Mass Field Trials on the Prevention of Coronary Heart Disease: Perspectives and Tasks

-- Report of an International Working Meeting
Makarska, Yugoslavia, 19-24 September, 1968

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Co-Sponsor:	Council on Epidemiology and Prevention, International Society of Cardiology
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An international working meeting on perspectives and tasks in the further development of mass field trials on the prevention of atherosclerotic coronary heart disease (CHD) was held in Makarska, Yugoslavia on 19-24 September, 1968. It was sponsored by the American Heart Association, through its Council on Arteriosclerosis, Council on Epidemiology, and International Program Committee, with co-sponsorship of the Council on Epidemiology and Prevention, International Society of Cardiology.

The purposes of the meeting were to:

1. review current status of mass field trials on the primary and secondary prevention of atherosclerotic coronary heart disease,* particularly in the areas of diet, hypolipidemic drugs, anti-hypertensive therapy, smoking control, and physical exercise;

*For purposes of this report, primary prevention was defined as the prevention of first clinical episodes of frank coronary heart disease, particularly myocardial infarction, and secondary prevention was defined as the prevention of subsequent episodes of frank clinical CHD in persons with a definite history of previous CHD, particularly myocardial infarction. It was recognized that the distinction between primary and secondary prevention of this disease is to a degree relative and arbitrary, since the basic pathologic process underlying clinical disease -- severe atherosclerosis of the coronary arteries -- develops gradually and intermittently over decades. Therefore, mass field trials on CHD prevention in adults (particularly middle-aged adults in developed countries) generally deal with populations with considerable atherosclerosis of the coronary arteries, even in the absence of symptoms and signs of clinical disease. Nonetheless the distinction is valid and important, since natural history and

prognosis (e.g. risk of electrical death) may be fundamentally altered once clinical disease -- particularly myocardial infarction -- has occurred. This may be a key consideration influencing decisions with respect to undertaking primary vs. secondary preventive trials.

This understanding of the natural history of coronary atherosclerosis serves also to emphasize the importance of the fact that in persons free of clinical coronary disease, substantial differences exist at any given age in extent of the pathologic process, and in degree of susceptibility to subsequent episodes. For young and middle-aged adults, differences in coronary proneness can be assessed actuarially, based on measurement of the common coronary risk factors (hypercholesterolemia, hypertension, cigarette smoking, etc.), plus recording of signs of cardiac impairment (e.g. by means of the electrocardiogram). These gradations of risk permit identification of a wide spectrum of individuals to be considered for acceptance into studies on primary prevention, as defined.

2. review problems of design for mass field trials on the primary and secondary prevention of atherosclerotic coronary heart disease, with particular attention to trials on effects of control of mild hypertension, correction of cigarette smoking, and increase of habitual physical activity;

3. prepare a report presenting a Conference evaluation of the two foregoing questions, and projecting recommendations concerning field trials for the years ahead, their scope, design, methodology, and standardization for purposes of international comparison and cooperation.

Introduction -- Basis and Need for Mass Field Trials on CHD Prevention

Morbidity and mortality rates from premature coronary heart disease (CHD) remain extremely high in many countries (particularly the economically developed countries), show no signs of diminishing and constitute tremendous challenges to medical science and public health, for preventive action. In the United States, for example, over 600,000 persons die annually from coronary disease. Approximately 165,000 of these deaths occur in persons under 65 years of age, with a much heavier toll (three to one) among males than females. And for each fatality, at least two nonfatal events occur. On the average, a healthy American man has

about a 20 per cent risk -- one chance in five -- of developing clinical coronary disease before age 60. In a majority of men developing premature CHD, the first episode takes the severe form of myocardial infarction. About 40 per cent of these first heart attacks are acutely fatal. One half of these fatalities -- about 20 per cent of all first attacks -- are sudden deaths, occurring within 60 minutes of onset of symptoms, often before any medical care can be summoned. And for the 60 per cent fortunate enough to make a reasonable recovery from a first attack, prognosis for longevity is markedly impaired. They are about five times as likely to die in the next five years as persons of the same age, sex and race without a history of previous CHD. And in over 90 per cent of cases, the cause of death is recurrent heart attack.

These data serve not only to demonstrate the scope of the coronary disease problem, and the challenge it represents. Above all, they compel the conclusion that major progress in controlling the CHD epidemic can be achieved only by means of a strategy emphasizing prevention, particularly primary prevention -- care before illness, to prevent first attacks with all their grim consequences. It is this situation that gives importance and urgency to mass field trials on coronary prevention. Can prevention -- particularly primary prevention -- be achieved by applying recent research knowledge? Can the epidemic be brought under control by nutritional, hygienic, pharmacologic means? Unequivocal and decisive answers to

these crucial questions can be obtained only through well-designed, well-controlled and well-executed mass field trials.

Important indirect evidence is already available on the etiology and pathogenesis of the disease, and on the possibility of prevention. Thus, extensive research data have been amassed demonstrating that the continuing epidemic of premature CHD in the relatively affluent countries is related to habits of eating, cigarette smoking and sedentary living, and associated risk factors (particularly hypercholesterolemia, hypertension, hyperglycemia)widely prevalent in the population. Many large-scale, prospective, descriptive-analytical studies have demonstrated these associations between these habits and traits, and occurrence of the disease. Although substantial direct proof from mass field trials is lacking, the findings of the observational studies support the inference that the relationships are probably causal -- since data on the associations are available from many sources, are strong and consistent, persist when confounding variables are taken into account, are in harmony with findings from other research methods (e.g. animal experimentation and clinical investigation) and are coherent in terms of reasonable pathogenetic mechanisms relating the presumed causes and the disease.

The living habits and risk factors contributing to coronary proneness can be controlled and corrected by nutritional, hygienic and/or pharmacologic means. Thus, reduction of serum cholesterol level can be safely effected and

sustained for years by modification of the usual diet in ways acceptable to large numbers of people. In addition to nutritional approaches, pharmacologic means are also available for the control of hypercholesterolemia, and for hypertension, hyperglycemia and hyperuricemia as well. Cigarette smoking and sedentary living are also potentially amenable to correction on a large scale.

All these facts indicate the possibility of prevention. At this juncture, however, sufficient direct evidence is not available from mass field trials to lead unequivocally to the conclusion that premature CHD can be prevented.

Whenever extensive inferential evidence concerning disease causation becomes available, indicating the possibility of prevention (as is the case for CHD), it becomes highly desirable to complete the process of scientific elucidation -- by acquiring definitive direct proof of causality and preventability from experimental studies on man (if that is possible). Such direct proof is particularly desirable when the proposed approaches to prevention would (if widely adopted) have considerable impact both on personal living habits and national economies -- as would certainly be true with regard to changes being recommended in diet, smoking and exercise habits, for CHD prevention. Direct proof is further desirable when uncertainty exists as to possible harmful effects of some forms of proposed prophylaxis -- specifically, exercise and drugs for control of risk factors.

Direct proof concerning the role of these habits and risk factors in the

etiology of CHD in man -- and ability to achieve prevention by modifying these traits -- can be obtained only by well-designed, well-controlled, well-exercise mass field trials. Therefore, such trials have great significance, both theoretical and practical. They are vital last steps in testing validity of scientific conclusions, and completing proof of disease causation. Moreover, positive findings from such trials are likely to be essential prerequisites for extensively and definitively convincing physicians, official health authorities, and the public to adopt new approaches to disease prevention and control.

For all these reasons, relating to both the potential and the need, it is appropriate that the highest priority be given to mounting effective mass field trials on CHD prevention.

Status of Mass Field Trials on Prevention of CHD

Studies on diet, and on drugs influencing lipid metabolism: During the last two decades, increasing research attention has been devoted to long-term studies on prevention of coronary disease. Many of these studies have investigated the prophylactic potential (primary or secondary) of diets, in free-living or institutionalized populations. A few have dealt with drugs influencing lipid metabolism. Some of these studies are still in progress. All of them have published meaningful reports ( ).

Undoubtedly these investigations, undertaken in the late 1940s and 1950s, made very useful contributions. They accrued invaluable experience and information concerning the design, methodological and practical aspects of such studies. They showed that mass field trials are feasible: It is possible to recruit sizeable numbers of persons, free-living and institutionalized, as participants in long-term studies on CHD prevention by nutritional or pharmacologic means. It is possible in diet and drug studies to retain a majority of recruits as active members for at least five years. In diet studies, it is possible to effect and maintain significant alterations in eating habits, both among participants with and without a history of CHD. As a result, sizeable long-term reductions can be effected in serum lipids and body weight. Adherence for years to drug therapy also can be accomplished in a high proportion of volunteers for secondary prevention studies.

In regard to the decisive end point, effect of diet or drug regimen on CHD incidence and mortality, these studies failed to produce conclusive and consistent data. In retrospect, this outcome is understandable, since all the "first generation" studies faced problems resulting from small sample sizes. In addition, some failed to utilize initial randomization into experimental and control groups to avoid the bias of selection. Other shortcomings in design are also disconcernable. Most of these were almost inevitable consequences of circumstances prevailing

when these studies were
/ launched -- e.g. scope of knowledge, experience, resources, funds available in the area of mass field trials on CHD prevention. Recognition of these limitations in no way detracts from the pioneering contributions made by the initial studies, including the suggestive and encouraging findings of several of them on ability to achieve primary and secondary prevention of CHD. Rather, recognition of these limitations serves to pinpoint the research remaining to be done and the road ahead.

Based on the results of the "first generation" studies, three major endeavors were undertaken in the 1960s, on diet, and on drugs influencing lipid metabolism. The first of these "second generation" investigations -- the National Diet-Heart Study -- was a study of feasibility of large-scale, tightly designed mass field trials on primary prevention of CHD by nutritional means in free-living and institutionalized persons. Its final report has been published ( ). Its recommendations for both primary and secondary prevention trials, in both free-living and institutionalized populations, are now being reviewed for possible implementation.

A second major endeavor is in progress in Europe. It is a definitive controlled double-blind mass field trial in men age 30-59 assessing ability of the lipid-lowering drug clofibrate (Atromid-S ^{R}) to achieve primary prevention of CHD, particularly in hypercholesterolemic men. Several thousand men have already been ... enrolled in this /

investigation in Edinburgh, Prague and Budapest. Its objective is to recruit 15,000 men and follow them for five years.

The Coronary Drug Project in the United States is a third large-scale definitive trial. It is assessing efficacy of several drugs influencing lipid metabolism -- clofibrate, dextrothyroxine, estrogens, nicotinic acid -- for secondary prevention in men age 30-64 with a previous history of unequivocal myocardial infarction. This national cooperative study, being conducted in 55 centers, has recruited 5,500 patients and plans to enroll up to 8,500 by July 1, 1969. Patients are to be followed for five years.

The Conference noted that these major undertakings represent positive advances of the greatest significance. It registered the conviction that additional studies along these lines should be mounted as soon as possible, particularly the mass field trials on diet recommended in the report of the National Diet-Heart Study.

In view of these major positive developments, the Conference deemed it unnecessary at this juncture to deal in further detail with mass field trials on CHD prevention by diet or drugs affecting lipid metabolism.

Hypertension, cigarette smoking and physical inactivity: Valuable data on ability to prevent complications from "moderately severe" hypertension (diastolic pressures 115-129 mm. Hg.) became available in 1967 in the report on the carefully

controlled study of the Veterans Administration research group ( ). However, this important evaluation of combined drug therapy yielded little information on prevention of CHD per se. Moreover, no findings have been reported on effects on CHD incidence and mortality of treatment for "mild" hypertension (diastolic pressures in the range 90 or 95 to 109 or 114 mm.Hg.), although it may be anticipated that some data on this matter will be forthcoming during the next years from one or more studies currently in progress.

No data are available from any field trials on ability to prevent CHD through elimination of the cigarette smoking habit. Insofar as the Conference could ascertain, only one major trial dealing exclusively with this risk factor is currently in progress. This is a recently launched study in British civil servants, aimed at assessing primary preventive potential of cessation of cigarette smoking in middle-aged men ( ). Primary end-points are deaths plus hospitalized cases of myocardial infarction.

No data are available from any field trials on ability to prevent CHD by exercise. In the knowledge of the Conference participants, no definitive trials on exercise are presently proceeding, and only a few small-scale pilot studies have been undertaken.

Obviously, efforts to assess prophylactic potential of control of hypertension, cigarette smoking and physical inactivity are at an early stage of development. Most of the studies currently in progress involve only small samples and/ are not likely to yield definitive information on CHD prevention. Therefore, the Conference dealt in detail with perspectives and tasks in the further development of mass field trials to test ability to prevent CHD by controlling hypertension, cigarette

smoking and habitual physical inactivity.

Mass Field Trials on the Prevention of Coronary Heart Disease by Control of "Mild" Hypertension

Certain basic principles are applicable in the design of all mass field trials assessing long-term prophylaxis for coronary disease. They are summarized in the Appendix. The discussion here focusses on the particular aspects of intervention trials to assess correction and control of "mild" hypertension, cigarette smoking and lack of exercise.

Primary prevention: The Conference deemed it appropriate to focus on the problem of so-called "mild" hypertension (diastolic pressures in the range 90 or 95 to 109 or 114 mm. Hg). This is a widely prevalent condition. In the United States, for example, examination findings of the National Health Survey indicate that almost ten million adults had diastolic pressures in the range 95-114 mg.Hg. in 1960-62 ( ). Hypertension is unquestionably associated with sizeable increases in risk of premature CHD. This relationship has been repeatedly demonstrated in major prospective studies on the epidemiology of CHD, and by actuarial analyses of life insurance data as well ( ).

To date, no definitive data are available from mass field trials concerning the ability to reduce CHD risk by treating "mild" hypertension. Previously reported positive results in controlled trials of drug therapy for patients with

malignant and "moderately severe" hypertension are encouraging. Nevertheless, widely divergent views prevail among physicians as to the whether pharmacologic treatment for "mild" hypertension is efficacious, without benefit, or harmful -- and no reliable information is extant to clarify the issue. These circumstances underscore the importance of trials to assess efficacy of treating "mild" hypertension.

Need exists not only for trials to assess drug therapy of "mild" hypertension, but also to evaluate such nutritional-hygienic measures as correction of obesity, moderate salt restriction, regular exercise and sanatorium treatment. All these measures have been advocated over the years in the treatment of "mild" hypertension. However, little or no information is available from controlled studies as to their efficacy.

At this juncture, information is lacking from controlled studies as whether these nutritional-hygienic measures have the ability to effect and maintain a reduction in blood pressure, or at least to prevent further progression and intensification of hypertension. Thus, prime attention should be given first of all to studies in which effect on blood pressure, short-term and long-term, is the key end-point.

A similar need still exists with respect to relative value of alternative methods of pharmacologic therapy for mild hypertension, including various combinations of drugs. Such studies should of course evaluate not only effects on blood pressure, but also side and toxic effects.

Clearly, investigations using blood pressure as the end-point are not by themselves sufficient to clarify ability to prevent CHD by controlling hypertension. Therefore, definitive mass field trials must also be developed with CHD morbidity and mortality as the prime end-points, along with other major forms of cardiovascular-renal disease common in hypertensive persons. Studies of this kind need to be started as soon as possible, since it is possible -- even likely -- that drug therapy for "mild" hypertension may become widely accepted routine medical practice in the years immediately ahead, despite lack of information as to its efficacy. This development would severely limit or negate the possibility

of well controlled studies to obtain reliable data on therapeutic efficacy.

It would be highly desirable to obtain information through such trials concerning consistency and magnitude of therapeutic effects, safety of treatment (particularly drug therapy), and generalizability of findings. To achieve these purposes, multiple studies are needed, in different population groups, involving large numbers of people followed for long time periods.

To be of greatest value in relation to the general problem of "mild" hypertension in the population, such studies should recruit their participants from the general population, not merely from the ranks of patients seen in medical care facilities. Population-based studies are of importance for at least two major reasons: First, if reasonably precise measurements are to be made of therapeutic and toxic effects, and their magnitudes, large sample sizes are needed, as well as long periods of follow-up. Often it is much easier to recruit large numbers of persons for field trials on CHD prevention, especially primary prevention, from the general population. Second, positive results from such trials would have widespread implications. Their accomplishment with hypertensive persons from the general population as participants would make it easier to assess the many questions that would arise concerning social, economic, organizational, etc. aspects of large-scale, long-term treatment of large numbers of persons with "mild" hypertension. Every effort should be made to conduct

trials in such a way as to encompass data collection and analysis in these areas, including assessment of possible psychological morbidity resulting from various anti-hypertensive treatment regimens.

Since treatment of "mild" hypertension -- if useful -- would ultimately entail long-term therapy for large numbers of persons in the population, mass field trials of pharmacologic treatment should focus on individual drugs and combinations of drugs that can be administered without prior hospitalization and without closely regulated, individual titration of dosage. Studies in this area are needed both to evaluate specific treatment regimens versus placebo, and to compare different treatment regimens with each other. It is possible that before many years have elapsed, trials of pharmacologic therapy for "mild" hypertension may have to be limited to drug versus drug trials, without a placebo group.

As experience has shown, it is possible to conduct such trials with a double blind design, and with either fixed or (within limits) flexible dosage schedules. When flexible dosage schedules are provided for in a protocol, it is essential that precise criteria be stipulated for change of dosage, e.g. in relation to defined blood pressure changes.

In all studies on therapy of hypertension, every effort should be made to standardize

methods and conditions for blood pressure measurement, to test and train observers and assure their optimal comparability, to evaluate sources of systematic bias and protect against them. Recent recommendations of the American Heart Association and the World Health Organization merit close attention in regard to these matters ( ).

Secondary prevention: Virtually no data are available concerning the efficacy hypertension treatment for secondary prevention. Data are available indicating that persons with mild hypertension have a poorer long-term prognosis for survival after development of myocardial infarction or angina pectoris than normotensive persons. Therefore secondary preventive studies in this area are urgently needed to assess whether control of mild hypertension will reduce risk and prolong life in persons with previous history of clinical coronary heart disease. In such investigations special precautions must be taken to avoid inordinate reductions c blood pressure, i.e. to exclude the hazard of insufficient pressure head for myocardial blood supply. The decisive end points for such secondary prevention trials must be disease incidence and mortality, including total mortality.

Mass Field Trials on Prevention of CHD by Cessation of Cigarette Smoking

Primary prevention: Extensive and unassailable evidence is available indicating that cigarette smoking is an undesirable habit, harmful to human health ( ). The data implicate cigarette smoking not only in the etiology

of lung cancer and chronic bronchopulmonary diseases, but also as a factor contributin /to the current epidemic of premature CHD in the economically developed countries.

As the Report of the Advisory Committee to the Surgeon General of the Public Health Service noted in 1964, "It is established that male cigarette smokers have a higher death rate from coronary disease than non-smoking males... If cigarette smoking actually caused the higher death rate from coronary disease, it would on this account be responsible for many deaths in middle-aged and elderly males in the United States. Other factors such as high blood pressure, high serum cholesterol, and excessive obesity are also known to be associated with an unusually high death rate from coronary disease. The causative role of these other factors in coronary disease, though not proven, is suspected strongly enough to be a major reason for taking countermeasures against them. It is also more prudent to assume that the established association between cigarette smoking and coronary disease has causative meaning than to suspend judgment until no uncertainty remains." ( )

Since the publication of this report in 1964, extensive additional evidence has accumulated on the association between cigarette smoking and risk of premature CHD ( ). In addition, evidence has been obtained indicating that cigarette smokers tend to have more severe atherosclerotic disease of major arteries, including coronary arteries, than nonsmokers. Thus, the latest findings underscore the soundness of the recommendation in the report to the Surgeon General.

In contrast to the situation with respect to the diet-lipidemia-CHD link, however, little or no experimental evidence is available concerning cigarette smoking and CHD. Moreover, knowledge is limited as to the mechanism(s) whereby cigarette smoking may operate as a contributory cause of premature CHD. Clearly, therefore, research is needed to clarify these matters. In the main, however, such research will be non-epidemiological in nature.

Since this area of scientific uncertainty remains, and since it would be useful to obtain data on ability to influence CHD risk by cessation of smoking, field trials on this matter are needed. These should be done in populations from those countries where clear-cut evidence of an association between cigarette smoking and CHD risk has been recorded.

Plans for these trials must be concerned first of all with ability to achieve and sustain cessation of smoking in a high proportion of participants. Experience in this regard is as yet limited. Hence there is a major need for further research on methods for aiding cigaret smokers to abandon this habit. Particularly since there is general scientific agreement on the overall health benefits of quitting cigarettes, and the improbability of negative consequences, such research is desirable for its own sake, and not only as a means to an end for mass field trials.

The design of definitive trials in this area will inevitably be conditioned

by ethical considerations arising from the fact that medical and public health practice emphasizes the desirability of persuading all cigarette smokers to stop smoking. Clearly, in this circumstance it is not ethically appropriate to assign persons randomly to control groups committed to continue cigarette smoking for purposes of the study. However, it may be acceptable to assign cigarette smokers randomly to control groups scheduled to experience no sustained systematic intervention from study sources with regard to smoking during the study. This could be done in trials involving informed volunteers, or alternatively individuals who serve as "unwitting" controls (see Appendix). It could also be accomplished by randomizing institutions rather than individuals into experimental and control groups, provided the number of institutions is large enough to minimize risk of bias. For example, large numbers of banks could be utilized for such a study, with random allocation of banks to experimental and control groups. Vigorous, sustained anti-smoking measures would then be carried out only among employees of banks assigned to the experimental groups.

Another possible approach is to accomplish trials involving comparison of different methods of effecting smoking cessation, with the expectation that different response rates will be obtained, permitting a comparison of impact on disease incidence and mortality. Insofar as this design leads to absence of a

true control group, it could lead to problems in interpretation of results. Moreover, it is likely that very large sample sizes would be needed to detect the small inter-group differences in disease rates to be anticipated in a study of this design.

In view of the limited experience to date, the first stage of trials in this area should focus on problems of methodology and feasibility in regard to both experimental and control groups.

Secondary prevention: While extensive evidence has been obtained indicating a strong association between cigarette smoking and risk of first episodes of CHD in middl age, only limited data are available concerning relationship of cigarette smoking to longterm prognosis after previous myocardial infarction. Here again, generally accepted medical practice at the present time is to encourage coronary patients to give up cigarettes. Experience indicates that this goal is difficult to achieve in a significant proportion of patients. Undoubtedly, mass field trials on the value of cessation of smoking for coronary partients are needed to determine definitively whether secondary prevention can be achieved in this way. In view of present medical practice, major problems exist with respect to design, particularly in regard to establishing control groups. Again, the possibility arises of randomizing to experimental and control groups by centers, rather than by individuals. However, this can be done satisfactorily -- with high-level assurance of comparability of the two groups and minimal risk of bias -- only if many centers are involved. Again, a possible alternative is to evaluate two or more approaches to reducing cigarette usage among coronary patients who are smokers, with the expectation that different ratesof success will be achieved, thereby permitting assessment of impact on survival.

Irrespective of the approach taken to this difficult problem, design of trials in this area must provide for a phase entailing careful study of

effectiveness of methods for achieving cessation of smoking in post-myocardial infarction patients who have persisted in using cigarettes.

Mass Field Trials on Prevention of CHD by Exercise

Primary prevention: At the present time, the adult population -- at least in some developed countries -- is being increasingly advised to abandon sedentary living habits and to embrace regular exercise, particularly of the endurance type (e.g. jogging, running, bicycling) as a major means for improving heart health. Recommendations along these lines are based primarily upon findings of several prospective, descriptive-analytical epidemiologic studies indicating a relationship between risk of premature CHD (particularly sudden death and fatal myocardial infarction) and habitual lack of exercise. However, research findings on this matter are not wholly consistent. A few studies -- particularly in the United States -- have apparently failed to confirm the relationship between lack of exercise and CHD risk. Moreover, evaluation of bias from confounding variables -- e.g. serum cholesterol level, blood pressure, and preselection in young adulthood -- has proved to be especially difficult in this area of research. Unquestionably, additional observational studies (as well as clinical and animal-experimental investigations) can help to clarify areas of continuing uncertainty with regard to the role of sedentary living as a coronary risk factor. However,

definitive information on this matter can be obtained only by controlled mass field trials, given the aforementioned complexities and difficulties.

A few small pilot studies have recently been carried out in this area. Based on knowledge and experience accrued to date, several problems require careful consideration in developing further protocols for preventive studies on exercise. First, it is still unclear whether a satisfactory proportion of previously sedentary middle-aged men can be retained as active participants for years in exercise programs. Since the matter of adherence is crucial for the success of field trials, studies in this area must be centrally concerned with it.

Uncertainty also exists concerning the exercise regimen of choice for assuring optimal adherence. Detailed data are not available to permit rational selection among such approaches as bicycle ergometric exercise, calisthenics, walking-jogging-running, games, swimming, done individually or in groups, supervised or non-supervised -- with various combinations of these. At this stage of limited knowledge, there is serious need for continued exploration of the forms of exercise to be utilized in field trials -- in relation to such key questions as potential for maintaining longterm adherence, achieving sizeable increments in fitness (as determined by objective tests), and ultimate mass applicability.

It is also essential to note that insufficient knowledge is currently available concerning the type, frequency and duration of exercise presumed

to be optimal for coronary prevention. In particular, uncertainty exists as to the efficacy of high-intensity short-duration exercise versus steady, sustained, moderate activity over hours during the day. Prospective observational evidence indicating that physical activity affords partial protection against premature CHD deals almost exclusively with the latter type of exercise. In contrast, pilot studies have focussed on high-intensity, short-duration exercise -- understandably, in terms of practical considerations for field trials and for possible ultimate mass application in preventive programs. Unquestionably, this type of exercise leads to conditioning and enhanced cardiopulmonary fitness, as measured by objective graded quantitative ergometric tests.

Knowledge and experience are also limited concerning methods of recording and qualifying type, intensity and duration of activity performed in long-term mass field trials -- unless it involves supervised ergometric exercise. Obviously, it is vital for mass fields trials to have means for describing the exercise performed. In this area, the need exists for development of improved methods of the diary type, to permit participants to record daily and weekly descriptions of type of exercise done. Experience also needs to be accrued with standardized apparatus for home exercise, with built-in sealed recorders of rate, duration and amount of exercise. Correspondingly, further experience is needed as to feasibility of self-recording of pulse by participants immediately at the end

of prescribed exercise.

Irrespective of these methods, periodic measurements must be made in trials on exercise of changes in cardiopulmonary fitness, as assessed by objective reproducible quantitative tests of the graded ergometric type ( ). Basically, this is the most valid measure -- in the absence of supervised individualized ergometric exercise -- of change from sedentary to active living habit, and consequent effect on physiological performance. It is an intermediate end point in exercise studies equivalent to serum cholesterol measurement in diet trials. Viewed in this light, it is apparent that efforts to improve and standardize fitness testing procedures should be consummated on national and international levels as soon as possible.

Safety considerations must also loom large in the design of trials on exercise. Laboratories established for testing fitness should be thoroughly equipped with modern instrumentation for monitoring cardiovascular function during testing, and for coping with emergencies. A competent staff should be available, trained in the use of modern equipment and methodology for emergency care. It should include a physician with special training in this area. The study protocol should clearly specify medical criteria leading to exclusion from testing ( ). Particularly in dealing with unconditioned, sedentary middle-aged men, precautions are in order with respect to the degree of physical activity demanded during testing.

For mass use in such populations, submaximal tests are preferable to tests demanding maximum exertion. With appropriate safety precautions and criteria for exclusion, exercise testing to assess fitness is possible in the overwhelming majority of middle-aged men available for possible participation in primary prevention trials, including men assessed to be highly susceptible to CHD based on their findings with respect to the common risk factors.

Precautions are also in order with regard to exercise prescription, particularly in the initial phases of a program, whether trials involve supervised or nonsupervised exercise. These should take into consideration not only measures to minimize risk of cardiovascular complications, but musculoskeletal difficulties as well. They should also include systematic means for the early recognition and care for complications of the latter type. This can be an important aspect of minimizing dropout from trials.

In general, the approach in the early stages should be one of starting previously sedentary men at a low level of exercise and building up intensity and duration gradually, at an easy pace. In both supervised and nonsupervised programs, consideration should be given to individualizing this pace, and competent staff should be available for this purpose. In addition, all participants should have ready access to medical advice, and full scope should be given to physician leadership, as a vital ingredient for maintenance of morale and safety.

Considerations of sample size lead to the conclusion that primary prevention studies on exercise should focus on previously sedentary, middle-aged males assessed to be highly susceptible to CHD based on their findings with respect to the common risk factors (see Appendix). In addition, one special group in the population may merit particular attention in planning mass field trials on exercise, i.e. the group of asymptomatic persons with a normal resting electrocardiogram, manifesting ischemic depression of the ST segment of the electrocardiogram during exercise testing.

Secondary prevention: Persons with unequivocal angina pectoris during exercise constitute a group meriting special attention in mass field trials on exercise.

An urgent need also exists for trials on the efficacy of exercise for the secondary prevention of coronary disease in persons with a history of previous myocardial infarction. Such trials are especially needed since active rehabilitation of post-myocardial infarction patients is being increasingly practiced by physicians, in the absence of clear cut data as to its efficacious (or harmful) influences. ~~Insofar as the Conference could ascertain, no consistent plan or policy currently exists for obtaining this vitally needed information. This is a deficiency that needs to be overcome as soon as possible.~~ It is a matter of urgency first of all because the possibility cannot be ruled out -- based on extant information -- that harm, rather than help, may be

resulting from this widespread shift in medical practice. It is furthermore a matter of urgency, since it is quite possible that in the next years exercise therapy may become a generally accepted form of treatment, in the absence of any assessment of its efficacy. This development would limit or preclude well-controlled mass field trials to assess its merit for long-term secondary prophylaxis.

In trials on the secondary preventive potential of exercise, the greatest care is in order with regard to safety precautions, both in the testing laboratory and in the exercise program. Particularly in the early months, supervision should be continuous and close; gradation and progression of exercise should be approached with great caution. Particular attention should be given to identification of patients who appear to be responding unsatisfactorily to the program, so that they can be excluded in a timely fashion.

Mass Field Trials to Assess Prevention of CHD by Control of Multiple Coronary Risk Factors

Primary prevention by change in living habits: At the present time, increasing emphasis is being given in many countries to development of public health and medical programs for control of coronary risk factors by general modification of living habits -- especially nutritional, smoking and exercise habits. More and

more, the public is being given general advice along these lines. Practitioners in the health professions are being encouraged to develop preventive programs based on the concept that early recognition and longterm control of coronary risk factors are fruitful approaches to mastering the current CHD epidemic.

In this developing situation, it is imperative that every effort be made as soon as possible to obtain definitive controlled data as to the efficacy of these approaches. Once again, time for well-designed trials may soon run out.

Trials to test the hypothesis that changes in living habits will prevent CHD deserve high priority for several reasons: First, they are of critical importance for the definitive testing of a key concept concerning etiology of the contemporary epidemic of premature CHD, i.e. the basic theory that this epidemic has supervened as a result of multiple major innovations in mode of life (diet, smoking and exercise habits) among wide masses of the population in developed countries during the twentieth century. Second, trials involving simultaneous alteration of two or three aspects of the mode of life -- by controlling two or three major coronary risk factors concurrently -- have the potential theoretically of recording much more substantial reductions in CHD morbidity and mortality (e.g. more than 50 per cent in some populations) than studies of single factors (See Appendix.) Hence the possibility arises that trials on altering living habits can be done with much smaller sample sizes than are necessary for trials evaluating one factor at a time

(see Appendix). Finally, considerations of available manpower, resources and funds make it likely that choices must be made among the several types of trials indicated at this stage of scientific development. In this regard, the Conference stressed the importance of trials testing the hypothesis that alteration in living habits -- with resultant effective control of major risk factors in coronary-prone adults -- will achieve primary prevention of the disease.

Primary prevention by combined drug treatment of multiple coronary risk factors: Trials are also needed to assess the preventive potential of long-term therapy with combinations of drugs to correct and control two or more coronary risk factors. As noted previously in this report, drug treatment for hypertension -- including "mild" hypertension -- is being advocated on an ever widening scale, and a similar situation is developing with respect to long term control of hyperlipidemia by pharmacologic therapy. With the introduction of oral medication for control of hyperglycemia, persons with this condition are also frequently advised to utilize drug treatment. A similar situation exists with respect to hyperuricemia, also implicated as a coronary risk factor. Since a sizeable proportion of the middle-aged adult population in the developed countries manifests two or more of these risk factors, combined drug therapy is being more and more frequently employed. The rationale is obvious: If hypertension, hypercholesterolemia, hyperglycemia, hyperuricemia are significant coronary risk factors, then correction

and control of these abnormalities by pharmacologic therapy offers the possibility of decreasing susceptibility to clinical episodes of CHD.

It should be emphasized, however, that no data are available from controlled trials to permit an objective assessment of the validity of this inference. Moreover, experience is still limited in the long-term use of the various drugs available for control of these coronary risk factors. If they are of any utility, it is only in the form of therapy over many years, to effect and sustain correction of hypertension, hyperlipidemia, hyperglycemia, hyperuricemia. Clearly, therefore, a great need exists to obtain more information concerning toxicity problems with large-scale, long-term use of the currently available drugs. Therefore, from two fundamental points of view -- the acquisition of sound knowledge concerning efficacy of drugs for primary prevention, and elucidation of problems of toxicity with combined drug therapy to control two or more risk factors -- mass field trials are needed.

Mass field trials to assess ability to achieve primary prevention through combined drug therapy readily permits utilization of protocols providing for double-blind design. It is entirely possible to undertake all studies in this area on this basis. In many instances side effects of the drugs are of such a minor nature as to permit preservation of the double-blind design, without unblinding, over

the several years of a study. This is of course not uniformally the case, since some drugs produce significant side effects resulting in a considerable degree of unblinding (e.g., nicotinic acid), nonetheless it is desirable that all drug studies proceed based on double-blind design.

As noted earlier in the discussion of trials to assess antihypertensive medication, it is possible to utilize a double-blind design even with a protocol providing for variation in drug dosage, under specified conditions and within specified limits. Therefore, the understandable desire of investigators to titrate dosage under certain circumstances should not result in abandonment of double-blind design.

It is also entirely possible with such a design to provide for ready access to coded information on drugs being utilized, should a valid medical emergency require this. Correspondingly, it is also possible to provide in the protocol for transfer of participants to known placebo, when in the judgment of managing physicians/this is indicated. Therefore, this design is fully compatible with accepted ethical principles for research with human beings.

Primary prevention by change in living habits plus drug therapy: Efforts are presently proceeding in medical practice to achieve primary prevention of premature clinical CHD by prescribing both change in living habits and drugs for control of CHD risk factors. For example, many patients are being advised by

their physicians with regard to diet, cigarette smoking and exercise, and are simultaneously being given drugs for the control of such risk factors as hypertension, hyperlipidemia, hyperglycemia, hyperuricemia. Again, no direct information is available as to the actual efficacy of such measures. Therefore, controlled mass field trials are needed in this area as well.

One possible advantage of a large-scale study of this type is that provision might be made for two control groups -- one double-blind, the second non-double-blind. The former would be on placebo drug therapy, and its participants would report to research centers for a full schedule of visits similar to that of experimental groups. The non-double-blind control group would be involved in only a minimal way in the activities of the research centers, so that impact of the study on it is minimal. Comparison of these two groups would afford at least partial insight into the question: Are non-double-blind trials on CHD prevention significantly confounded -- as hypothesized by some investigators -- because intense exposure to a research study on coronary prevention has non-specific influences (e.g. psychological effects) on CHD risk, independent of influences on known and measureable risk factors?

Factorial designs: Clearly, trials to assess prophylactic benefit of multiple alterations in living habits or of combined drug therapy for control of risk factors lend themselves readily to factorial designs. These experimental

designs are useful for simultaneously studying the individual and joint effects of several factors. While such designs have been widely used for years in such fields as experimental agriculture and industrial process control, they have only rarely been applied to problems of human health and disease. For that reason, a basic exposition of some of their properties in the present setting may be useful ( ).

The simplest such design is the 2^2 factorial in which two factors (here, two types of intervention) each appear at two levels (here, presence or absence of the particular mode of intervention). To be specific, suppose factor one is a diet and factor two is a drug. In this case, subjects would be randomly allocated to one of four groups: drug plus diet, drug alone, diet alone, neither form of intervention. The table illustrates the situation:

		Drug: Present	Drug: Absent
Dietary Intervention	Present		
	Absent		

Such a design makes it possible to analyze the main effect of diet by comparing that half of the patients on the diet (with and without drug) with that half not on the diet, and to analyze the main effect of the drug in a similar manner. Every subject contributes his experience to the assessment of both these

effects. This accounts for the basic potential saving of sample size in factorial designs.

In addition, it is possible to study the interaction of the two factors, i.e., to determine whether the effect of the diet is similar in drug-treated and untreated subjects. Specifically, the interaction between the two factors is the difference between the effect of diet when drug is present and its effect when drug is absent. This interactive difference may be due to inhibition of diet effect by the drug, potentiation of the effect, or possibly some other type of joint action. If interaction is present, then the joint effect of the two factors may not be explicable from knowledge of their individual effects. The presence of interaction obviously makes the interpretation of main effects more difficult, and such effects then become average effects across the levels of the remaining factor. However, the factorial design permits quantitative assessment of such interactions, while a study based on a single factor -- or on two or more factors in a two group design (experimental and control) -- does not permit this refinement.

In addition to the difficulties presented by interactions, the administrative management of a factorial study may become complicated due to the necessity of allocating and supervising a larger number of patient subgroups. In spite of these difficulties, however, it seems likely that factorial designs can contribute to our knowledge of CHD prevention.

Priorities: Clearly, as indicated earlier, theoretical considerations concerning the etiology of the 20th Century epidemic of premature CHD in the developed countries, and the probable role of mode of life (particularly "rich" diet, cigarette smoking and lack of exercise) in its etiology, lead to the conclusion that mass field trials involving simultaneous correction and control of these probable causative factors merit the highest priority. Nevertheless, the Conference emphasized that field trials are needed on the primary preventive potential of both mode of life intervention and pharmacologic therapy of risk factors. It underscored the conclusion that it would be unwise at this juncture in knowledge to place sole reliance on any one approach, and consequently to limit development of trials to any one approach. On the contrary, the need of the moment is to encourage concerned investigators to develop a variety of approaches, in order to assure that the current lag in developing trials on coronary prevention is overcome in the most rapid and fruitful fashion.

Secondary prevention by control of multiple risk factors: The foregoing observations with respect to field trials on primary prevention by control of multiple risk factors apply also to secondary prevention. The entire field is virgin territory. No data are available concerning the long-term effects on prognosis, for persons with clinical coronary disease, of either multiple changes in living habits or control of risk factors by drugs. Since no therapeutic

trials have been done, the critical evidence is totally lacking to determine whether various combinations of long-term management are helpful, without efficacy or harmful. While recommendations to coronary patients concerning diet and smoking habits are almost certainly danger-free, this estimate cannot be made with full confidence at this juncture with regard to exercise or drug therapy. Despite the lack of data from controlled field trials, and despite the potential problems, doctors are nevertheless widely recommending that their coronary patients alter their living habits and utilize drugs for control of risk factors. And their efforts along these lines are understandable, in view of the prognostic situation of their patients with CHD, and the mass of indirect, inferential evidence indicating the possibility that such multiple approaches can break the chain of causation of the underlying disease and therefore improve life expectancy.

Obviously, this situation -- of partial, incomplete knowledge, and consequent uncertainty, insecurity and indecisiveness for medicine and public health -- is not satisfactory, all the more so, since the matter of optimal long-term therapy for the millions of persons with clinical coronary disease is one of today's most pressing challenges. Obviously, therefore, an urgent need exists to proceed with the work necessary to solve this massive problem, and place long-term therapy for coronary patients on a more solid scientific foundation. This can only be done by controlled field trials to test the efficacy of at least the

most promising combinations of approaches to secondary prevention.

Conclusion

Since World War II, tremendous research advances have been made in clarifying the pathogenesis and etiology of atherosclerotic disease. In particular, extensive new findings have been amassed indicating the role of mode of life (particularly habits of eating, smoking and sedentary living) -- and related risk factors -- in causing the epidemic of premature clinical coronary disease in the developed countries.

This new knowledge -- available in its essential features by the late 1950s -- pointed to the possibility of an historic breakthrough: the large-scale prevention for the first time in human history of a major chronic non-infectious disease. It led over a decade ago to the initiation of several small-scale field trials, aimed principally at assessing preventability of premature CHD by dietary means. These "first generation" trials have accrued invaluable positive experience on the feasibility of such long term studies. They have also yielded suggestive -- but not conclusive -- evidence that both primary and secondary prevention of clinical CHD can be achieved by dietary means.

Based on this knowledge and experience, medical research is in a scientific position to proceed rapidly and effectively to develop a series of "second generation" mass field trials on coronary prevention. These studies could be calculated

to yield definitive answers within a decade concerning ability to bring the epidemic of premature CHD under control by widespread application of the new research knowledge. They could explore a variety of approaches indicated by the research findings -- e.g. diet, exercise, cessation of cigarette smoking, drugs to correct hypertension, hyperlipidemia, hyperglycemia, hyperuricemia -- singly or in combination. They could be developed on a national and international scale, with extensive cooperation among competent, dedicated research groups in several countries, with an effective division of labor and with assurance of a high degree of scientific standardization and comparability.

At present, a few "second generation" studies are under way, chiefly dealing with pharmacologic agents influencing lipid metabolism. In the main, however, the principal work remains to be launched. The task lies ahead of completing definitive protocols, assembling cooperative research groups, identifying populations for study and beginning the actual trials.

In this connection, the Conference recognized that priority decisions were essential. Although -- as this report indicates -- the potential and need exist for many types of trials, the complexity, duration, manpower demands and costs of such studies compel selectivity in implementation. For reasons noted in the previous section, the Conference emphasized the importance of giving highest priority to field trials aimed at assessing ability to achieve primary

prevention by simultaneously altering the habits of eating, cigarette smoking and sedentary living estimated to be at the root of the current epidemic of premature CHD. At the same time, the Conference urged that multiple studies be encouraged, since no single study can give definitive answers to the complex of questions on coronary prevention confronting the community.

The Conference also took pains to emphasize the fact that little or no further significant scientific knowledge on coronary prevention is likely to be forthcoming without large-scale, well-designed, well-controlled, and well-organized mass field trials. At this juncture, their accomplishment does not depend primarily on initiatives by concerned investigators or their organizations. The scientists are ready to proceed. The next steps are possible now only if appropriate action is forthcoming from the key policy-making and grant-supporting organizations, particularly governments. They must make the decisions and commitments concerning the funds necessary for the scientists to proceed with the work.