart disease, may be associated with an increase in the subsequent mortality risk from various types of cancer. Two of the most clear cut conclusions by the panel were, "The panel agreed that available data are insufficient to conclude that there is a causal relationship between low cholesterol and cancer risk... It may turn out that the lowest end of the blood cholesterol distribution (levels below 180 mg per cent) may not be optimal from the standpoint of overall mortality, even as the upper end of the distribution is disadvantageous from the standpoint of cardiovascular disease mortality. The former remains to be demonstrated; however, the latter is well documented."

Another workshop sponsored by the National Institutes of Health's National Heart, Lung, and Blood Institute and the National Cancer Institute concluded, "Data from 17 international studies presented recently at the Workshop on Cholesterol and Non-Cardiovascular Mortality did not substantiate any direct cause-and-effect relationship between low blood cholesterol levels and cancer."

These "official" reports should have ended the matter — but they didn't! Abraham M. Y. Nomura, M.D. and his team at the Japan-Hawaii Cancer Study and Honolulu Heart Study, in the 16 April 1982 issue of the *Journal of the American Medical Association* contends that a low serum cholesterol in cholecystectomy (surgically removed gall bladder) patients may be related to an increased risk for right-sided colon cancer. The International Collaborative Group, in their paper entitled "Circulating Cholesterol Level and Risk of Death from Cancer in Men Aged 40 to 69 Years" contend "... that lower cholesterol levels in cancer decedents are due to the effect of undetected disease on cholesterol level."

The one inescapable agreed-upon-point is that the relationship of low cholesterol should continue to be monitored.

The fourth point — the possibility that both low and high blood cholesterol may be associated with the same or similar medical problems. We here at the University of Alabama Medical Center in 1969-1970 studied 391 dentists and their spouses in a survey in which a comparison was made of reported cancer versus nonfasting serum cholesterol concentration. First, and foremost, we discovered that the relationship was not linear but curvilinear (parabolic). In other words, the greatest incidence of reported cancer occurred at both extremes, hypo- and hypercholesterolemia. What was even more significant was the fact that, actually, the least evidence of cancer correlated with a relatively narrow range of blood cholesterol. The findings which we reported in the August 1971 issue of the *Journal of the American Geriatrics Society* showed, in 45 + year olds, the least number of cases of cancer (10%) with a serum cholesterol range of 210 to 240 mg per cent. The greatest number of cancer cases, actually 30%, was noted in those persons with a blood cholesterol below 210 mg per cent; 26% of those with high blood cholesterol reported cancer. In short, the point to be underscored is that reported cancer was threefold greater in the hypercholesterolemic group; 2.6 fold greater with high blood cholesterol. Here we demonstrated the possibility that blood cholesterol, at both ends, parallels cancer.

This was not the end of the story. Approximately ten years later, Bo Peterson, M.D., and his colleagues from the Departments of Preventive Medicine and Pathology at the University of Lund and the Malmo (Sweden) General Hospital reported 86 deaths which occurred from zero to five years after a screening survey of 10,000 middle-aged men in Malmo. The mortality pattern showed two peaks, one at the higher end of the blood cholesterol distribution and the other at the lower of the scale. The first peak corresponded to the cardiovascular deaths while the second peak corresponded to the noncoronary death causes including cancer (which is relevant here) and alcohol-related deaths (which will be mentioned later in this report).

What is evident, for the first time, is the fact that blood cholesterol appears to be a marker or signal of wellness and what might be called the syndrome of sickness with significance at both ends of the scale.

Apropos, as we have been told, the emphasis in scientific medicine has been that high blood cholesterol parallels heart disease, specifically heart attacks. Implied is that the lower the blood cholesterol, the less the risk of a heart attack and possibly the lower the risk for all cardiovascular problems. The fact of the matter is that Doctor Hirotsuga Ueshima and his team in the Department of Epidemiology and Mass Examination for Cardiovascular Diseases at the Center for Adult Diseases in Osaka (Japan), in a fascinating report released in 1979 in *Preventive Medicine* questioned the practice of maintaining the total serum cholesterol as low as possible to prevent coronary heart disease and cerebral (brain) stroke. From a ten-year study which they conducted in Japan (where heart attacks are relatively rare but strokes are common), they reported a significant negative correlation between total serum cholesterol (cholesterol levels between 150 and 200 mg per cent) and both cerebral hemorrhage and cerebral infarction. In their own words, "The mortality rate for strokes increases in groups with a total cholesterol level lower than 160 mg per cent." They note further that "our results suggest that the desirable level of total serum cholesterol in men may be somewhere between 180 and 200 mg per cent, where incidence rates for both coronary heart disease and stroke are low." Hence, here is an excellent demonstration that high and low are both undesirable and that they are both in parallel with cardiovascular problems.

But the last of the vignettes is the thriller—the what might be rightly called the mystery miniseries, "The case of the accidental accidents."

Without question, one of the most famous scientific as well as public news-breakers was the project on high blood cholesterol and coronary heart disease (CHD) known in the scientific trade as the Lipid Research Clinics Coronary Primary Prevention Trial. More often referred to by the awkward LRC-CPPT, it is a mul-ticenter, randomized, double-blind and very costly study intended to test the efficacy of cholesterol-lowering in reducing the risk for coronary heart disease in 3806 asymptomatic (meaning presumably healthy) middled-aged men with so-called primary hypercholesterolemia.

The therapy group was administered the bile acid sequestrant cholestyramine resin, while the control subjects were provided a placebo for an average of 7.4 years. Additionally, both groups followed a moderate cholesterol-lowering diet. The experimental groups, that is the cholestyramine-treated subjects, experienced an average plasma total cholesterol reduction of 13.4% which was 8.5% greater decrement than observed in the placebo group. More to the point of the project, the cholestyramine group demonstrated a statistically significant 19% decline in the risk of the primary end-point-definite CHD disease and/or clearcut nonfatal myocardial infarction (meaning heart attack). All in all, this translates into a 24% decline in cardiovascular deaths and a 19% reduction in nonfatal myocardial infarctions.

In the abstract which appears at the beginning of their report (released in the 20 January 1984 issue of the *Journal of the American Medical Association),* they add, "the risk of death from *all* (italics added) causes was only slightly and not significantly reduced in the cholestyra-mine-treated group." The fact that heart disease deaths declined but overall death

did not requires an answer and it is indeed provided in that report. "... because of a greater number of violent and accidental deaths in the cholestyramine group." Much later in the report, the possibility that CHD events could have been the underlying cause of violent and/or accidental death was indeed examined. In fact, all of these deaths were evaluated by the Cardiovascular Endpoints Committee without any knowledge of the treatment category. In their august opinion, none had met the study criteria of a cardiovascular demise. None had even a suggestion of a reduced blood supply to the heart muscle (so-called myocardial ischemia). Follow-up studies revealed that 7 were due to homicide or suicide and in none was there any question about the diagnosis. Autopsy studies for 7 of the 8 accidental deaths disclosed that 7 were due to automobile or motorcycle accidents. Absolutely not one had new evidence of coronary thrombosis (blood-clot) or muscle infarction. And they concluded well along in the report, "Excess mortality in (this study) was confined to violent and accidental deaths. Since no plausible connection could be established between cholestyramine treatment and violent or accidental death, it is difficult to conclude that this could be anything but a chance occurrence."
The matter seemed closed.

Not quite. The issue appeared finished until Matti Virkkunen, a Finnish medical physician on the staff of the Psychiatric Clinic at the Helsinki University Central Hospital picked up the story in a Letter-to-the Editor (1 February 1985 issue) of the *Journal of the American Medical Association* entitled, "Lipid Research Clinics Coronary Primary Prevention Trial Results." Responding to the earlier conclusion of a chance occurrence, he retorts "... There have recently been findings that impulse homicidal and suicidal aspects can be connected with low cholesterol levels. .." He continues to remind us of information obviously not available to the LRC-CPPT experts, "low serum cholesterol levels have been found to be related to poorly internalized social norms, irresponsibility, and poor self-control. And one earlier coronary heart project, which used prisoners as a control group, found that the prisoners had very low cholesterol levels. .." And on the basis of this information, he concludes, "So there is the possibility that the high figure of violent and accidental deaths was not a matter of chance but the result of cholesterol lowering or some metabolic aspects connected with this, making some males more prone to impulsive violent death."

And so, perhaps there is less of a mystery than we had thought. It just may be that, with the current consuming interest in high blood cholesterol and heart disease, it has been overlooked that, during the twenty-year period between 1925 and 1945, the principal thrust and concern dealt with the possible interconnections of blood cholesterol concentrations to the diagnosis and prognosis of mental health and disease. The general consensus during those days was threefold. First, acutely disturbed and so-called excited schizophren-cis displayed higher blood glucose levels than the more chronic and anergic schizophrenics. Secondly, during exacerbations of manic-depression psychosis, blood cholesterol levels were higher than during episodes of comparative mental health. Third and lastly, high blood cholesterol scores during acute psychiatric periods paralleled better prognosis for recovery.

With time, the emphasis then shifted from so-called classical mental disease to observations in the general population and to correlations between general behavioral characteristics and cholesterol. Under this approach, it was observed that medical school examinations, end-of-month reports, and other psychologic stressors tend to raise blood cholesterol. It was also during this era that it was recognized that personality profiles characterized by competitiveness, strong drive, high energy output are paralleled by sustained elevations in blood cholesterol.

In that time and with that backdrop, Ivan W. Sletten and his colleagues in the Department of Physiologic Hygiene at the University of Minnesota in Minneapolis and the Hastings State Hospital in Minnesota in January 1962 completed serum cholesterol determinations on the male patients of Hastings State Hospital between the ages of 35 and 65 years. Of the 184 patients sampled, the 20 with the highest

cholesterol scores were put in one, the high, group; the 20 with the lowest values in another, the low group. Subsequent measurements were repeated in February and in July as well as August of the same year. The consistency was remarkable as judged by the fact that all but 5 remained in the same category. Two former psychiatric-nurse supervisors rated all 40 patients after several weeks of ward contact. On two different occasions, separated by two weeks, they graded each patient using the Brief Psychiatric Rating Scale (developed by Overall and Graham), and Nurses Evaluation Scale (utilized routinely in the Veterans Administration), and the Psychotic Reaction Profile (originated by Lorr). The raters were unaware of the blood-lipid levels.

To make a very long story short, the low-cholesterol subjects were statistically significantly more regressed and withdrawn with distinctly less evidence of initiative and positive mental health.

Just two years later, there appeared an editorial in the May 1966 issue of *Circulation* by Howard B. Sprague, M.D. What this researcher and his colleagues did was to compare by means of a battery of metabolic tests 20 young men who survived an acute myocardial infarction and compared the findings with those obtained from twenty age-matched "healthy subjects — 10 business and professional men and 10 prisoners." And, in his own words, he concludes, "One interesting finding was the low serum cholesterol, and small variance, in the prisoners."

Here we observe, in a different group of allegedly "healthy" persons (prisoners), the same pattern earlier reported in mental hospital patients with a specific behavioral constellation.

That was in 1966 — three years later Jenkins and his team published a report in *Psychosomatic Medicine* the result of administering the California Psychological Inventory (also known as the CPI) to 34 California firemen. This same psychometric instrument was tested in male supermarket employees in Georgia. In simple lay language, the clinical interpretation of the findings is that the man who is especially adherent to social norms, places high value on being dependable and conscientious, and is self-critical, is more likely to show a relatively higher serum cholesterol level.

And so, once again, in a more common population, in this case firemen and supermarket workers, we find the same trend.

Doctor Matti Virkkunen, the investigator, you may recall, who blew the whistle on the not-so-accidental-accidents reported earlier in the multicenter study described in the *Journal of the American Medical Association,* published a paper about ten years after the firemen-supermarket report in Neuropsychobiology. His data were collected from criminals who, on court order, in the years 1973 to 1976, were subjected to mental examination in a special ward of the Psychiatric Clinic at Helsinki University Central Hospital. Fasting serum cholesterol concentrations were measured in 274 subjects with personality disorders, who had committed criminal offences. Of this entire group, 139 were found to possess what is defined in psychiatric circles as antisocial personality. The others were considered as controls. There was no question but that, age-matched, the group of subjects with antisocial personality displayed a distinctly lower mean level of serum cholesterol than the group with other personality disorders. For example, the 15 to 19 year old with the antisocial personality had a mean serum cholesterol of 179 mg per cent; those with other personality disorders 224 mg per cent.

The studies continue, and largely in Finland, and mostly by Matti Virkkunen and his colleagues at the Helsinki University Central Hospital. For example, fasting serum cholesterol concentrations were ascertained in 280 male homicidal offenders (and reported in 1983 in *Neuropsychobiology).* It was discovered that those with an antisocial personality or an intermittent explosive disorder with habitually violent tendency in both, when under the influence of alcohol, showed a lower mean level of serum cholesterol than did other offenders.

Finally, Matti Virkkunen and Hannu Penttinen released a report in March 1984 in *Biological Psychiatry* as a preliminary investigation to discover whether a low serum cholesterol in boys and male

adolescents with attention deficit disorders can be employed as an indication that they also have an aggressive conduct disorder. Of the 47 boys with attention deficit disorders, 22 (47%) also had aggressive conduct disorders. These youngsters did not differ from the other attention deficit disorders in age, weight, or height. However, the cholesterol levels were clearly lower in the aggressive conduct disorder group versus the controls.

The case is not closed; there are obviously many still-to-be-found pieces in the puzzle. However, four points are already crystal-clear. First, since extremes in all studied physiologic and biochemical parameters are unhealthy, sheer common-sense suggests that low blood cholesterol must also parallel pathosis. Secondly, what evidence there is suggests that, when studied more extensively, every cell, tissue, organ and site will reflect pathology associated with hypercholesterolemia. Third, most of the clinical information is correlative and, therefore, may not necessarily reflect cause-and-effect. However, the data may sharpen up once we've established how low is low. In this regard, parenthetic mention should be made that the studies reported in this report cited levels from as low as below 100 mg per cent to as high as less than 210 mg per cent as endpoints for low blood cholesterol.

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