9

PROGRESS IN CARDIOLOGY

Edited by

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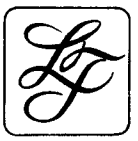

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PREFACE

Volume 9 of PROGRESS IN CARDIOLOGY is comprised of eight chapters contributed by cardiologists and scientists from five continents.

In the first chapter, Dr. Michael F. Oliver reviews critically and thoroughly six clinical trials in which plasma cholesterol was lowered in healthy individuals, in an effort to prevent coronary heart disease. Detailed discussions focus on three trials, and the results of the three other trials are briefly mentioned. The data suggest an appreciable reduction of plasma cholesterol as a result of treatment, a significant reduction in the incidence of nonfatal myocardial infarction, but no change in the incidence of angina pectoris or fatal myocardial infarction. On the other hand, in the populations studied there was a significant increase in the mortality rate due to noncardiovascular diseases, as well as a substantial increase in the incidence of gallstones. Dr. Oliver concludes, based upon available information, that reduction of plasma cholesterol by a diet low in saturated and high in polyunsaturated fats or by use of clofibrate cannot be recommended on a community-wide basis.

Management of the late phase of acute myocardial infarction is discussed by Dr. J. Graeme Sloman in the second chapter. An outline is presented of those clinical indices that should be assessed during this recovery period and that may be associated with an unfavorable prognosis. Although the impact of an intermediate coronary care unit (CCU) remains uncertain, Dr. Sloman concludes that it would be advisable to transfer patients out of a CCU to an area where continued monitoring, resuscitative equipment, emergency drugs, and trained nurses are readily available. The rationale for performing a limited exercise stress test prior to discharge from the hospital is discussed. In the posthospital phase, certain unfavorable prognostic factors also can be identified. The chapter concludes with a succinct description of various secondary preventive mea-

sures and a comprehensive rehabilitation program.

In Chapter 3, Dr. Benjamin N. Chiang and associates present a lucid summary of their experience in the detection of postinfarction ventricular aneurysm, using cross-sectional echocardiography and radionuclide ventriculography. They feel that clinical, electrocardiographic, and radiologic findings are either insensitive or nonspecific for definitive diagnosis of a ventricular aneurysm. Combined use of cross-sectional echocardiography and radionuclide ventriculography successfully identified the presence of postinfarction ventricular aneurysm in 18 patients, confirmed by ventricular angiography. No false positive finding was encountered in a control group of 17 patients with documented coronary artery disease but no ventricular aneurysm. It would appear that these two noninvasive techniques are useful for the detection of possible ventricular aneurysm and may obviate the necessity and risk of invasive studies in many patients in whom global left ventricular hypokinesia, but no aneurysm, is observed.

Drs. Hugh A. Fleming and S. S. B. Newsom summarize in Chapter 4 the recent advances in investigation, prophylaxis, and management of infective endocarditis. Causative organisms, experimental endocarditis, and various types of antibiotics are discussed. The authors emphasize the high-risk situations and procedures that may lead to occurrence of infective endocarditis, and they identify groups of patients who are highly susceptible to this disease. Specific measures for medical prophylaxis, particularly for high-risk patients, are recommended. In the final section of this chapter, a comprehensive account of both medical and surgical treatment of endocarditis is presented.

In the fifth chapter, Drs. Jonathan J. K. Best and Brian R. Pullan review the current status of computed tomographic (CT) scanning of the heart. The basic principles of CT scanning, with special reference to cardiac scanning specifications, are discussed. At the present time CT scanning is useful for two clinical problems: (1) distinction between cardiac and pericardial masses and (2) detection of occlusion of aortocoronary vein grafts. It also has been applied with some success to the diagnosis of ventricular aneurysm, intracardiac calcification, and some congenital cardiomyopathies. CT scanners specifically designed to image the heart appear technically feasible and promise to be powerful research tools in the future. However, clinical application of this technique is still limited because of many factors, including total amount of intravenous contrast required, magnitude of radiation dose, and high costs.

In Chapter 6, Drs. Jay W. Mason and Margaret E. Billingham give a detailed, timely, and authoritative report of the history, technique, complications, and diagnostic value of myocardial biopsy. This procedure is indicated and specifically useful in the assessment of acute cardiac transplant rejection, diagnosis and grading of adriamycin cardiotoxicity, and detection of acute inflammatory myocarditis. It is also helpful in the diagnosis of cardiac sarcoidosis, cardiac amyloidosis, endomyocardial fibrosis, and hemochromatosis. However, in cases of idiopathic congestive cardiomyopathy the overall results of myocardial biopsy have been disappointing.

Dr. George Cherian and co-workers report in Chapter 7 some problems encountered in the practice of cardiology in India. No appreciable reduction has been observed in the incidence of chronic valvular heart disease, although there has been a decline in incidence of acute rheumatic fever. The role of viral infection as a cause of myocarditis and valvulitis has been speculated upon, but the clinical evidence is not strong. Unusual features of rheumatic heart disease and various aspects of purulent pericarditis are described. Isolated pulmonary valvular stenosis is encountered frequently. A section of the chapter is devoted to the description of a plant, *Cerbera odollam,* the active glyco-

side (cerebrin) of which has a profound vagotonic inhibitory effect resulting in bradyarrhythmia, hypotension, and atrioventricular block.

In the last chapter of this volume, Drs. C. O. Adesanya and Eldryd H. O. Parry discuss heart disease in Africa. There is no specific pattern of heart disease in Africa. Cardiac infections and idiopathic cardiomyopathy or congestive cardiomyopathy are observed frequently. Peripartum cardiac failure, a special form of congestive cardiomyopathy, has been observed in healthy women during their last trimester of pregnancy and the first few months postpartum. The clinical features, course, and pathologic changes encountered in this disease are described. Although the etiology is still unknown, a combination of increased left ventricular preload and afterload as contributing factors is suspected. As the life-style changes and various risk factors become more dominant among local residents, the incidence of coronary artery disease and hypertension will probably rise.

Volume 10 of PROGRESS IN CARDIOLOGY is in preparation and will include chapters dealing with predictions of future trends in cardiovascular disease, written by leading experts from both sides of the Atlantic Ocean.

We are grateful to Mrs. Beth Nestorowycz and Mrs. Sharon Postwick for their assistance and support in handling the correspondence, mansucripts, and proofs.

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CONTENTS

Chapter 1

PRIMARY PREVENTION OF CORONARY HEART DISEASE: AN APPRAISAL OF CLINICAL TRIALS OF REDUCING RAISED PLASMA CHOLESTEROL

Michael F. Oliver

Does reduction of raised concentrations of plasma cholesterol lead to a decrease in the incidence of coronary heart disease (CHD)? The last decade has witnessed extraordinary confusion about this question in the minds of many scientists, physicians, and educationalists. This is partly due to the cursory attention given to the available facts and to casual interpretation of them and partly to medical prejudices and wishful thinking. Polarized lobbies, formed to protect vested interests and designed to influence national policies, have added to the confusion.

The only responsible way to answer the question is on the basis of available facts. An apparent consensus of opinions is not enough. It is the purpose of this chapter to review these facts succinctly and to attempt an assessment of them. The facts can be separated into three components. One is the indisputable epidemiologic data showing an approximate exponential relationship in otherwise healthy adults between increasing concentrations of plasma cholesterol and increasing incidence of CHD. A second is that it is relatively easy, under conditions of clinical research, to reduce elevated concentrations of plasma cholesterol; but this has had the non sequitur that the incidence of CHD can be presumed to be less in individuals so treated. A third is the actual results of clinical trials specifically designed to document the effects of lowering raised plasma cholesterol on CHD incidence and morbidity and mortality from all causes. This last approach is the only one which provides firm evidence concerning what can be done in middle-aged men and women *and should be the only admissible evidence in determining future policy with regard to prevention and treatment.*

This chapter will provide an appraisal of the existing primary prevention trials. It is timely for this to be done, since two of the three major studies have recently reported their findings and the fourth will not be completed for at least another 5 years. Furthermore, these trials are often regarded as too difficult to interpret. Nevertheless, there

is a considerable degree of consistency in the outcome of the major trials and new and potentially fundamental questions have also been raised, and these need to be examined.

CLINICAL TRIALS OF LOWERING PLASMA CHOLESTEROL

The "lipid hypothesis" asks the question whether reduction of elevated serum cholesterol in middle-aged men leads to reduction in CHD events and, if so, whether the extent of this is commensurate with that to be expected from the degree of lowering of plasma cholesterol, as derived mathematically from the known positive relationship between increasing concentrations of serum cholesterol and increased CHD risk.[1] The three clinical trials, which will be appraised, concerning the effectiveness of reducing raised concentrations of plasma cholesterol on the incidence of CHD in healthy men are two in which a dietary change was made so that there was a decrease in saturated and an increase in polyunsaturated fat (the Los Angeles Veterans Administration Study[6] and the Helsinki Mental Hospital Study[16]) and one in which a drug was used without a dietary change (the WHO Clofibrate Trial[21]). Brief mention will be made of the Anti-Coronary Club Trial using a polyunsaturated fat diet,[22] the United Airlines Clofibrate Trial,[12] and the ongoing Lipid Research Clinic Trial using cholestyramine.[18] Smaller studies, shown by subsequent experience to contain too few numbers or to be conducted for too short a time to provide any definitive answer, will not be included. These clinical trials were designed to lower elevated plasma cholesterol and are, by definition, single risk factor control trials not taking into account spontaneous or related changes which may occur in other risk factors. One view, increasingly heard, is that the control of one risk factor is only of academic interest, probably not practicable anyway, and what is really required is to judge the effects of controlling all available risk factors at the same time. There are good studies under way to assess the effectiveness of multiple risk factor intervention.[9,23] These arguments should not obscure, however, the need to gain information about the value or lack of value of lowering a single risk factor, particularly when it is, as in the case of plasma cholesterol, a fundamental part of the body's metabolism.

There are many problems with regard to testing the effectiveness of primary control of hypercholesterolemia apart from the complexity of mounting huge trials. One is the heterogeneous nature of the population under study with regard to other risk factors. This has, to an extent, been resolved by the use of large numbers with consequent randomization of characteristics in the populations allocated to active and control treatments.

A problem receiving scant attention, however, is that many differences exist in the metabolism of cholesterol in individuals with raised concentrations of plasma cholesterol. Until recently it has not been possible to construct a large primary prevention trial taking into account in the randomization procedures differences in lipoprotein concentrations, such as the low density (LDL)/high density (HDL) ratio.[1,8] Even now, the measurement and evaluation of lipoprotein or apoprotein abnormalities is insufficiently advanced to allow random allocation of those who are metabolically alike to treatment and control groups. Furthermore, uniform reduction of plasma cholesterol is unlikely to be achieved because of different sizes of body pools of cholesterol, different kinetics of synthesis and removal, and differences in dietary intake of fat and cholesterol. Even if it were possible to achieve uniform reduction of plasma cholesterol, the biologic effects could not for the same reasons be expected to be uniform.

Another problem is that there is no way of knowing the proportion of men with a given serum cholesterol concentration, of say, 7.5 mmol/l, who have had this level for many years, for a few years, or even had

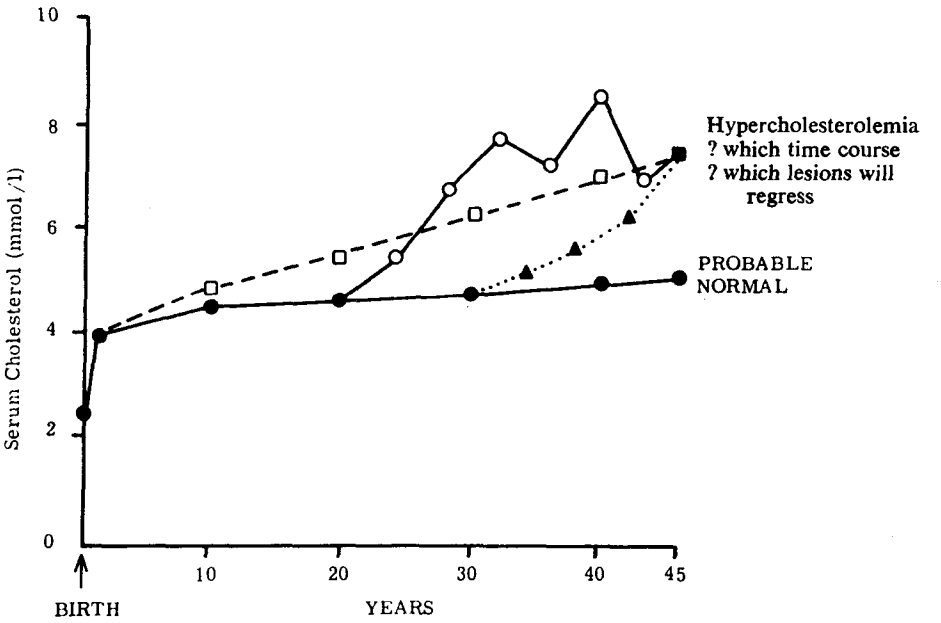

Fig. 1. Significance of serum cholesterol levels in relation to age. This illustrates how little we know about the natural history of serum cholesterol, or other serum lipid concentrations, in relation to age and time. It is generally assumed that a steady increase of serum cholesterol from childhood is a worse situation than either of the other two represented possibilities. This need not be so, since abrupt fluctuations or a sudden rise in serum cholesterol concentrations might be associated with more florid arterial disease.

higher levels a year or two ago (Fig. 1). Each of these patterns (and others) is likely to be associated with different degrees of responsiveness to any uniform reduction of raised plasma cholesterol. We have little idea which alternative pattern may have worse implications for the arterial wall. The popular concept is that a gradual increase in plasma cholesterol from the age of 5 until the age of 45 is the worse situation, but is this so? The Muscatine Study showed that there is no reliable "tracking" for serum cholesterol concentrations in children between the ages of 5 and 15,[18] and it is fallacious, therefore, to assume that children whose plasma cholesterol lies in the top decile at the age of 5 will be the same children whose plasma cholesterol lies in the top decile at age 15. Indeed, example C—where there has been a recent and rapid rise in plasma cholesterol—may be associated with more florid arterial atheroma than example A; example B may be associated with a variable LDL receptor response, more proliferative smooth muscle growth, and a greater autoimmune local response compared with those of example A, where the actual extent of obstruction of the arterial wall may be more advanced due to extensive fibrosis.

Another unknown, not taken into account by clinical trials designed to test the effect of lowering elevated cholesterol, is population and individual differences in bile acid-neutral sterol excretion and reabsorption.

RANDOMIZED CLINICAL TRIALS

Randomized clinical trials should be the basis for testing new methods of intervention in most chronic diseases, and this applies particularly to vascular diseases, whether it is CHD, cerebral vascular disease, or peripheral vascular disease.

The science of clinical trials has grown up over the last 15 years and has been described on several occasions.[3,4,17] The essential requirements are that they should be randomized and that the end points should be counted without bias. The rigor required for their design, conduct, and completion is a discipline in itself. Nobody, least of all pharmaceutical companies anxious to prove the efficacy of their products, should forget this. The basic needs for a successful randomized clinical trial include a double-blind design (neither the individual who is receiving the treatment nor the investigator responsible for testing the treament is aware of the nature of the treatment), balanced randomization at the outset of the major influences known to be related to the end point or end points being examined, and random allocation of treatment. The chief purpose of useful clinical trials must be to distinguish reliably between treatments that do or that do not differ materially in their effects on some important measure of disease outcome. In order to ensure this control, both the systematic and the random errors in the treatment comparisons should be substantially smaller than the real differences between the treatments which we would wish to detect. Randomization eliminates all systematic errors, and large randomized trials have small random errors.

Thus, one of the most critical aspects of randomized clinical trials is the choice of adequate numbers. There are numerous permutations on this, depending upon the expected incidence of the disease, the extent to which it is assumed that a given treatment will reduce this incidence, the significance level at which it is hoped to show a positive result (α value or type I error), and the size of the β value (or type II error) which determines the chance of missing a positive result. Some of the sample sizes likely to be relevant to trials directed at CHD are shown in Table 1; these have been taken from the Diet-Heart Feasibility Study.[14] Huge numbers are required for truly randomized trials, although some economy of numbers is possible by the use of matched pairs or, in the case of secondary prevention, case controls. A finite period is necessary for recruitment, so that concurrent controls are included and the entry period into the trial is not adjustable according to initial and early analysis of the results. Randomization in less than 20% of a population is undesirable, since it may in some unforeseen way be a selected population not representative of the remaining 80%. If the numbers are large enough and balanced randomization has been achieved, stratification should not be necessary. In principle, stratification is undesirable. It is permissible at the start of a trial, if it is quite clear what the subsidiary question or questions to be asked are at that time. Retrospective stratification and retrospective subgroup analyses are undesirable, since they usually result from post-hoc hypotheses and may therefore be made with bias.

In designing a randomized clinical trial, care should be taken to use the risk factors appropriate to the end points being studied. For example, some of the trials being conducted on antiplatelet and antithrombotic drugs have been designed with the well-established risk factors related to CHD end points rather than those which might be expected to be closely associated with intravascular coagulation; thus cigarette smoking, hypercholesterolemia, and hypertension are not necessarily appropriate risk factors for antithrombotic trials, but transient ischemic attacks may be. It is often easier to spread a trial over 20 to 50 centers in order to obtain adequate numbers and speedy recruitment, but this has serious dis-

Table 1. Sample Size for Each Group for a 5-year Trial
Objective—50% Reduction in Attack Rate

Attack Rates/Year Control %	Attack Rates/Year Treatment %	Statistical Alternatives*	Numbers Required: No Loss During Trial	Numbers Required: 30% Loss During Trial	Numbers Required: 50% Loss During Trial
0.75	0.375	A	1700	2600	3300
		B	2400	3800	4800
		C	1300	2100	2600
		D	2000	3100	3900
1.00	0.500	A	1300	2000	2500
		B	1800	2900	3600
		C	1000	1600	2000
		D	1500	2400	3000
1.25	0.625	A	980	1600	2000
		B	1430	2300	2900
		C	780	11300	1600
		D	1170	1900	2400

*Statistical Alternatives: A Type 1 error or α = 5% Type 2 error or β = 5%; B 1% 5%; C 5% 10%; D 1% 10%

Compiled from data in the U.S. National Diet-Heart Study Report, 1968 and Mass Field Trials of the Diet-Heart Question, 1970.[34]

advantages with regard to standardization of clinical and therapeutic practice, maintenance of blindness in certain drug trials, implementation of identical follow-up procedures and therefore of recording of data, and logistics. Thus, 1,000 individuals studied in each of 5 centers are likely to produce a more reliable result than 200 in each of 25 centers. Early analysis of results should be undertaken by statisticians who have previously agreed with the principal investigators not to divulge results to them, unless one of the sensitivity points (see next paragraph) has been reached. Early analysis of results by any of the investigators is most undesirable, since the knowledge provided by such analysis may lead to early termination of the trial. Early results can be erratic and misleading when the numbers of individuals in the trial are still small. Complete follow-up is essential. Not only should this apply to the individuals who participated in the trial and continue after the end of the trial, but it is also essential to implement full follow-up for those who have been withdrawn for one reason or another during the course of the trial. Some of these principles are illustrated in Table 2.

In drug trials, it is necessary to decide at the start on the degree of statistical sensitivity when any apparent adverse reactions against the drug should be imparted by the statisticians to the principal investigators. As said before, the principal investigators should not themselves be aware of these analyses. An appropriate early warning would be the 10% level of significance and, after reaching this point, if the adverse

Table 2. Some Principles of Randomized Clinical Trials

Balanced randomization without stratification
Use of appropriate risk factors
At least one half of subjects as controls
No early analysis to avoid premature termination
Rigorous follow-up: withdrawals
after trial

effects appear to get worse and reach or pass the level of 5% significance, it may be necessary to discontinue the trial. The level of sensitivity for a result in favor of the drug should be more; specificity is less essential and a significance level of about 1% should be the aim.

There are special problems with regard to long-term clinical trials using drugs (Table 3). Tests of compliance are important, whether through determining blood or urinary concentrations or by incorporating some marker into the preparation, and these tests should be conducted at irregular intervals and on unexpected occasions, as well as routine follow-up visits. Knowledge of the pharmacokinetics is sometimes far from adequate—the distribution of the drug in the plasma space, binding or nonbinding of the drug to protein, the half-life of the drug in tissues, and its method of excretion are often incompletely established, particularly

Table 3. Some Problems in Drug Trials

Trial of the drug
Trial of the mechanism of action
Test of compliance
Dose response often unclear
Pharmacokinetics not fully studied
Side effects
Adequacy of monitoring
Sensitivity of warning
Monitoring of commonly occurring diseases

when given over many months. The cumulative dose response of some drugs is not always clear. Although most countries, but not all, now have systems for the reporting of side effects, these should be recorded independently within the protocol of the clinical trial, and, although time-consuming, this documentation cannot be too comprehensive. A new dimension of measurement has been introduced into clinical trials recently by the evident need to record precisely the incidence of commonly occurring diseases however remote their biological association with the theme of the clinical trial may seem to be.

With these principles in mind, it is appropriate to examine the existing primary prevention trials of plasma cholesterol lowering.

Los Angeles Veterans Administration Trial[6]

The Los Angeles Veterans Administration (VA) study was the first of the major primary prevention trials to be completed. The trial was comprised of 846 men: 422 were randomized into a control group and received a conventional diet and 424 were randomized into an experimental group with a diet designed to achieve substitution of unsaturated for saturated fat to the maximal degree compatible with palatability. A double-blind technique was used. Recruitment was begun in 1959 and carried on till 1967, but most of the subjects were recruited in the first two years. Geometric age for the control group was 65.6 years and for the experimental group 65.4 years.

A veterans' institution was chosen because the length of stay of domiciled men was relatively long; the situation was favorable for serving meals, the characteristics and composition of which could be monitored; adherence of the subjects to the diet could also be monitored; and randomization could be achieved. The chief disadvantages were that the participants were relatively old and that the normal institutional turnover would result in a disturbingly high loss of subjects from follow-up.

The control diet was a conventional food pattern containing 40% fat calories, mostly of animal origin. The design of the experimental diet involved substituting vegetable oils for about two thirds of the animal fat, the total fat content being kept about 40%. An attempt was made to stabilize the iodine value of the mixed fat in the control diet at 55 and that in the experimental diet at 100. Multiple vegetable oils were used, including corn, soya bean, sunflower, and cottonseed.

The subjects were told (1) that two diets were to be studied, one of them differing radically from the regular institutional diet and the other less so; (2) that neither diet was expected to be asociated with a higher instance of cardiovascular complications; and (3) that no option as to diet assignment could be offered to a volunteer. Since it was not possible to achieve two diets in which the sensory qualities were indistinguishable, double-blind conditions were established by providing a control diet which, like the experimental diet, appeared to be a modification of the regular institution fare. Therefore, both groups of participants were told at the outset that their diets would differ from the regular diet but would resemble ordinary institutional food. Biochemical analyses of homogenized meals were carried out on 1 week and 8 week samples of diet for total lipid, individual fatty acids, and sterols.

Rigid adherence could not be enforced, since the participants had access to the community and to a canteen; total adherence to the study diet was the exception; the level of adherence was monitored by meal tickets and, more importantly, by gas liquid chromatographic analysis of subcutaneous fat aspirated from the buttocks.

All physicians associated with the study were kept uninformed about diet assignment of individual participants. Annual examinations were conducted, and a full account of morbidity requiring hospitalization was recorded. There was a 99% complete assessment of deaths.

Clinical, enzyme, and electrocardiographic assessments of end points were conducted with acceptable criteria, precisely documented. Autopsies were obtained in 80% of the participants who died within the institution and in 65% of all deaths in the study; analyses were made of the fatty acid concentrations of atheromatous lesions.

Randomization of the major clinical characteristics was achieved. Being an elderly population, some already had clinical features of CHD, and there was a 12% prevalence of definite angina pectoris, approximately 22% of the population had had a myocardial infarct, and approximately 12% had previous signs of cerebral ischemia or infarction. There was no significant difference in the distribution of these overt vascular disorders between the two treatment groups. Baseline serum cholesterol concentrations were similar. Cigarette smoking habits were also similar.

Although the ultimate serum cholesterol level in the experimental group was about 20% below the starting level, there was a small progressive fall in serum cholesterol in the control group and the mean difference between the groups, construed as reflecting the true effect of the diet, was approximately 13%. While changes in serum cholesterol concentration among the experimental subjects were poorly correlated with adherence to the diet, application of the multiple regression equation of Keys and his associates[11] showed that the main observed difference in serum cholesterol between the control and the experimental groups was close to that which would be predicted. Changes in fatty acids in subcutaneous fat were impressive and showed a three times increase in concentration of linoleic acid at the expense of all other fatty acids, except linolenic. Oleic and palmitic acids accounted for most of the decline. There was a correlation of +0.71 between adipose tissue linoleic acid and percent adherence to the experimental diet after 5 or more years.

Results of Study

The main results of the study are shown in Table 4. The primary end point in the study was considered to be new coronary events in the form of sudden death (defined as unexpected, occurring within a few minutes, or instantaneous) or definite myocardial infarction. In these categories, including silent myocardial infarction, there were 78 events affecting 65 men in the control group and 60 events affecting 52 men in the experimental group. The subcategory which showed the most marked difference

Table 4. Main Results of Los Angeles Veterans Administration Trial

Type of Event	Number of events			Number of men
	Fatal	Nonfatal	Total	
Definite myocardial infarction, by ECG only				
Control	0	4	4	4
Experimental*	0	9	9	9
Definite, overt myocardial infarction				
Control	23	24	47	40
Experimental*	23	10	33	27
Sudden death due to coronary heart disease				
Control	27		27	27
Experimental*	18		18	18
Definite cerebral infarction				
Control	9	16	25	22
Experimental*	3	10	13	13
Ruptured aneurysm				
Control	5	0	5	5
Experimental*	2	0	2	2
Amputation				
Control	3	2	5	5
Experimental*	0	7	7	5
Miscellaneous				
Control	3	3	6	6
Experimental*	2	1	3	2
	—	—	—	
Total				
Control	70	49	119	96†
Experimental*	48	37	85	66†
Chi^2 on totals	4.45			6.63
P	<0.05			0.01

*A diet low in saturated and high in polyunsaturated fat (P/S ~ > 1.5).

†Because a number of subjects have multiple events in these categories, this figure is smaller than that obtained by totaling the column.

From Dayton, S., et al.: A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. Circulation *39* and *40* (Suppl. 2), 1, 1969. By permission of the American Heart Association, Inc.