The Makarska Conference 1968. Nodal Point in Cardiovascular Disease Epidemiology

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Abstract

U.S. National Heart Institute (NHI) officials were thrust into a quandary by the 1968 Report of its Diet-Heart Feasibility Study investigators that recommended an explanatory diet trial in coronary heart disease (CHD) prevention. Else, it provided an alternative: a pragmatic trial of multiple risk-factor intervention. The Institute envisioned its staff and budget wholly consumed by experiments of such magnitude and complexity. Several years of deliberations followed, among serial special review commissions, on the "inevitable ordeal" of trials, creating a major pause in Institute policy and plans for research in cardiovascular disease (CVD) prevention. Meanwhile, a vigorous community of investigators was persuaded that the common modifiable characteristics, which they had found associated strongly and consistently with CVD risk, were probably causal. Thus, they clamored, the time had arrived either to conduct trials of risk modification or move on to safe preventive action among the general population. Frustrated by apparent Institute inaction, they gathered in September, 1968, at Makarska, on the Adriatic coast of Croatia, to review and strategize.

This historical note recounts the story of the Makarska Conference on Mass Trials in Prevention of CHD, and dissemination of its Report, as a nodal point in chronic disease epidemiology. It proposes that the institutional actions the conferees directed, or their conference report stimulated, helped end the "pause" in prevention policy at the center of research and introduce the modern period of CVD epidemiology on the world scene.

235 words

Text

It is difficult now to reimagine the vigor, intensity, and expectations of the new science of cardiovascular disease (CVD) epidemiology and prevention in the late 1960's. Equally intense at that juncture was the reaction from its scientific community to the balk on the part of the National Heart Institute (NHI) on its research policy for CVD prevention. This unusual pause was precipitated by the strong recommendation from distinguished investigators of the National Diet-Heart Feasibility Study that, based on their findings, a "definitive" diet-heart trial was both needed and feasible (1). Clearly such an undertaking would overwhelm the Institute staff and exhaust its budget. NHI leaders seemingly panicked. They withdrew to counsel together and to enlist carefully chosen review groups to address the painful recommendations on trials. The resulting pause in evolution of the Institute's prevention research policy would last for some years!

By the late '60's, meanwhile, the first-phase epidemiological evidence was in: the major CVD risk factors of diet, tobacco use, and serum cholesterol and blood pressure levels were well established from prospective studies among healthy people and whole populations. These characteristics were strong, independent, and universal predictors of CVD events among and within populations. Moreover, the risk factor relationships in populations were congruent with evidence from the clinic and the laboratory; the pathways from them to the CVD event were either established or plausible. Therefore, causal inference from risk factor findings was strong, the potential for CVD prevention by their modification was promising, and causation was now susceptible to experimental "proof." If health promotion was not to proceed on the evidence, then trials were inevitable.

Yet, at that very moment within the National Heart Institute, the chief international engine of CVD research, two solid proposals for experimental tests of the risk factor hypothesis--an "explanatory" National Diet-Heart Trial (1) and a "pragmatic" National Multiple Risk Factor Prevention Trial ("JUMBO") (2-5)--were dying on the twin barricades of academic resistance and "protection" of resources. This Institute dilemma resulted in a portentous pause in policy decisions and grant activity on CVD prevention research. From 1968 to 1972; serial discussions were held in the National Heart Institute among expert consultants on prevention trials; a select review committee was engaged to review the diet-heart trial; all without resolution of the quandary. "The Pause" then became a major concern and prime focus of the flourishing new community of researchers, champions of CVD prevention (6).

A few clear heads in a few critical institutions then began to address this crisis at the center. Two of their leaders, an "old-boys club" of Ancel Keys and Paul Dudley White, co-chairs of the International Society of Cardiology (ISC) Research Committee, reflecting on the crisis, conjured a course of action they thought might carry the day for CVD prevention. This happy duo of assertive physiologist-epidemiologist, Ancel Keys, and Master Cardiologist-diplomat, Paul White, had, over the two previous decades, successfully cajoled the international cardiological elite into recognition of epidemiology as a discipline and its incorporation into the research and

training of their academic departments. They had presided over a 1963 international conference in Makarska, on the Dalmatian Coast of Croatia, in which plans were formulated for researches and for training seminars in epidemiology and preventive cardiology (7). This plan was adopted by the ISC in 1966 at the New Delhi World Congress of Cardiology, at which time the ISC established scientific councils modeled after those of the American Heart Association, including a Council on Epidemiology and Prevention. The first order of business of that council was to plan the Ten-Day International Seminars on CVD Epidemiology and Prevention that became a 50-year tradition and introduced generations of young cardiovascular scientists and clinicians to epidemiology and a population or social view of cardiovascular disease and health (8).

To address the crisis of 1968, Keys and White planned another Makarska conclave of experts to summarize the evidence about modifiable causes of CVD and to recommend needed international researches, including mass field trials of prevention. They appealed to the programmatic interests among research support agencies internationally and found them eager to participate. Leaders of the American Heart Association (AHA), the ISC, the U.S. National Heart (not-yet-Lung-and Blood) Institute and U.S. Public Health Service, the World Health Organization, the London School of Hygiene and Tropical Medicine, and leading cardiological research centers; all were represented (see Appendix I & II for attendees and their institutions) (3).

Already scheduled to be present in Makarska that fall were an international team of the 10th anniversary field survey of the Seven Countries Study, Croatian cohort (9), and faculty of the first Ten-day International Seminar on CVD Epidemiolgy and Prevention of the newly established ISC Scientific Council of the same name (8). Jeremiah Stamler, the charismatic flame carrier of CVD prevention, was delegated to chair the conference. All were brought together on the Adriatic coast in fall of 1968.

Insert photo

Faculty and discussants of the Makarska Conference and First Ten-Day International Seminar on CVD Epidemiology and Prevention

Left to right: Henry Taylor, Thomas Chalmers, Austin Heady, Jeremiah Stamler, Richard Remington, Samuel Fox, Gösta Tibblin, Igor Glasunov, Geoffrey Rose, Frederick Epstein, Martti Karvonen, Ancel Keys, Jerome Green, and not visible, taking the photograph, Henry Blackburn.

A younger contingent was also present at Makarska: members of the Seven Countries Study survey team and fellows of the first ISC Ten-day Seminar. The seminar curriculum, with didactic sessions on "Causation" and visits to an actual field survey, became an important component of the intellectual feast that Makarska became that fall (3).

It is difficult now to separate the architects from the builders from the purveyors of the Makarska Report. But in the salubrious ambiance of Makarska their deliberations yielded a powerful summary of the evidence about possible causes and prevention of CVD, plus a master plan for needed new researches. The intent of the Makarska Report was to provide not only the rationale but a major prospectus and impetus for implementation of specific prevention trials, including the yet-untried pragmatic trial involving multiple risk factors for CVD. The message was intended to be disseminated by the Makarska discussants, many of whom were strategically poised to provide their agencies with ready plans for the needed researches and to unlock the means for their realization (see Appendix II for "Conduits to Action").

The Makarska Conference Report

The Makarska delegates focused on the chief issues at hand: the strength of the evidence about prevention of CVD and recommendations acceptable to those skeptics, mainly from clinical and

laboratory sciences, who largely determine what medical research is funded. The Conference summary, quoted here, recommended further intervention studies, in healthy and patient populations, using specific explanatory, single-risk factor trials and also, with emphasis, a pragmatic, multiple-risk-factor intervention trial (3):

> "Since WWII, tremendous research advances have been made in clarifying the pathogenesis and etiology of atherosclerotic disease. In particular, extensive new findings have been assessed indicating the role of mode of life (particularly habits of eating, smoking, and sedentary living) and the elevated risk factors causing the epidemic of premature clinical coronary disease in developed countries. This new knowledge – available in its essential features [since] the late 1950s – points to the possibility of an historic breakthrough: the large-scale prevention for the first time in history of a major chronic non-infectious disease. [A series of] 'first generation' trials have accrued valuable, 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 coronary heart disease 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 disease prevention. These studies could be calculated to yield definitive answers within a decade concerning ability to bring the epidemic of premature coronary heart disease under control by widespread application of available research knowledge. They could explore a variety of approaches indicated by the research findings--for example, diet, exercise, cessation of cigarette smoking, drugs to correct hypertension, hyperlipidemia, hyperglycemia, and 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.
>
> 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 Makarska Conference recognized that priority decisions were essential. Although – as this report indicates – the potential need exists for many types of trials, the complexity of duration, manpower demands, and costs of such studies compels selectivity in implementation. The Conference emphasized the importance of giving highest priority to field trials aimed at assessing ability to achieve primary prevention by concurrently altering 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 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 (3)."

After summarizing the evidence and its potential for CVD prevention, the Makarska conferees proposed a series of initiatives to be carried away by the representatives of the agencies of action. Attention to the listing of participants (in Appendix I & II) indicates the level of expertise brought to the Makarska deliberations and of authority to disseminate and implement the recommendations. In the immediately ensuing years the agencies represented at Makarska: the AHA, NHI-USPHS, WHO, and the Joint Commission on Heart Disease Resources, would develop seminal policies for research and programs on CVD prevention. The more complete and influential of these were the 1970 Report of the Joint Commission on Heart Disease Resources (10), the 1971 National Heart and Lung Institute (NHLI) Task Force on Atherosclerosis (11), and the WHO Expert Reports on preventive trials and community strategies (12-14). Among the more effectual of these was the plan for a generation of trials and cohort studies of the U.S. NHLI Task Force, reformulated and presented by Theodore Cooper, NHLI Director, at the annual scientific sessions of the American Heart Association in 1971(see Appendix III and reference 15). This ambitious plan provided direction for a rigorous multimodal NHLI research policy related to the prevention of CVD. And it ended "The Pause."

The Modern Era of CVD Epidemiology and Prevention

The Makarska message took hold; the particpants dispersed and soon helped initiate plans worldwide for the Modern Era of CVD epidemiology. That era began in the early 1970s with new institutional policy, new cohort studies, trials, surveillance, and community programs in CVD prevention. This impetus to research was bolstered by a rapid growth of training programs and the academic discipline of non-infectious disease epidemiology (16). Preventive cardiology took off to such a degree that even neurologists caring for stoke and bariatric surgeons dealing with morbid obesity added "Preventive . . . ." to their identities. National programs and legislation on risk screening, dietary recommedations, and tobacco regulation, all with prevention and health promotion as their intent, were implemented in the 70's and 80's. A "Great Leap Forward" of CVD prevention and health promotion was under way. It didn't last (17).

Update

There was a small and active minority at Makarska-1968, and throughout the scientific community at the time, strongly representing the view that community-wide health promotion studies, with rigorous evaluation of the effects of various intervention modalities, was the logical next step to follow the risk factor paradigm; rather than the period of difficult and costly field trials proposed at Makarska. The trials meant more delay for indicated health promotion strategies among the population, because trials were in the medical model and focused on change by the individual. There was also a sense that the major motivation for these tiresome experiments was to meet never-ending requirements for "proof" from a skeptical core of laboratory scientists and academic clinicians. They were inclined to insist on ever more evidence before *any* intervention was proposed, even safe hygienic ones. But the costly, complex trials won out at Makarska; perhaps in a Pyrrhic victory?

In the end, many of the post-Makarska generation of primary prevention trials had inconsistent or little effect on CVD risk and rates. Mainly they were underpowered. The interventions attempted were individual rather than sociocultural. They were carried out during a period notable for major changes in health knowledge, attitudes, and behavior, especially eating, exercise, and smoking patterns. Also they happened during rapid advances in cardiac care, all of which tended to narrow the differences between treated and control participants in the trials (17,18). A few community demonstration studies were undertaken in parallel with the mass trials of the '70s and '80s. They, too, were low-powered, "quasi-experiments," carried out without prior researches to establish the more effective interventions at a population and community level. Their mixed and small effects have had an enduring negative influence on the genesis and support of community-level researches for chronic disease prevention (17).

Then, in the 1990s, came the Human Genome Project at NIH and the dawn of genomics and "precision" medicine. This ultimate focus on the individual came to dominate the panoply of research and curriculum in cardiovascular medicine and prevention science. That focus is largely unrelated to the prime function of epidemiology as the basic science of disease prevention and public health. It has demonstrably broadened interest in and understanding of disease mechanisms. But rigorous tests of population-wide approaches to prevention of the common chronic diseases and the promotion of health, in community-wide research interventions, is largely abandoned.

Meanwhile, a dramatic decline is documented in cardiovascular death rates of many industrial countries from the 1960s to the present (17). Epidemiological surveillance in the 1980s established that the early phase of this decline was mainly related to a favorable shift in the distribution of CVD risk factor levels. This was manifest as a decline in sudden cardiac deaths outside hospital, apparently due to mass changes in health behavior and exposures (18). This predominantly social influence was overtaken, from the 1980s to the present, by the documented effects of improved medical care for CVD, established by a greater proportionate decline in CVD deaths in-hospital over those outside (18).

The downward trend in CVD death rates continues today with an abatement of the rate of decline and coincident with a new epidemic of obesity and metabolic diseases (17). In addition, a long-predicted epidemiological transition has emerged among societies on an upward economic course, with increasing CVD mortality rates and decline in infectious and traumatic death rates (19). Moreover, for the first time in modern history, average life expectancy in the U.S. has for several recent years failed to increase (20).

Clearly, these trends require attention, including by research. NIH focus, meanwhile, follows not at all the trends in public health. It remains squarely on its mantra: "from the bench to the bedside" rather than with research "on the population outside." It seeks a pipe-dream of "health for all," but through high-tech, "precision medicine," personalized for each individual. Research languishes on how best to achieve a healthy society.

2632 words

Competing interests: None

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Appendix I

Makarska Conference Sponsors and Participants

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

Sponsors:	Council on Arteriosclerosis, Council on Epidemiology, and International Program Committee, American Heart Association
Co-Sponsor:	Council on Epidemiology and Prevention, International Society of Cardiology
Chairman:	Jeremiah Stamler, M.D.
Co-Chairmen:	Frederick H. Epstein, M.D. Jerome G. Green, M.D. Ancel Keys, Ph.D.
Rapporteurs:	Jerome G. Green, M.D. Jeremiah Stamler, M.D.

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Appendix II

Makarska Conference Participants as Direct Conduits to Policy Implementation

Makarska Conference participants, soon after returning from the conference of September, 1968, began planning and implementation of major preventive trials and research strategies in the prevention of CVD. This association does not prove the causal role of the Makarska Conference in such a major therapeutic reform. However, the close and consistent relation of these select conferees with the subsequent research activity, based on the position, status, and executive function of their unique careers, is strongly suggestive that the Makarska deliberations and recommendations directly influenced the subsequent research policy and activity. At the outset, William Zukel, then Associate Director of the National Heart Institute, states that the Makarska Report especially influenced Institute consideration of the pragmatic multiple risk factor intervention trial (MRFIT) as a rational and feasible model to test prevention (21). Note these other examples of a direct conduit to action:

Thomas Chalmers, Makarska participant, was already an established authority on clinical trials from his executive role in the pioneering U.S. Veterans Administration clinical trials on the control of hypertension. He later became a leader of therapeutic reform in modern medicine with his classic 1975 editorial on "Randomization of the first patient," which practice he recommended with *any* new or experimental drug (22). In the late '60s he became a major consultant and advisor to NIH on trial design and operation and brought his experience from service on the steering committees of pioneering NIH-supported multicenter preventive trials, including the Coronary Drug Project and the University Group Diabetes Program.

Richard Remington, statistician, was a designer of the first investigator-initiated proposal to NIH for a multiple-risk factor intervention trial (MRFIT) on the prevention of CHD ("JUMBO"), submitted to NIH in February,1969, promptly following on the Makarska Conference (2). He was co-investigator of the late 1960s Pilot Trial of Physical Activity in Prevention of Coronary Heart Disease in which the MRFIT model was honed (4). He went on to head coordinating centers in Ann Arbor and Houston for NIH-funded prevention trials of the 1970s.

Henry Taylor and Jeremiah Stamler were pioneer CVD epidemiologists and Remington's colleagues on the "JUMBO" MRFIT proposal to NIH in 1969, *de facto* a product of their experience and the Makarska deliberations (4,5). Taylor was Co-P-I of the later U.S. Multiple Risk Factor Intervention Trial (MRFIT) and P-I for the 1960s Physical Activity Pilot Trial, as well as of the LRC Population Survey of the early 1970s. Stamler directed the pioneering multiple risk factor Coronary Prevention Evaluation Program among Chicago workers and the multi-centered Coronary Drug Project trial of the 1950s and '60s. He served on the Steering Committee for the U.S. MRFIT and the

Hypertension Detection and Follow-up Program (HDFP) and was Principal Investigator and proposer of the "JUMBO" multi-risk trial in 1969, a direct intellectual outgrowth from Makarska (4,5).

Geoffrey Rose, from the London School of Hygiene, was a pioneer in British CVD epidemiology and preventive trials and co-author of the WHO manual "Cardiovascular Survey Methods" published the same year as the Makarska Conference, 1968. He headed the WHO Multifactorial CVD Prevention Trial in Industry from 1970, a direct intellectual product of the Makarska Conference (13).

Gösta Tibblin was a pioneer CVD epidemiologist of Sweden who designed the Gothenburg Study of Men of 1913 and, directly following his participation in Makarska, designed and initiated the Gothenburg Multiple Risk Factor Intervention Trial (14).

Igor Glasunov represented the Copenhagen World Health Organization (WHO) CVD Unit as a participant at Makarska, which conference was central to WHO planning and operation of subsequent international activities in prevention of CVD and non-communicable diseases, including the WHO Multiple Risk Factor Trial in Industry and the WHO Comprehensive Community Programs that flourished in the early 1970s (12-14).

Jerome Greene was a central authority of the U.S. National Heart Institute involved in policy and review of all NHI trials, including the U.S. Multiple Risk Factor Intervention Trial formulated in the early 1970s (11).

Austin Heady was statistical expert in the design and management of the London School of Hygiene's pioneering observational studies and trials in chronic disease prevention, including the WHO Multifactor Trial in Industry led by Geoffrey Rose, which was a direct outcome from Makarska (13).

Martti Karvonen was a Finnish pioneer in CVD epidemiology and preventive trials, the former Surgeon General of Finland, founder of the Finnish Public Health Institute, P-I of the Finnish component of the Seven Countries Study, and consultant to WHO (9). He also directed the Finnish Mental Hospital Trial in CHD Prevention and founded the North Karelia Project, the first community demonstration project in CVD that began in 1971 (24).

Ancel Keys was a pioneer of CVD epidemiology and Co-chair, with Paul White, of the Research Committee of the International Society of Cardiology, which implemented the Makarska Conferences of 1963 and 1968. He headed the Seven Countries Study and the Minnesota Clinic of the National Diet-Heart Pilot Trial and was Co-P-I of the JUMBO MRFIT proposal to the NHI in 1969 (1,2,7). Paul White was the pre-eminent American cardiologist of the day, the first Executive Officer of the Advisory Council of the National Heart Institute, and oversaw the review and funding for all the National Heart Institute's early epidemiological studies and trials. With Keys, he was a founding father of CVD epidemiology and preventive cardiology and co-chair with Keys

of the ISC Research Committee that planned and sponsored the Makarska Conferences (3).

Frederick Epstein was a pioneer of CVD epidemiology and P-I of the Tecumseh Community Study. As Chair of the American Heart Association (AHA) Committee on Criteria and Methods and consultant to WHO, Geneva, he was centrally involved with the design and operation of population studies and preventive trials internationally in the 1970s.

Henry Blackburn served on the Steering Committee of the pioneering Coronary Drug Project trial and the Pilot Study on Physical Activity in CHD Prevention in the 1960s and served as Project Officer of the Seven Countries Study (2,3,7,9). Immediately following Makarska he was a co-proposer of the JUMBO Multiple Risk Factor Trial (4,5) and then Vice Chair of the U.S. MRFIT (21), and published with Geoffrey Rose the WHO Manual: "Cardiovascular Disease Survey Methods." Also immediatlely following the Makarska Conference, he wrote a text chapter on "Multiple Risk Factor Trials in CVD Prevention" (23). Subsequently, he was P-I on surveillance research and community trials of the 1980s: the Minnesota Heart Survey and Minnesota Heart Health Program (26).

Prof. H M Whyte was a leading Australian cardiologist who, at Makarska, represented the Board of Directors of the International Society of Cardiology (ISC), sponsor of the Makarska Conference.

Appendix III

NHLI Research Policy of 1971-72 Introduced the Modern Period of CVD Epidemiology, Preventive Trials, and Preventive Cardiology, as Influenced by the Makarska Report (15)

Theodore Cooper outlined the new National Heart and Lung Institute (NHLI) prevention policy in his Lyman Duff Memorial Lecture at the AHA Scientific Sessions in Atlantic City on November 9, 1971(15). For a "named" lecture, it was remarkably chatty and laced with self-deprecating humor. In it, for the first time, an Institute director outlined the triangular research strategy that was to become heralded and highly effective: the parallel conduct of laboratory, clinical, and population studies on the causes, control, and prevention of a chronic disease, coronary heart disease (CHD). Epidemiology was thereafter identified and included as a "basic science" as well as an applied one in NIH operations. Cooper made clear, one would have thought for all time, that a productive national research program required forward motion among *each* complementary discipline: clinical, laboratory, and population science.

Cooper also laid the groundwork for both primary and secondary prevention trials, that is, among those not yet victims of heart attack or stroke and those already manifestly involved. He set into motion a vast program of Lipid Research Centers, a program more oriented to the individual at risk than to the population-wide strategy proposed by many. Eventually, however, research with population-wide, public health approaches to intervention was also embraced at NHLI, with the undertaking of surveillance studies and demonstrations of intervention programs at the community level.

With this forward motion in mass trials, a major new operational strategy was also implemented. In it, NIH staff, with consultants, designed the national studies centrally and then implemented them through requests for proposals, central review, and cooperative agreements or contracts. In these, the government would appoint the chairpersons and steering committees for the projects and assign NIH project officers from "Bethesda Central" to oversee each study. This tight central organization and direction of major prevention researches by the NHLI (later renamed the National Heart, Lung, and Blood Institute or NHLBI), succeeded in recruiting to its fold virtually all experienced U.S. investigators in the field; its bevy of new prevention-oriented studies became "the only game in town." The field of CVD prevention moved forward briskly and for a while appeared to flourish under such central direction.

Among the categorical Institutes of NIH, NHI led strongly, and still leads comparatively, in preventive research policy, savvy, and enterprise. Most cardiovascular disease investigators in the 1970s and '80s were busily occupied with these good works. A few, however, laid plans for more original things to do, and to do more independently, in community-wide prevention researches (24-26).