CHICAGO HEALTH RESEARCH FOUNDATION

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Dear Colleagues:

Enclosed at last is my draft of the Summary of the Makarska meeting. I would greatly appreciate your comments.

You will be pleased to hear that the report has been approved in principle by the Executive Committee, Council on Epidemiology, American Heart Association, and hopefully will be given detailed endorsement when this summary -- the essence of our policy statement -- becomes available. Dr. Jerry Green, Dr. Fred Epstein and I will be meeting with the Executive Committee, Council on Arteriosclerosis, American Heart Association, on the report later this week. I will let you know the outcome.

Hopefully, this document will be available in final form, endorsed by at least the two foregoing Councils of the American Heart Association, in good time to transmit to the National Heart Institute before the June meeting of the National Advisory Heart Council. Hopefully also it can be transmitted to the World Health Assembly gathering in the United States in June.

I look forward to your comments at your earliest convenience.

Kindest regards.

Cordially,

Jerry Stamler per JS

Jeremiah Stamler, M.D.
Executive Director

Dictated but not read.

JS:gp
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SUMMARY

An international meeting on mass field trials on the prevention of 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 CHD;

2. review problems of design, with particular attention to mass field trials on effects of control of mild hypertension, correction of cigarette smoking, and increase of habitual physical activity;

3. prepare a report on the two foregoing questions, with recommendations concerning field trials for the years ahead.

Basis and need for mass field trials on CHD prevention: Morbidity and mortality rates from premature CHD remain high in many countries, show no signs of diminishing, and constitute tremendous challenges to medical science and public health for preventive action. Major progress in controlling this epidemic can be achieved only by means of a strategy emphasizing prevention, particularly primary prevention -- i.e. 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 CHD 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 available on etiology and pathogenesis, and on the possibility of prevention. Thus, extensive research data indicate that the CHD epidemic in affluent countries is related to habits of eating, cigarette smoking, and sedentary living, and associated risk factors (e.g. hypercholesterolemia, hypertension, hyperglycemia) widely prevalent in the population.

The living habits and risk factors contributing to coronary-proneness can be controlled and corrected by nutritional, hygienic, and/or pharmacologic means. These facts indicate the possibility of prevention. At this juncture, however, sufficient direct evidence is not available from mass field trials to permit an unequivocal 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 can be obtained only by well-designed, well-controlled, well-executed 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 may be essential for convincing physicians, official health authorities, and the public to adopt new approaches to disease prevention and control.

For all these reasons, it is appropriate that the highest priority be given to mounting mass field trials on CHD prevention.

Mass field trials on CHD prevention by diet, and by drugs influencing lipid metabolism: During the late 1940s and 1950s, several "first generation" studies investigated the prophylactic potential (primary or secondary) of diets, particularly fat-modified diets, in free-living and institutionalized populations. A few dealt with drugs influencing lipid metabolism. These studies accrued invaluable experience and information, and showed that mass field trials are feasible. However, these investigations involved relatively small groups of participants, and in several instances had other deficiencies in design. They therefore did not yield conclusive and consistent data on the decisive end-point, effect of diet or drug on CHD incidence and mortality.

At present two major "second generation" trials are in process assessing the preventive potential of lipid-influencing drugs. One is recruiting 15,000 healthy middle-aged men in Edinburgh, Prague, and Budapest, to assess ability of clofibrate (Atromid-s®) to achieve primary prevention of CHD in hypercholesterolemic men. The second -- the Coronary Drug Project being conducted in 53 centers in the United States, under the sponsorship of the National Heart Institute -- is evaluating efficacy of four drugs (clofibrate, dextrothyroxine, estrogens, nicotinic acid) for secondary prevention in 8,400 middle-aged men with previous myocardial infarction.

In addition, based on the positive results of the National Diet-Heart Feasibility Study, consideration is currently being given in the United States to trials on prevention by dietary modification.

The Conference concluded that the two major undertakings currently in progress represent positive advances of the greatest significance. It recommended that mass field trials on primary and secondary prevention by diet -- proposed in the report of the National Diet-Heart Feasibility Study -- be mounted as soon as possible.

Mass field trials on CHD prevention by control of "mild" hypertension: Valuable data on ability to prevent complications of "moderately severe" hypertension (basal diastolic pressures 115-129 mm.Hg) are available from the 1967 report of the U.S. 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 treatment for "mild" hypertension (diastolic pressures in the range 90 to 114 mm.Hg). "Mild" hypertension is a widely prevalent condition, involving millions of persons in the United States. It is unquestionably associated with sizeable increases in risk of premature CHD.

The Conference concluded that there is a need for trials to assess therapy of "mild" hypertension -- not only drug treatment, but also nutritional-hygienic measures (e.g., correction of obesity, moderate salt restriction, regular exercise, and sanatorium care). Trials should be designed to obtain information not only on effects on blood pressure, but also on CHD incidence and mortality, and on total mortality. They should also carefully assess safety, particularly of drug therapy and exercise. For these purposes, multiple studies are needed, in large groups recruited from different strata of the general population and followed for long periods of time.

Since treatment of "mild" hypertension -- if useful -- would ultimately entail long-term therapy for large numbers of persons in the population, trials of pharmacologic treatment should focus on drugs that can be administered without prior hospitalization and without closely regulated, individual titration of dosage. Such trials should be conducted double-blind.

Data are available indicating that persons with "mild" hypertension have a poorer long-term prognosis for survival after developing CHD than normotensive persons. Therefore, secondary preventive studies are needed to assess whether control of "mild" hypertension prolongs life in such persons.

Mass field trials on CHD prevention by cessation of cigarette smoking: Massive evidence is available demonstrating that cigarette smoking is an undesirable habit, generally harmful to human health, and specifically associated with increased risk of premature CHD. Scientific uncertainty exists as to the mechanisms whereby cigarette smoking contributes to CHD susceptibility. Further, no data are available from any field trials on ability to achieve primary or secondary prevention of CHD through elimination of the cigarette smoking habit.

In view of these facts, the Conference concluded that field trials are needed in this area, and noted with gratification that one study has been launched among high-risk British civil servants.

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. They must also consider the fact that medical and public health practice emphasizes the desirability of persuading all cigarette smokers to stop smoking. Hence it is not ethically appropriate to assign persons randomly to control groups committed for research purposes to continued cigarette smoking. In this circumstance, one possible design might be to utilize institutions as units for randomization, rather than individuals (provided the number of institutions is large enough to minimize risk of bias). For example, large numbers of banks could be drawn into such a study, with random allocation of banks to experimental and control groups. Special, vigorous, sustained anti-smoking measures would then be carried out only among employees of banks assigned to the experimental group. Other possible approaches were noted.

In view of these problems and the limited experience to data, the Conference recommended that the first stage of trials in this area focus on methodology and feasibility.

Only limited data are available concerning relationship of cigarette smoking to long-term prognosis after development of CHD. The Conference therefore recommended that trials be undertaken on the value of cessation of cigarette smoking for coronary patients. It was again noted that -- in view of present medical practice -- a problem exists with respect to establishing control groups for such studies. The possibility was again noted of randomizing by centers, rather than by individuals. It was also recommended that the initial endeavor be evaluation of methods for achieving cessation

of smoking in CHD patients who have persisted in using cigarettes.

Mass field trials on CHD prevention by exercise: Although findings of some studies indicate a relationship between habitual lack of exercise and risk of premature CHD, data on this matter are not consistent or unequivocal. No results are available from any controlled field trials on ability to prevent CHD by exercise. A few small pilot studies have recently been carried out. Those in the United States indicate that it may be difficult to retain a satisfactory proportion of previously sedentary middle-aged men as long-term participants in exercise programs. Since this 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 such key design questions as type, frequency, and duration of exercise for CHD prevention; methods of recording and quantifying exercise performed (unless it be supervised ergometric exercise). One key method is to measure effects of exercise on cardiopulmonary fitness, using a graded ergometric test. For mass use in middle-aged, coronary-prone populations, a submaximal test is preferable to a test demanding maximum exertion. This objective, reproducible, quantitative procedure can serve as a key intermediate end-point in exercise studies (equivalent to serum cholesterol and weight measurements in diet trials). The Conference therefore recommended that encouragement be given to efforts to improve and standardize fitness testing procedures.

Utmost care must be given to safety considerations -- both in fitness testing and exercise prescription. Medical criteria leading to exclusion should be clearly specified. A qualified staff is essential, equipped with modern instrumentation and trained to cope with emergencies.

Trials are urgently needed to evaluate the role of exercise in secondary prevention of CHD, especially since active rehabilitation of coronary patients is being increasingly practiced by physicians, in the absence of clear-cut data as to its efficacious or harmful influence.

Mass field trials on CHD prevention by change in living habits to control multiple coronary risk factors: Increasing emphasis is being given in many countries to public health and medical programs for control of coronary risk factors by general modification of living habits -- especially nutritional, smoking, and exercise habits. Mass field trials are urgently needed to test the efficacy of these approaches. Such trials deserve high priority for several reasons: They are important for testing the basic theory that the CHD epidemic has been caused by several concurrent major innovations in mode of life. They also aim at answering a most decisive practical question: Is there validity to the most promising preventive approach -- simultaneous change in several environmental causative factors? Trials involving alteration of two or three living habits -- thereby controlling two or three major coronary risk factors -- have the potential of recording much more substantial reductions in CHD morbidity and mortality (e.g. more than 50%) than studies of single factors. Hence, multifactor trials can be undertaken with much smaller sample sizes than trials evaluating one factor at a time.

Limited availability of manpower, resources, and funds compel choices among several types of trials. The Conference stressed the importance of trials testing the hypothesis that primary prevention of CHD can be achieved by alteration in major living habits -- particularly diet, smoking, and exercise.

Mass field trials on CHD prevention by combined drug treatment of multiple coronary risk factors: Trials are also needed to assess preventive potential of long-term therapy with combinations of drugs to correct and control two or more coronary risk factors -- e.g. drugs for hypertension, hyperlipidemia, hyperglycemia. Since a sizeable proportion of middle-aged adults manifest two or more of these risk factors, combined drug therapy is being more and more frequently employed to decrease susceptibility to CHD.

However, no data on efficacy or toxicity are available from controlled trials assessing large-scale, long-term use of available drugs.

The needed mass field trials of combined drug therapy should uniformly proceed on a double-blind basis, and should consider use of factorial designs.

Mass field trials on CHD prevention by change in living habits plus drug therapy: Efforts are presently proceeding in medical practice to achieve primary and secondary prevention of CHD by prescribing both change in living habits and drugs for control of CHD risk factors. 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.

Priorities: Theoretical and practical considerations indicate that highest priority should be given to primary prevention studies in high-risk, middle-aged men, to test efficacy of simultaneous correction and control of major living habits. 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. The need of the moment is to encourage concerned investigators to develop a variety of approaches, to overcome the current lag in developing trials on coronary prevention.

This approach applies to both primary and secondary prevention. No data are available concerning 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, 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 regard to exercise or drug therapy.

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 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 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(especially 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 points 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. To make a definitive assessment of the potential for coronary prevention, mass field trials are needed, planned with the aim of obtaining clear-cut answers within the decade. They can and should 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. Their cost would be modest compared to the price exacted by the CHD epidemic, and to the potential saving from successful prevention.

At present, a few studies are under way, dealing chiefly 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.

The Conference underscored the importance of high-level decisions on priorities, and on the overall commitment to trials. 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. 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.