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TRENDS IN EPIDEMIOLOGY

Application to Health Service Research and Training

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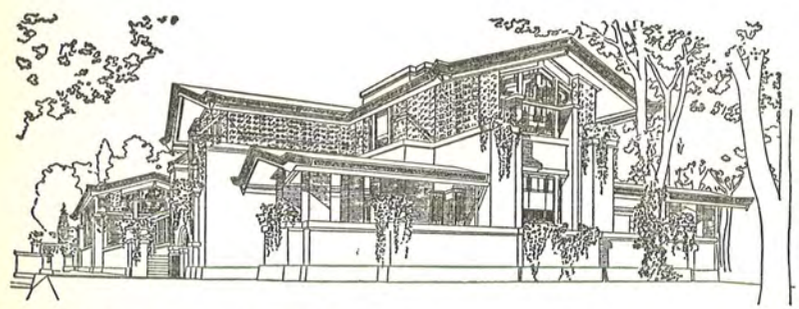

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Chapter 7

MULTIFACTOR PREVENTIVE TRIALS (MPT) IN CORONARY HEART DISEASE

HENRY BLACKBURN

IN THE INTRODUCTION to this volume about trends in epidemiology, Gordon Stewart clearly sets the high priority due preventive trials in chronic disease. In Chapter 5 of this same volume, Frederick Epstein provides the background and rationale for such trials in the prevention of coronary heart disease (CHD).

All the available evidence about the frequency and the nature of CHD compels the conclusion that a major reduction in premature death and disability from this disease will be achieved only through a strategy of primary prevention. Most physicians and official bodies in the United States accept the strategy that CHD patients and those at very high CHD risk, based on certain characteristics, should receive the benefit of potential though unproven preventive measures. Nevertheless, two sharply conflicting bodies of opinion exist about whether public health application of the available knowledge on coronary risk factors should be made as a primary preventive approach in the population as a whole. This lack of unity applies particularly to the question of a qualitative change in the diet and, to a lesser degree, to the question of treatment of mild hypertension. Unity of opinion is likely to come about only through the results of an adequately designed and executed preventive trial, the "inevitable ordeal." A definitive, positive, and major effect in a preventive trial would likely set in motion the considerable changes—personal, socio-

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cultural, and economic—requisite to a substantial reduction in the national burden of CHD.

With respect to such a definitive trial, a trend is now in progress in cardiovascular epidemiology toward the Multifactor Preventive Trial (MPT). A body of thought, developed over the past few years, has led to the design, planning, and recent institution of such trials, the aim of which is to test whether intervention on the multiple major CHD risk factors will in fact influence the incidence and risk of CHD.

This body of thought, these plans, and the protocols already developed merit critical attention. They may offer the most rapid and efficient evaluation of the possibility of CHD prevention. They embody a concept which is highly appropriate and widely applicable to chronic diseases associated with multiple risk factors. They apply an approach which is compatible with the experience and precepts of clinical medicine.

The MPT concept is a simple one. In the case of CHD, the risk is firmly related to multiple characteristics. Several of these risk factors measured in health, i.e. serum cholesterol and blood pressure level and cigarette-smoking habit, have consistently and independently been shown to explain much, though by no means all, of subsequent CHD experience. It has been found that their individual effects are at the least additive.[1-3] In addition to the multiple factors influencing CHD, it has been found impossible, practically, to modify single CHD risk factors in trials which involve giving health advice, without at the same time modifying other CHD risk factors. Thus, a great deal of evidence, as well as logic, supports the attempt to simultaneously modify the major CHD risk factors in a MPT. The results will concern the practical question whether, and to what degree, the incidence of CHD may be influenced by simultaneous intervention on multiple risk factors. The MPT is therefore a pragmatic public health approach rather than an explanatory research one.[4]

The purpose of this presentation is to expose briefly the historical development of the thinking on, the evidence in support of, and the developing plans of this trend to MPT in cardiovascular epidemiology.

HISTORICAL DEVELOPMENT OF THE MPT IN CHD

The MPT in CHD is a relatively recent and a truly international development. Much of the early thinking and design grew out of the direct experience of investigators in the major first-round preventive trials. Included, among others, were members of the Diet-Heart Study,[5] the Collaborative Study on Physical Activity,[6] the Chicago Coronary Prevention Evaluation Program,[7] and the Coronary Drug Project.[8] A planning group met during the period 1966-69 and prepared a detailed design and protocol for a MPT in CHD.[9]

Concurrently, a series of international discussions was instituted to consider the need, priorities, and methods for clinical trials in CHD and hypertension. The first of these, the Makarska Conference on Clinical Trials,[10] was held in Yugoslavia in September 1968 under joint sponsorship of the International Society of Cardiology, the American Heart Association, and the U.S. Public Health Service. Subsequent discussions were carried out in conjunction with successive Cardiovascular Epidemiology Seminars of the Council on Epidemiology and Prevention, International Society of Cardiology.

Participants in this series of discussions proceeded to prepare careful and detailed protocols. The first, for a MPT in the U.S., using a partially factorial design among randomly allocated high-risk individuals, was submitted in 1969 as a grant application to the National Heart and Lung Institute. There it was rejected. In contrast, two unique European protocols have been effectively implemented. One is in London and involves randomization among industrial units[11] and the other in Gothenburg, with randomization of individuals from a population sample of that city.[12] These studies are well into the screening and run-in periods.

In November 1970, the European office of W.H.O. assembled a working group to consider the design and possible extension of these MPT to other countries.[13] Subsequently, steps have been taken to integrate other units into those protocols.

Meanwhile, in 1971, decisions have been made in the U.S. and

in France to initiate controlled trials and community programs for hypertension. During 1971, a recommendation is expected from the National Heart and Lung Institute Task Force on Atherosclerosis about implementation of U.S. trials in CHD. The task force has been provided with expert testimony on all aspects of such trials, blind and nonblind, in open and in closed populations, and involving intervention on single or on multiple risk factors.

MULTIPLE CHD RISK FACTORS AS A BASIS FOR THE MPT

"Important" Risk Factors

Within populations, the individual risk of CHD is strongly related to the number and the levels of multiple characteristics. Serum cholesterol and blood pressure levels and cigarette smoking are considered risk factors of major importance because of (a) their strong individual-independent and combined predictive relationship to CHD morbidity and mortality, (b) the consistency of this relationship in many studies among differing cultures, (c) the great frequency of their presence in elevated form in middle-aged men in prosperous countries, and (d) the concordance of the evidence about the role of these particular factors between the major methodologies of clinic, laboratory, and population studies[1,2,7,14] (see also Chap. 5 of this volume). A number of other important and interesting predictors of risk will not be considered here because they are not as fully documented or have lesser predictive power or lower frequency of occurrence.

Multivariate Risk Functions

Simple cross-classification of combinations of the major CHD risk factors allows discrimination between men with an eightfold difference in CHD risk.[2] Their combination in multivariate analyses such as that of Cornfield[3] (see also Chap. 6 of this volume) discriminates those having CHD events from others with considerable precision, within the populations from which the regression coefficients were themselves derived. Much more important is the fact that this logistic function has also been found

to rank individuals successfully, from lower to higher risk, in other populations, including those with greatly differing absolute risk of CHD.[1,15,16]

The risk function explains a significant part, clearly not all, of the population and individual differences in CHD risk. It indicates the potential for prevention, but, of course, cannot prove whether a population or an individual, after a generation or a lifetime of exposure to a given risk, will experience a change in risk predicted from a given reduction of the level of risk characteristics. The evidence from trials so far provides also a crude estimate of the reduction of incidence possible and the time it may take to achieve any reduction in CHD incidence.

The risk function provides a useful base on which to predicate the possible effects of multiple risk factor reduction. This is illustrated in Table 7.1, reproduced from Cornfield,[17] and indicates a potential reduction of 12-year CHD incidence from about 200 to about 50 per 1000 at age 45.

In sum, the evidence suggests that multiple risk factors operate in CHD, that they operate at least in an additive fashion, and that their simultaneous modification in a MPT would allow a more efficient test of prevention, in terms of time and sample size required, than reduction of single factors, one at a time.

TABLE 7.1
TWELVE-YEAR RISK OF CORONARY HEART DISEASE FOR DIFFERING LEVELS RISK FACTORS BY AGE, FRAMINGHAM MEN, 1948-60

Serum Cholesterol Value	Systolic Blood Pressure	Relative Weight	Smoking	Entrance Age (yr) and New Events per 1000		
				35	45	55
250	150	110	1 pack	67	209	261
220	150	110	1 pack	35	175	212
220	130	110	1 pack	23	152	164
220	130	100	1 pack	20	120	154
220	130	100	0 pack	6	54	95

Note. Age group at exam 1:30-39y = $\log_2 [P/(1-P)] = -17.6 + 0.023 \times_1 + 0.022 \times_2 + 0.014 \times_3 + 0.598 \times_4 + 0.092 \times_5$; 40-49 y = $\log_2 [P/1-P)] = 13.7 + 0.0.007 \times_1 + 0.09 \times_2 + 0.027 \times_3 + 0.434 \times_4 + 0.120 \times_5$; and 50-62 y = $\log_2 [P/(1-P)] = -11.1 + 0.009 \times_1 + 0.016 \times_2 + 0.008 \times_3 + 0.272 \times_4 + 0.072 \times_5$. From Cornfield and Mitchell, 1969, with permission of the authors and publisher.

THE POPULATION FREQUENCY OF CHD RISK FACTORS

The frequency of CHD risk factors in a population, as well as the degree of concentration of eventual cases within risk categories, determines the efficiency of the risk factor approach. Roughly 10 percent of middle-aged men in the United States have *three or more* risk factors elevated.* These men are at far greater relative risk than those having only a single factor elevated, but, in fact, they produce only about 20 percent of the eventual CHD cases, a rather small fraction of the total population disease burden.

At the other extreme, approximately 80 percent of the male U.S. population has *one or more* risk factors elevated, and they account for something over 90 percent of future CHD events. This emphasizes the need for the broadest social approach in order to significantly reduce the disease. Between these extremes is the fraction of the population "carrying" *two or more* of the major CHD risk factors, i.e. something under 40 percent, and which "produces" about 60 percent of the new events. This is the proportion which it is perhaps reasonable and surely desirable to identify and among which to concentrate preventive efforts.

Despite these limitations encountered in prosperous countries where the society as a whole is at great risk, multifactor risk detection has, in fact, brought us to a level of prediction of CHD which is unequaled for any other major disease entity.

The combinations of risk factors and their associated mortality have been summarized from the Pooling Project.[1] (Fig 12) This provides another basis for a crude estimate of the potential for prevention. For example, let us assume that the 10-year CHD incidence for middle-aged men with two or more elevated risk factors (about 100 per 1000) were "converted" to the observed rate for men having no elevated risk factors (about 20 per 1000). There would have been 56 deaths from CHD instead of 280 in the 2773 Pooling Project men with two or more risk factors (38% of the total population). This would result in a decrease of 47

*"Elevated"—based on a level for each factor associated with twice the expected disease of the remainder of the population.

percent in total mortality from "correcting" high risk in the total pooling group (224 expected fewer deaths per 479 observed total deaths).

Finally, multiple intervention "according to the need" is a concept quite compatible with traditional clinical therapy. The individual "need" is determined by the presence and level of one or more risk factors. The population "need" is determined by the frequency of risk factors and their combinations in the population.

"PURE" SINGLE-FACTOR PREVENTION TRIALS

While the multiplicity of risk factors in CHD provides the main conceptual basis for MPT, a compelling practical reason for the MPT is the difficulty of modifying single risk factors selectively. When intervention involves health advice, it is apparently impossible, outside a double-blind design, to intervene on one risk factor without affecting others.

As examples, we will consider the National Diet-Heart Study[5] and the Minnesota contribution to a collaborative physical activity project.[6] These attempts at intervention on diet and on physical activity in free-living, middle-aged U.S. men resulted in the unintended modification of other characteristics related to CHD risk.

The National Diet-Heart Study

A common protocol was adopted in five U.S. metropolitan centers for modification of the amount and composition of dietary fat. The primary endpoint studied was the change in serum cholesterol level, but other risk factor changes were monitored. The design was double-blind, the randomization process was successful, and the double-blind was unbroken. The volunteers, men 45 through 54 years of age, were recruited by letter from the U.S. Census Bureau and encouraged by local advertising.

The volunteers differed in several respects of health and health attitude from the general population. Intervention was on diet alone and the subjects were specifically requested, for the sake of the experiment, not to change their mode of life otherwise. Because of the integrity of the double-blind, no bias in respect to diet or nondiet changes is likely between diet and control groups.

Later in the study a nonblinded diet and nonblinded control group were added to test the feasibility of an open study. The overall dropout rate for the one-year period was 9.7 percent.

The results showed a similar and significant reduction of 11 percent in the serum cholesterol level among the blind and the nonblind diet groups at the end of one year. There was a fall of 3 percent in serum cholesterol level in the blind control group and of zero percent in the nonblind controls. Specific instructions were given to the nonblind control group in order to avoid diet and habit changes.

Specific instruction was also given in the double-blind group to encourage no change in energy expenditure or smoking habits, but some got advice on calorie restriction. Nevertheless, at the end of one year, these changes were recorded:

1. Twenty-five percent of cigarette smokers had stopped smoking and another 25 percent had reduced the amount smoked.
2. A rapid and significant weight loss occurred in all groups, and the final loss in both blinded groups was a mean of 2 kg.
3. There was a significant fall in blood pressure, up to 5 percent, which could not be adequately accounted for by weight loss but which might be, at least in part, attributable to familiarization.

In sum, it appears to be impossible, even in a double-blind diet trial involving highly motivated subjects and staff, to intervene on diet habits without influencing other variables related to CHD. The double-blind design, of course, assures that there is no bias in the influence of confounding variables. But the open trial which is recommended by all of the diet-heart investigators and which is an essential aspect of conducting any mass prevention program may not allow secure conclusions whether effects of intervention on diet are in fact due to diet change, to other changes, or to combined changes. This is a key problem for a MPT as well.

Physical Activity Program

A collaborative feasibility study on physical activity among sedentary men ages 45 through 54 was carried out at the Universities of Minnesota, Wisconsin, and Penn State. The Minneapolis

volunteers were recruited by a letter and telephone survey in the southern and western urban-suburban areas. Intervention consisted of one-hour progressive group exercise programs three times a week for fifteen months. The primary endpoints studied were work capacity and heart rate, but other risk factor changes were monitored.

The eventual Minneapolis volunteers differed little in characteristics from those of the general population. Their high CHD risk status was determined by a screening examination in schools near their homes, and the men and their physicians were unequivocally informed of the detected high-risk status. Risk class was based on serum cholesterol and blood pressure levels and on cigarette-smoking habit. The men were then offered a preventive program based on regular physical activity. All men were specifically requested, for the sake of the experiment, to avoid other changes in mode of life. The randomization process was generally successful. Both exercise and control groups were examined and tested every three months, and the following changes refer only to Minneapolis subjects.

The exercise group followed the program with an adherence rate around 50 percent of the "ideal," based on full participation in three weekly sessions.

The exercise group showed highly significant increases in work capacity and in cardiovascular efficiency at a given submaximal work load. The control group showed no change in these measurements.

During the course of the study there was a significant weight loss in experimental and control groups, up to 1.6 kg on the average the first year, but the weight loss was insignificant by the end of the study.

Systolic blood pressure fell by about 3 mm Hg in exercise and control groups by the end of the program.

Serum cholesterol fell by 6 mg/deciliter in exercise and control groups, but reached a significant level of fall only at one period in the study.

There was an association between serum cholesterol reduction and weight loss in the exercise group.

Four of 28 regular smokers in the exercise group stopped smoking during the course of the study.

This feasibility trial on physical exercise demonstrated that vigorous intervention on physical activity habits, an important factor in the mode of life, is accompanied by expected changes related to exercise and by unexpected changes in other habits and factors of risk.

Since it is quite impossible to conduct blinded experiments on exercise, or for that matter on smoking habit, it may never be possible to avoid entirely, or to estimate closely, the influence of associated changes in confounding risk factors on the final results of prevention trials in the open population.

EXPERIMENTAL RESULTS OF A MPT

More information is provided by a long-term study which purposely attempted to modify five major CHD risk factors, the Coronary Prevention Evaluation Program of Chicago.[2,7] The findings are useful, though the conclusions are limited by the small numbers of subjects and the absence of a randomly assigned control group.

Five hundred and nineteen volunteers to a general community campaign were identified to have two or more elevated risk factors (or a serum cholesterol alone of $\geqslant$ 325 mg%). Intervention in these men, aged 40 to 59, was in an intensive, well-organized, and continuing program.

Skilled diet advice was given to subjects and to their families for diets moderate in calories and unsaturated fat and low in saturated fat and cholesterol. Reasonable personal programs of physical exercise were proposed. Management of elevated blood pressure and glucose intolerance was carefully coordinated with the attending physician. Continuing advice and support was given to help the subjects stop cigarette smoking.

The general experience of this multifactor risk factor program is summarized as follows:

The majority of men, free-living urban volunteers, remained in the program (37% dropped out in seven years).

Significant measurable change occurred in eating habits, and

there was a 7 percent average weight loss early, which has been maintained.

Serum cholesterol was reduced 19 percent and the reduction largely maintained (15% mean fall after five years).

Over the years, about 50 percent of original cigarette smokers who continued as active participants stopped completely or successfully switched to pipe or cigars in moderation.

Heart rate was slowed at rest and in response to a standard exercise load on the bicycle ergometer.

Age-adjusted seven-year total mortality rate was 30 per 1000 in the CPEP. In 2900 closely matched men from similar groups involved in the American Heart Association Pooling Project, the rate was 50 per 1000.

PROBLEMS OF THE MPT

The MPT presents a number of special considerations in design, execution, and interpretation.

Sample-size Questions in the MPT

For example, there remain some conceptual questions about sample size in the MPT having "factorial" design (see below); i.e. How much expansion of the estimated sample size is required if risk factor subgroups are employed in an attempt to study the individual contributions and interaction of these factors? In general, the sample-size requirements for the MPT are estimated to be smaller than those for single-factor trials because of the greater theoretical potential of multifactor risk intervention in reducing CHD incidence.

MPT sample-size estimates from the U.S. group are modest[9] compared with others in single-factor trials of primary prevention.[18] Nine thousand "high-risk" subjects in each of the control and treatment groups were estimated to be sufficient to detect a 25 percent treatment effect on total mortality in a seven-year study experiencing a control group total mortality rate of 63 per 1000, with an estimated 45 percent total seven-year dropout rate, and with an δ of 0.05 and a β of 0.10.[19] Moreover, it was estimated that several important interactions, and particularly the relative effect

of diet change, could be studied in a factorial design based on an estimated 50 percent treatment effect on *all CHD incidence* with a study among the same number of individuals, with the same dropout rate and error limits.

Execution Problems

Certainly the design and conduct of a MPT is more complex and the staff and organizational requirements greater than for a single-factor prevention trial. A wider team approach and competence are required. The various approaches necessary to modify multiple factors in large groups may attenuate the effectiveness of the trial. For example, eminence and experience of the investigator in management of lipid disorders or hypertension may not suffice to persuade free-living men to change habits of eating, exercise, or smoking. The W.H.O. group[13] states: "There is a real danger that a negative outcome to the MPT may indicate not necessarily the failure of [disease] incidence to respond to changes in risk factors, but merely the failure of subjects to do as they were advised."

The problems of standardization in selecting the several cohorts and in administering the multiple treatments are obvious. The greater difficulty in securing homogeneous treatment groups has important implications in the interpretation of results. These points all suggest the greater requirement for organization and experience. This experience is best gained in a well-planned initial run-in phase of a larger trial.

Organizational Structure of the MPT

The greater complexity of the MPT led the U.S. group to recommend the organizational structure tested in the Coronary Drug Project.[9] This structure includes a Policy Board, a Steering Committee, a Coordinating Center, individual Research Centers, a Data and Safety Monitoring Committee, an Electrocardiographic Center, Central Laboratories, a Drug Distribution Center, and a National Heart and Lung Institute Liaison Office. The detailed function of each of these components is worthy of consideration.[8]

Problems of Interpretation and Application of MPT

Perhaps the greatest problem of and the strongest argument against the MPT concerns the interpretation and application of trial results. This problem hinges on the fact that most MPT designs do not allow definition of the relative contribution of a particular treatment to the final result. Since most investigators now agree on the "desirability" and "acceptability" of reducing body weight, hypertension, and smoking habits, the argument is posed primarily by those concerned with the diet-heart question.

The researcher argues that the MPT fails to disclose the relative causal influence, if any, of diet. The administrator argues that national habits and the food economy should not be deranged by public health action leading from possible MPT results when, in fact, the real contribution of diet is not disclosed in a MPT. This problem and these arguments are indeed important and may be considered in several lights.

In the first place, the MPT is not meant to replace the single-factor trial in CHD and is clearly not a suggested alternative to trials already in operation. The MPT simply offers the chance of greater efficiency in answering the primordial question on CHD prevention. The MPT should properly be carried out *in parallel* with existing single-factor trials, especially those which obviate the confounding problem by double-blind design in closed populations.

Diet-heart investigators call for an open trial in the free-living population. They and their review commission[18] also recommend a double-blind diet trial in closed institutional populations, such as the Minnesota Study and the VA Domiciliary Study. Therefore, in multifactor and single-factor trials, double-blind and nonblind, in open and closed populations, each provides information which complements that from the other, in respect to causes and to the universality of application. Thus, the question may be reduced to one of priorities in setting up the interrelated studies needed to "wrap up" the issue.

Factorial Design of the MPT

Another option already mentioned to estimate the relative contribution of individual treatments and their interaction in

MPT is the use of "factorial design," in which relevant combinations of risk factors are managed within subgroups. The factorial design requires that each subject or unit have the same or predetermined probability of assignment to each treatment group. However, it is not possible to advise a thin man to lose weight or to treat a normotensive with antihypertensive drugs. Therefore, factorial design requires subgroups of subjects or randomized units having levels of risk factors sufficiently elevated to merit treatment by each of the methods under study; for example, "fat, hypertensive, hyperlipidemic cigarette smokers."

The National Cooperative Trial group[9] proposed a MPT design to obtain a maximum amount of precise information on the contribution of any and all treatments while intervening on groups contributing a substantial part of the total CHD incidence. Stratification of high-risk subjects into four cells was suggested as follows, each of which would then be randomized into treatment and control groups:

1. Hypercholesterolemia as the only risk factor.
2. Hypercholesterolemia plus hypertension.
3. Hypercholesterolemia plus cigarette smoking.
4. Hypercholesterolemia plus hypertension plus cigarette smoking.

Experimental subgroup 1 would be advised only in regard to diet and exercise, because recommendations on blood pressure and smoking control are not indicated for them. The sample size would be kept "reasonable" by the use of more frequently occurring endpoints of CHD morbidity rather than the rate of total mortality alone. Comparisons would be made to the randomly assigned control group having hypercholesterolemia as the only risk factor. Information on the individual contribution of each intervention would be obtained by providing the treatment appropriate to each subgroup. The definitive aspect of the MPT would be maintained by comparison of total mortality among *all* experimental and *all* control subgroups combined. The design would resolve the key question about the effect on the total mortality rate.

A subsequent conceptual development in this question of the

individual contribution of diet therapy is summarized here from the report to the National Heart and Lung Institute Task Force on Atherosclerosis:[14] The MPT is essential to determine whether application of the general body of knowledge on CHD risk factors can lead to significant reduction of CHD and death. There is a need to obtain a specific answer to the diet aspect of this question. The need for definitive answers on the benefit of treating hypertension and reducing cigarette smoking is less compelling because of the general acceptance of the desirability of their control. However, it is important to minimize the effect of change in confounding variables in any nondouble-blind study, including the MPT. Therefore, a design is proposed in which high-risk candidates are men with hypercholesterolemia who smoke cigarettes. Randomization into four groups would be performed:

1. Control (no intervention on diet or smoking).
2. Smoking intervention only.
3. Diet intervention only.
4. Diet plus smoking intervention.

Maximum similarity of design, measurement, and endpoints is recommended in all proposed programs, including double-blind studies among closed populations and nonblinded studies among the free-living population.

THE W.H.O. WORKING GROUP ON MPT

In November 1970 a group of cardiologists and epidemiologists were convened in Rome by the European Office of W.H.O. to discuss the concepts, problems, and detailed protocols for multifactor preventive trials in coronary heart disease. The two current European programs were reviewed in detail, one designed by Geoffrey Rose of London with randomly allocated industries, and another by Gosta Tibblin of Gothenburg with individual randomization from a community sample. Plans were made for extending these studies to other countries.

The arguments for MPT are succinctly summarized in the report of this working group:[13]

1) At some stage, multifactor trials will certainly be necessary, since without them there can be no indication of the total effectiveness of applying current beliefs on IHD prevention. The urgency of the situation is such that they should not be postponed until the completion of single-factor trials.

2) Single-factor trials fail to measure the extent of any interaction (positive or negative) between the various factors. For example, the results of stopping cigarette smoking and at the same time lowering the serum cholesterol level may be greater or less than the sum of their two separate effects.

3) In trials of health advice it is impossible to prevent (or measure) a form of contamination within the intervention group: namely, when subjects are told to do one thing, they do other things as well. In other words, where the "treatment" consists of advice, a pure single-factor trial is impossible anyway.

4) The total effectiveness of a multifactor approach may well be greater than that of any single-factor treatment. This implies that there is a better chance that the trial with a multifactor design will provide a positive conclusion. In the present state of our knowledge, it would be helpful to provide *any* objective evidence that IHD can be prevented.

5) In the event of a negative outcome from a multifactor trial it could reasonably be inferred (subject to sufficient numbers) that each of the individual treatments, as well as the combinations, was probably ineffective. Thus a multifactor trial provides a means for more rapid, simultaneous evaluation of each of several different factors.

6) However, the strongest argument for multifactor trials in practice is their appropriateness to the real-life situation in which health policy must be determined. The medical approach to the management of high-risk individuals and groups is commonly multifactorial: a doctor offers more than one item of advice or treatment if this seems appropriate, selecting those particular items that seem suitable in the particular situation. The task of the public health researcher is if possible to estimate the efficacy of the policy which the majority of clinicians believe to be the most helpful, that is a multifactorial approach.

SUMMARY

The MPT in cardiovascular epidemiology marks a trend in epidemiology which merits critical attention.

The MPT concept is highly appropriate to chronic diseases associated with multiple risk factors.

The MPT allows tailoring of the treatment to the need, thereby following precepts widely acceptable in medicine.

The MPT tests the most fundamental and urgent hypothesis, whether primary prevention of CHD, with an associated reduction in total mortality, is indeed possible.

The MPT probably provides the best likelihood of demonstrating soon and with greatest efficiency any possibility of a major reduction in the incidence of CHD.

"Pure" preventive trials on single-risk factors are not possible when the treatment involves health advice in the open population; other changes occur which confound the conclusions.

MPT design, organization, and execution are more complex than in a single-factor trial and require greater staff experience.

More precise information on the contribution of individual treatments to prevention can be determined by parallel single-factor trials and multifactor trials with factorial design.

The knowledge obtained and the conclusions allowed from single-factor and multifactor trials are complementary.

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REFERENCES

1. The Pooling Project Report. Current developments in North America. In Jones, R.J. (Ed.) *Atherosclerosis: Proceedings of the Second International Symposium.* Springer Verleg, New York, 1970. Council on Epidemiology, American Heart Association.
2. Report of the Inter-Society Commission for Heart Disease Resources. Primary prevention of atherosclerotic diseases. *Circulation, 42:*A55, 1970.
3. Truett, J., Cornfield, J., and Kannel, W. A multivariate analysis of the risk of coronary heart disease in Framingham. *J. Chronic Dis., 20:*511-524, 1967.
4. Schwartz, D., and Lellouch, J. Explanatory and pragmatic attitudes in therapeutic trials. *J. Chronic Dis., 20:*637, 1967.
5. National Diet-Heart Study Research Group. The national diet-heart study final report. *Circulation, 37* (Suppl. 1), 1968.
6. Taylor, H.L., Balke, B., Blackburn, H., Buskirk, E., Hamrell, B., and Remington, R. Studies of methodology and feasibility of physical activity in trials of prevention of coronary heart disease. *Medicine and Science in Sports,* in press.
7. Stamler, J. *Lectures on Preventive Cardiology.* New York, Grune & Stratton, 1967.
8. Report of the Coronary Drug Project Research Group. The coronary drug project. *J.A.M.A., 214:*1303-1313, 1970.
9. National Cooperative Trial on Multifactorial Prevention of First Heart Attacks and Coronary Mortality in Free-Living, High-Risk, Middle-Aged American Men. Submitted to the National Heart and Lung Institute, 1969.
10. Makarska Report on Clinical Trials in Ischemic Heart Disease. Council on Epidemiology and Prevention, International Society of Cardiology, 1968.
11. Rose, G. A proposed trial of heart disease prevention in industry. *Trans. Soc. Occup. Med., 20:*109-111, 1970.
12. Tibblin, G. Preventive cardiology in Gothenburg. *Pehr Dubb Journalen, 3,* 1969.
13. Report of a W.H.O. Working Group. Methodology of multifactor preventive trials in ischemic heart disease. Rome, Nov. 1970. Euro 5011 (3) Regional Office for Europe. W.H.O. Copenhagen, 1971.
14. Stamler, J. Position paper on the diet-heart issue for the National Heart and Lung Institute Task Force on Atherosclerosis. Aug. 19, 1970.
15. Keys, A. (Ed.) Coronary heart disease in seven countries. *Circulation, 41* (suppl. 1), 1970.

16. Stamler, J., Berkson, David M., and Lindberg, Howard A. Risk factors: Their significance for the etiopathogenesis and prevention of the atherosclerotic diseases. In Geer, J.C., and Wissler, R.W. (Eds.) *Proceedings of a Symposium of the American Society of Bacteriologists and Pathologists.* Montreal, Mar. 9, 1971. In press.
17. Cornfield, J., and Mitchell, S. Selected risk factors in coronary disease. Possible intervention effects. *Arch. Environ. Health, 19:*382-391, 1969.
18. Report of the Diet-Heart Review Panel of the National Heart Institute. *Mass Field Trials of the Diet-Heart Question.* American Heart Association Monograph No. 28, 1969.
19. Schork, M.A., and Remington, R.D. The determination of sample size in treatment-control comparisons for chronic disease studies in which dropout or non-adherence is a problem. *J. Chronic Dis., 20:*233, 1967.
20. Dayton, S., Pearce, M.L., Hashimoto, S., *et al.* A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. *Circulation, 39-40* (suppl. 2), 1969.