

REPORT
of the
NATIONAL HEART AND LUNG INSTITUTE PANEL
on
HYPERLIPIDEMIA AND PREMATURE ATHEROSCLEROSIS
June 12-13, 1970 Bethesda, Maryland

Report of the National, Heart and Lung Institute Panel on
Hyperlipidemia and Premature Atherosclerosis, June 12-13, 1970,
Bethesda, Maryland. (Origin of the U.S. Lipid Research Clinics.)

Panel consisted of Donald S. Fredrickson, Chairman, Edwin S. Bierman, David H. Blankenhorn, William Castelli, William E. Connor, Gerald R. Cooper, Theodore Cooper, Seymour Dayton, Howard Eder, Ivan D. Frantz, William Friedewald, DeWitt S. Goodman, Frederick T. Hatch, Richard J. Havel, Peter Kuo, Robert S. Lees, Robert I. Levy, Robert P. Noble, Isidore Rosenfeld, Daniel Steinberg.

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BACKGROUND

This meeting was held at the invitation of Dr. Theodore Cooper, who wished a group of experts on hyperlipidemia or atherosclerosis to evaluate the opportunities and requirements for a program to improve the detection and management of persons susceptible to premature atherosclerosis associated with hyperlipidemia.

As explained in Dr. Cooper's letter of invitation and amplified in his opening remarks at the meeting, the National Heart and Lung Institute is embarking upon an enlarged program of research and prevention, with the purpose of reducing the morbidity and mortality from premature expression of atherosclerosis. In planning this program, the Institute must rank its objectives in priority order and develop an operational plan with identifiable decision points. An aspect of the program that is of particular and immediate interest relates to the group of susceptibles with hyperlipidemia who can now be better identified and treated because of new techniques. These techniques are not yet used properly in general medical practice. Their wider application would benefit many patients, offer an opportunity for further research that could provide a greater understanding of the relationship between lipids and atherosclerosis and also provide a solid base for prevention on a large scale.

To obtain an evaluation of opportunities and requirements for such an effort, Dr. Cooper asked the panelists to consider such questions as the techniques and resources that would be required, the desirability of obtaining pooled information about hyperlipoproteinemias, the degree of interest in the community at large in detection, classification and treatment of patients with these disorders, and how to assess the impact of information about hyperlipidemias on medical practice and on the incidence of atherosclerosis. Dr. Cooper emphasized the public health problem of premature atherosclerosis, the Institute's need for both long-range and short-term plans, and the importance of a report that will tell not only how to approach the problem but also how results will be assessed.

The report of the meeting is to serve a dual purpose: It will provide guidance to the Institute on a particular facet of the problem of atherosclerosis, and will also be made available to the recently designated Task Force on Arteriosclerosis that will, within a period of one year, report to the Institute on the more encompassing disease problem - arteriosclerosis.

As Chairman of the meeting on Hyperlipidemia, Dr. Donald S. Fredrickson provided participants in advance with a staff document (Attachment I) that summarizes some opportunities regarding a national program aimed at hyperlipidemia, and a summary statement on classification and definitions of hyperlipidemias (Attachment II). Dr. Fredrickson also asked participants to respond to a questionnaire (Attachment III) in order to determine

prior to the meeting the scatter of opinions of the group on specific topics, permitting more time for discussion of questions on which agreement was not obvious.

Participants are listed on the next page. The agenda for the meeting is attached (Attachment IV).

On June 12, the group met from 9 a.m. to 6 p.m. It discussed all topics on the agenda, achieving a consensus on some, identifying differences of opinion on others. It also heard summary presentations on: the association between coronary heart disease and serum cholesterol, a partial analysis of Framingham data, (Dr. Friedewald); the NHLI experience relative to possible simplified measures for estimations of low density lipoproteins and detection of Type III (Dr. Levy); the possibilities of quality controls on lipid and lipoprotein measurements (Dr. G. Cooper); and recent analysis of a VA study pointing to possible problems associated with dietary management of hyperlipidemia (Dr. Dayton). The group reconvened at 9 a.m. on June 13, reviewed the deliberations of the previous day and developed recommendations for a national program, as embodied in the following report. The meeting terminated at 1 p.m.

HYPERLIPIDEMIA AND PREMATURE ATHEROSCLEROSIS

PANEL

Bethesda, Maryland

June 12-13, 1970

PARTICIPANTS

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*Unable to attend the meeting.

OBSERVERS

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William J. Zukel, M.D.
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SUMMARY REPORT

I. The association between hyperlipidemia and premature atherosclerosis and the application of present techniques and knowledge to medical practice.

On the basis of responses to the questionnaire and from subsequent discussion, it was evident that members of the panel were in agreement on the following:

- 1) Available evidence indicates that more serious attention to the detection, classification and treatment of certain patients with hyperlipidemia is warranted as a step to decrease the risk of susceptibility to premature heart disease.
- 2) Present practice in the medical community is now far from optimal with regard to use of present knowledge and techniques for this purpose.
- 3) Wider dissemination and proper application of present knowledge could upgrade considerably current medical care of hyperlipidemic patients, could save some patients considerable expense, and remove much confusion now present among both physicians and public concerning this public health problem.
- 4) Such improvement in current medical practice would probably retard the development of premature coronary heart disease in many Americans, although necessary proof for this conclusion is still lacking.

Opinions differed about the most desirable cut-off points to be used in defining hyperlipidemia. For example, two panelists suggested that the upper limit of "normal" for cholesterol be 220, while most favored cut-off points of either 250 or 270 mg per 100 ml. Opinions also differed on the sex or age limits of the populations that should be included in a program to detect those especially susceptible to premature vascular disease.

Dr. Friedewald's report on the association of coronary heart disease and serum cholesterol levels served to focus discussion on the question of what fraction of total expected premature coronary events might be found in men with plasma cholesterol above different levels. It was noted that a cut-off point of serum cholesterol set low enough to include most potential cases would encompass a large segment of the total American population. For example, in men aged 45 to 64 the limit would have to be set at 260 mg per 100 ml to include even half of the potential cases. If the upper 5% of cholesterol values (280 mg per 100 ml) were used in the age group 35 to 44, it would bring only one-quarter of the potential coronary cases under management. During discussion, it was asked whether evidence that the upper 5% was helped would necessarily mean that the next 5% would also be helped by treatment, or whether lowering lipids for the upper 5% to "normal" could reduce their risk to that of patients who had had "normal" levels all their lives. It was also noted that the inclusion of cases with hypertriglyceridemia in the group to be managed would appreciably increase the number of patients to be handled in a prevention program.

While the panel did not reach agreement on the question of cut-off points the tenor of discussion indicated that, on balance:

It is preferable to select the more obvious and severe cases (i.e., those representing the upper 5% of cholesterol and triglyceride values) because 1) this is a population group about which there is no serious disagreement as to the necessity of treatment, and 2) the probability of improving the health of this group by conservative and accepted treatment of hyperlipidemia seems now to outweigh evidence that such treatment might be harmful.

II. Detection of hyperlipidemia and translation of hyperlipidemia into hyperlipoproteinemia.

The panel was in agreement that management of hyperlipidemia is best achieved by a conceptual translation of this disorder into different types of hyperlipoproteinemia. The classification into five major types of lipoprotein pattern was found acceptable for the present, with the cognizance that added experience would expose much heterogeneity within each type in regard to cause and management. The detailed definitions ^{1/} provided in the staff document were not discussed at the meeting, but it was evident that 1) a national program for detection would require acceptance of standard definitions, and 2) little difficulty would be encountered in establishing agreement upon useful definitions.

^{1/} In this regard, it is of interest that an *ad hoc* committee, convened by WHO in Geneva several weeks after the Bethesda meeting, recommended international use of a classification of hyperlipoproteinemia consisting of the five major Types described in Attachment II.

Considerable discussion was devoted to screening tests for detection of hyperlipidemia and its further classification. Because the requirements for the practicing physician as a guide to management will be different from those for the researchers, the panel agreed on the use of three screens:

A) Primary Screen (for initial detection of hyperlipidemia)

- 1) The panel favored cholesterol and triglyceride determinations on fasting serum or plasma.
- 2) Agreement was unanimous that electrophoresis should not be part of the primary screen.
- 3) In the event that samples cannot be obtained in the fasting state, non-fasting cholesterol and triglyceride should be used.
- 4) If this alternative is not possible, there should be at least measurement of cholesterol and observation of serum, non-fasting.

It was noted that with available automated techniques it may be little more expensive to measure both triglyceride and cholesterol than to measure cholesterol alone.

The recommendation not to use electrophoresis in the primary screen is counter to the existing practice of many physicians, which is a source of

appreciable extra cost to many patients and of much confusion to physicians.

In discussion of screening procedures it became evident that those panelists who had earlier indicated in the questionnaire that they recommended non-fasting serum had done so because they anticipated practical problems if community physicians had to obtain fasting samples. Several panelists with extensive experience provided assurance that fasting samples are not difficult to obtain, except in epidemiologic studies. However, the panelists agreed that little is known about the effect of meals and that data are needed on fasting vs. non-fasting levels of cholesterol and triglycerides. It was also suggested that it might be feasible to eliminate chylomicrons by filtration procedures to measure very low density lipoproteins in the non-fasting state.

B) Secondary Screen

All patients judged to have "abnormal" cholesterol or triglyceride should then be subjected to a secondary screen consisting at least of:

- 1) A repeat of fasting cholesterol and triglyceride.
- 2) If triglycerides are elevated, a qualitative assessment of lipoprotein pattern, including either a) establishment of presence of chylomicrons (observation of serum after overnight stand at 4 degrees and, possibly, nephelometry); or b) electrophoresis; or c) both.

Here opinion of the panel was divergent. Some favored, for the practicing physician, moving from step 2 in the secondary screen to the elimination

of secondary hyperlipidemia, which is hyperlipoproteinemia due to other known diseases such as hypothyroidism, nephrosis, insulinopenic diabetes, dysglobulinemia, and many others. Because treatment of the underlying disease usually eliminates hyperlipoproteinemia, it can be argued that the classification of "type" is immaterial until therapeutic trials or diagnostic tests fail to reveal a distinct cause for lipid abnormalities.

Other panelists favored a third step in the secondary screen before or concurrent with tests to determine etiology. Recent studies suggest that this third step might include a) simple exclusion of Type III (by combinations of polyacrylamide gel and other electrophoresis as tested at NHLI), and b) a more explicit diagnosis of Type II (by estimation of low density lipoprotein by precipitation procedures).

C) Tertiary Screen

All panelists agreed that for experimental purposes, for determination of prevalence of mutations, and for other refined studies, tests should be widely available for:

- 1) Diagnosis of Type III hyperlipoproteinemia, and
- 2) Measurement of low-density lipoprotein concentrations.

These same tests should also be available for practical counseling and for assistance in management of therapeutic problems encountered by physicians.

Both of these tests now require the preparative ultracentrifuge, which is generally only available in research laboratories. The panel viewed the inaccessibility of these tests to physicians as a major practical problem and discussed other tests to achieve a definition of type by simpler means.

III. Quality controls

Dr. Gerald Cooper described the encouraging experience of the Communicable Disease Center, which has been able to establish satisfactory quality control for cholesterol and triglyceride determinations. Essential to such quality control are: the proper use of primary standards; the availability of stable serum reference materials; checks against the reference method; a careful watch over methods of collecting, storing and shipping of samples; and continuous internal and external surveillance by a trained, motivated and competent staff.

More specifically, Dr. Cooper indicated that purified primary standards and stable serum reference materials are available for cholesterol and triglyceride, but have not as yet been developed for lipoproteins. Recent developments suggest that suitable automation will be available to determine cholesterol, triglyceride and lipoproteins in large numbers with a precision and accuracy sufficient for clinical usefulness. However, control and surveillance of lipoprotein analyses might have to be supplemented by on-site visits. By using the same primary standard preparation and the same serum reference materials of different concentration, comparability of results can be increased.

During discussion of quality controls the panelists emphasized the problem of interpretation, particularly with regard to electrophoresis, and felt that it is highly questionable whether electrophoretic determinations can be adequately standardized across the nation.

The panel agreed that:

A national effort to study hyperlipidemias should include the widely publicized caveat that cholesterol and triglyceride determinations must be subject to quality control. Such control is both desirable and feasible. While the panel believes that control of lipoprotein analyses is important, it is not feasible at this time except by direct comparisons; this is not a practical procedure in more than a few laboratories.

IV. Management of hyperlipidemia

Discussion of the treatment of hyperlipidemia began with Dr. Dayton's presentation of some findings of the dietary trial at the Veteran's Domiciliary in Los Angeles. He emphasized the higher incidence of death from cancer now appearing in followup of the experimental subjects, who were given a diet high in polyunsaturated fats, low in saturated fats and low in cholesterol. The divergence between the experimental and control subjects became apparent about two years after the beginning of the trial. The ratio overall was 32 vs. 17, which is significant at the 95% level of confidence. Age stratification has not been completed in these analyses. Lack of evidence from other studies of such possible harmful effects of this diet and possible reasons for this difference were discussed. The panel agreed that Dr. Dayton's observations are of great interest and potential importance and that additional evidence should be actively sought for possibly harmful effects of this now popular therapeutic diet. After considerable discussion the panel concluded that in dealing with younger patients with severe hyperlipoproteinemia,

especially Types II and III, the evidence of possible hazard associated with treatment of any kind is still of much less weight than that indicating enhanced risk of heart disease. The wisdom of concentrating on those most susceptible, in contrast to the entire population, was reiterated.

The panel agreed that:

Stereotyped algorithms are now possible for treatment of all five types of hyperlipidemia, with the understanding that certain steps--particularly diets--are empirical and in need of further research. The issue of specific therapy and heterogeneity of response is of high priority as is continuing observation for possible harmful effects of treatment.

The general experience of the panelists was that for many of the milder forms of these disorders, dietary treatment will correct the hyperlipidemia. Caloric restriction in overweight subjects with Types III, IV and V is universally effective. Because of its safety over the lifetime, dietary therapy has certain advantages and should be attempted initially in preference to drugs. The two methods of therapy--diet and drugs--are usually additive in their effects.

The panel then reviewed therapeutic regimens for five types of genetically determined hyperlipoproteinemia. The details are not reviewed here since no attempt was made to agree upon exact therapeutic prescriptions at this meeting. It was noted that dietary research in relation to some Types

(I and II) had advanced further than for others (Types III, IV and V) and that drugs of definite efficacy and low toxicity are not yet available to help all patients with hyperlipoproteinemia. At the same time, the panel noted that the present-day ability to reduce lipoprotein levels in certain other patients is extremely encouraging. In fact, it is the recent advances in therapy that lend a sense of urgency to detection and management of younger patients with hyperlipoproteinemia.

V. A national program for improving detection and management of hyperlipidemia.

A. Objectives

After extensive discussion, and without dissent, the panel felt that further Federal assistance is necessary to improve detection and management of hyperlipidemia in this country and to permit optimal application of new knowledge acquired by many man-years of research. It foresaw an opportunity to benefit a very large number of Americans now beset by uncertainty about management of their plasma lipid problems and at hazard for premature vascular disease. The panel also foresaw opportunities to obtain extremely important information that cannot be obtained without some coordination of the efforts now being made by experts engaged in individual studies. The panel repeatedly returned to the fact that no one knows for certain that treatment of hyperlipidemia by present methods-- or by any methods--will decrease premature coronary heart disease. It was almost unanimously concluded that this vital question probably can be answered more economically and more definitively by studying population segments with selected types of hyperlipoproteinemia than by studies of

any other population groups.

The panel devoted most of the second day to consideration of the specific objectives of such a national program. It concluded that:

- 1) The highest priority should be given to obtaining information on the effectiveness with which therapy of hyperlipidemia delays the onset or effects regression of its vascular complications. The panel was reluctant to recommend any program that did not plan for and contain the elements of eventual solution of this problem through a randomized intervention trial.

The language of this recommendation was carefully selected by the majority of the panel. It does not convey the significant differences in opinion felt by various panel members concerning it. All endorsed the primacy of the need for an answer to the question addressed by the recommendation. A few felt that studies of the effect of therapy on coronary artery disease must be planned and launched concurrently with any other aspect of a national program directed toward hyperlipoproteinemia. At least an equal number strongly believed that to tie the onset--and the bulk of resources--of the program to an intervention trial would delay the accumulation of patients and of appropriate methodology necessary for an optimal intervention trial and would also seriously narrow and hamper achievement of other worthwhile objectives.

- 2) There is an urgent need for data on prevalence of different types of hyperlipidemia among younger age groups and, particularly, on the nature and frequency

of different genetic factors (major mutants) leading to hyperlipidemia.

While some data on prevalence are being collected as part of the Framingham, Massachusetts; Claxton, Georgia; Puerto Rico; Albany, New York; Tecumseh, Michigan; and the Honolulu, Hawaii and San Francisco, California studies of Japanese populations, there is a dearth of such information from unbiased samples in younger age groups and different ethnic and cultural groups that present an important public health problem. For example, the gene frequency for Type II or Type III hyperlipoproteinemia, both highly associated with vascular disease is unknown. For Type II it could be as high as 1:100 in the general population and account for a disproportionate share of coronary heart disease.

- 3) High priority should be given to upgrading medical care for hyperlipidemic patients by providing guidance and assistance to physicians on the management of these patients. This guidance must of necessity be local in nature to be maximally effective.

The panel believes that the following problems also merit urgent attention:

- 4) Evaluation of current techniques, to develop better ones for diagnosis of hyperlipoproteinemia.
- 5) Improved therapy (both diet and drugs) for specific disorders, tested with appropriate controls, randomization and a double-blind design.

- 6) Better data on the prevalence and incidence of vascular disease in different types of hyperlipoproteinemia.
- 7) Development of prototypes for local programs, dealing with hyperlipidemia, that are sponsored by such groups as American Heart Association, Regional Medical Programs, industry and the private sector.
- 8) Facilitate better information exchange about hyperlipoproteinemia through information centers, standard protocols and central coordination of data.

Other problems that are to varying degrees tangential to the focus of this meeting, but were identified during discussion as warranting attention, included: (1) weight control research, because attaining ideal weight is an essential first step in treatment of several forms of hyperlipidemia and is often notably difficult to achieve; (2) utilization of the abundant but largely untapped population resources for detection and intervention trials offered by industrial health programs, many of which are now urgently seeking guidance about the hyperlipidemic fraction of their patient populations; (3) pathogenesis of hyperlipidemia and atherosclerosis; and (4) detection of atherosclerosis by non-invasive techniques.

B. Means

Having agreed upon the principal objectives of a national program, the panel considered the best means to achieve these objectives. It recommended:

Special funding for a number of coordinated lipid laboratories or clinics where quality control of both methods and interpretation will be monitored, new diagnostic tests developed and evaluated, physicians provided consultation on diagnosis and therapy (including assistance from dieticians), data on prevalence uniformly collected and forwarded for central collation, and important research questions relevant to hyperlipoproteinemia studied by the sophisticated techniques.

The panelists provided educated estimates from their individual experiences as to the cost of such lipid clinics; these estimates ranged from one hundred thousand to three hundred thousand dollars, annually.

Personnel should include a program coordinator(s), administrative assistant(s), public health nurses, laboratory technicians, and dietician(s). Equipment should include at least two autoanalyzers, electrophoresis apparatus and preparative ultracentrifuge.

Realizing that funding restrictions may limit the extent to which this proposal can be implemented, the panel recommended that:

If choices must be made, available funds should be used for one well developed lipid center in preference to several that are not wholly adequate.

However, in agreeing on this recommendation, the panel noted that the services of one laboratory to the community, and many of its other functions, cannot extend over too wide a region and that a network of centers, of

whatever size, would be collectively more effective than one or two operating alone.

The success of the program envisaged by the panel depends upon assurance that adequate time is available for planning a clinic, implementing its plans, coordinating its activities and assessing results. Therefore, the panel recommends that:

Lipid clinics should be planned for a minimum of five years.

While in agreement on the general features of these clinics or centers, the panel referred to the Institute, or to subsequent deliberations by a panel, consideration of other specific questions that should be addressed in developing plans to implement their proposal: Should lipid clinics be regional? Begin as pilot operations? To what extent should they act as reference laboratories to serve as prototypes? If the centers are involved in physician education, how can they avoid becoming overwhelmed to the detriment of needed research studies? How can the centers achieve randomization of data if they are dependent on physician referrals? Should such centers be developed even if they are not engaged in intervention trials? How can the centers best obtain the needed data on younger age groups?

The panel adjourned with the unanimous opinion that the topic of its deliberations was a matter of extraordinary relevance to the problem of premature atherosclerosis and that a more concrete opportunity or more urgent need to apply new laboratory knowledge to medical practice could

not be found in cardiovascular medicine today. It sensed a high probability that a network of lipid clinics or hyperlipoproteinemia centers might at least contribute to better control of one of the most important risk factors in atherosclerosis. At best, with truly adequate funding, such a network might provide the answer to the single greatest outstanding question in chronic diseases today: Shall dietary measures to lower blood lipids be aggressively extended to the general population?

The panel expressed the hope that the Institute and the Task Force on Arteriosclerosis would give serious and early consideration to its recommendations. It felt that a commitment to the concept, a preliminary indication of the funds to be available for the present and future years, an indication of the organization desired, and the provision of planning and management staff, are the necessary steps for proceeding further. For its part, the panel agreed wholeheartedly to serve--together or as individuals--in whatever capacity it should be requested to do so to implement its recommendations.