

AN INTERNATIONAL RESEARCH PROGRAM ON EPIDEMIOLOGY  
OF HEART DISEASE

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A research program on heart disease epidemiology in different populations would cover, by examination, annual follow-up, and re-examination five years later, substantially all men aged 40-59 in from 15 to 20 areas, selected to provide contrasts in the diet and/or apparent frequency of heart disease, each area containing 600 to 1000 such men (total 9000 to 14,000 men). Trials in 5 areas in 4 countries (over 3000 men) yielded 98.5 percent coverage and showed the feasibility of using international teams and detailed objective recording of findings in form suitable for statistical analysis.

The program is aimed at discovery of actual prevalence and incidence of clinical heart disease in the areas and demonstration of interrelationships and the predictive values of observed characteristics, including relative obesity, body type, blood lipids, habitual diet, electrocardiographic details and clinical findings.

Organization comprises a Central Organization and Advisory Committee and Responsible Investigators and Advisory Committees in each of the countries involved, with international teams participating in the surveys. Financial support is sought from U. S. P. H. S. and local sources in each country.

[ The basic hypothesis is that there are major differences between populations in the age-specific frequency of certain kinds of heart disease, notably coronary heart disease, that these differences are related, at least in part, to differences in the mode of life, particularly the diet, and that the discovery of these relationships may have practical application. ]

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A. HYPOTHESIS

{ The basic hypothesis is that there are important differences between populations in the age and sex-specific frequency of heart disease, particularly coronary heart disease, and that these differences are related, at least in part, to differences in the mode of life, especially in the diet, and to measurable differences in the personal characteristics of the members of the populations who are clinically healthy at the time of examination. } The hypothesis does not deny a role to other factors, including genetic constitution and emotion, in the development of clinical heart disease. [ It is probable that there are multiple causes in the etiology of coronary heart disease, either in the initial pathogenesis or in the precipitation of clinical manifestations or in both, but, if so, these should be additive and the control of a single important etiological factor should have a substantial effect on the total susceptibility to the disease. } In terms of possible application in preventive programs, attempts to control a genetic factor seem impractical. The same may be true of emotional factors which have the additional handicap of being extremely difficult to define and measure if, indeed, they actually have an influence. Accordingly, [ the hypothesis emphasizes the factors of diet, physical activity, and personal habits, which are both measurable and alterable, and factors of physico-chemical constitution which are at least measurable with available methods. ] It is noted also that genetic constitution and emotional characteristics may have representation in dietary habits, physical activity, personal habits and physico-chemical characteristics so that the study of these latter features of the individual does not entirely exclude genetic and emotional factors even though it may be impossible to identify these, as such, at present.

{ A further part of the hypothesis is that such relationships as may exist between the tendency to develop heart disease on the one hand and, on the other, the mode of life, particularly the diet, can be most readily discerned by comparing populations representing the widest possible range of differences between populations in regard to the frequency of heart disease and to the characteristic diet. Though complete isolation of the variables may be impossible in such comparisons, the simultaneous comparison of many populations should disclose relationships that may be common to all. The discovery of such universal relationships will be facilitated by selecting populations so as to minimize other variables that may be influential such as degree of urbanization, occupational instability and gross differences in the frequency of malnutrition and infectious diseases. }

[ Finally, the hypothesis holds that follow-up study of such populations after initial examination should discover the statistical prognostic significance of characteristics recorded for the individuals at the time of the initial examination, particularly if the populations have a relatively high degree of stability in regard to mode of life, including the diet and physical activity. ]

#### B. PURPOSES

{ The purpose of the proposed program of cooperative international research is, ultimately, to contribute to the knowledge of the etiology of heart disease in a fashion that may have application to the problem of prevention. More immediately, the purposes are:

- 1) To discover and measure differences between populations in the prevalence and incidence of heart disease, especially coronary heart disease and hypertensive disease,
- 2) To attempt to learn to what extent these differences may be related to differences in the mode of life, particularly in the habitual diet and physical activity,

and to differences in various characteristics of possible significance (obesity, body type, blood pressure, electrocardiographic characteristics, blood cholesterol concentration, personal habits, etc.),

3) To examine into the prognostic significance for the development of heart disease of these variables measured in individuals,

4) To analyze all of these findings with a view to identification of etiological factors and possible application to the problem of prevention, and

5) To promote international cooperation in research, professional training and the exchange of personnel and of scientific information on a world-wide basis.

### C. GENERAL FEATURES OF THE PROGRAM

It is proposed to examine and study, with subsequent follow-up, substantially all of the men aged 40 - 59 at the time of initial examination, in a number of limited geographical areas selected as being especially suitable to this epidemiological research:

1) Providing a series of contrasts in the apparent frequency of one or more important kinds of cardiovascular disease or differing in the characteristic diet of the area or in both respects,

2) Containing from 500 to 1000 men aged 40 - 59, in each area, thus meeting certain statistical requirements without exceeding practical limitations of cost and investigating personnel,

3) Each area being relatively homogeneous in regard to the character of the habitual diet of the area,

4) The men in each area being relatively stable in residence and occupation, with no remarkable differences between the areas in regard to the distribution of different levels of physical activity among the men,

5) Good grounds for assurance that local interest and cooperation would allow substantially all the men (at least 95%) to be examined and provide essential information on any men unable or unwilling to participate,

6) Responsible investigators in each country able and desirous of planning and operating the program, within the common collaborative scheme, for the area (s) selected for study in that country,

7) A total of 12 to 16 (or more?) areas to be studied so as to provide a total of the order of 6,000 to 10,000 men for cross-sectional and follow-up study, the latter to continue for at least 5 years with re-examination at the end of that period of time.

8) Adoption of carefully standardized methods of observation, measurement, recording and analysis in all of the areas, with a view to statistical needs and separation of observation from opinion and interpretation.

It is now clear from preliminary explorations that there are major differences between populations in the age- and sex-specific frequency of heart disease, particularly coronary heart disease which are not accounted for by climate or, apparently, by race. Parallel consistent differences in personal habits such as the use of alcohol and tobacco have not been found. Seemingly very large differences in the frequency of coronary heart disease in comparing populations of farmers differing greatly in regard to the diet but not in regard to physical activity. On the other hand, it is reported that some populations differ considerably in mortality rate ascribed to coronary heart disease though these populations are not known to differ greatly in the diet. In none of these populations have either diet or frequency of heart disease been studied adequately to judge the validity of the apparent consistencies and inconsistencies. The proposed program aims to correct such deficiencies.

Experience in the past year in 5 areas, each containing from 600 to more than 800 men 40 - 59 (or 45 - 65) years old, in Greece, Japan, Italy and Yugoslavia, has shown that it is possible to select areas and to prepare the ground so as to be able to carry out full medical examination and other studies on 96 to 100 per cent of the men of specified age in each area and to obtain relevant information about all of the few men unable or unwilling to cooperate. Experience in these and other areas previously studied has shown the great difficulty - or virtual impossibility - of obtaining accurate quantitative information about the long-time diet of individuals for comparison with each other. On the other hand, it has been found that selected areas can be found which differ greatly from each other in regard to the fat composition of the average diets of the areas but within the areas the diets are relatively homogeneous. The proposed program plans to take advantage of these facts so as to allow statistical comparisons between areas, or sub-groups within areas, in regard to diet, blood chemistry, the frequency of specified kinds of heart disease and other characteristics of the areas and groups.

All of the men in each area would be queried briefly about their diets, primarily to discover deviations from the group diet pattern. Major reliance about the diet of each area would be placed on detailed household interviews and measurements of food actually eaten in a series of households chosen as being representative of the area. Sub-sampling would be made in cases where it is suspected that there may be several dietary patterns within the area. Further, actual food samples corresponding to recorded menus would be locally collected and subjected to detailed chemical analysis to cover the various fatty acids as well as nutrients more commonly covered in dietary surveys. The feasibility of this procedure has been tested recently in Finland, Greece and Italy and is currently being applied in Yugoslavia.

An important feature of the proposed program is the use of identical methods, highly standardized, in all of the areas, with the participation of international teams of experts in the work in each area. Such standardization applies not only to obvious items such as anthropometry, chemical methods and electrocardiographic work, but also to history taking and the objective recording of the findings in the clinical examinations. Sample forms for the latter purpose, now in trial in several countries, are attached. Also attached is an outline of the system proposed for the classification of the electrocardiographic findings. This system, as well as the clinical forms, provides a maximum of objective detail and a minimum of present interpretation, with a view to future statistical analysis. For the chemical analyses a considerable degree of centralization of the work is proposed so as to guarantee complete comparability of results from all of the areas.

One such survey in an area would provide valuable information about the prevalence of disease, about characteristics of the population that may be related and, extended to other areas, would allow valuable comparisons to be made. Much greater value would accrue from subsequent follow-up of the status of the populations and this is proposed. Periodic inquiry into the health status of the men (by annual visit to the area, consultation with the local physicians and examination of such men as indicated), would be followed by a complete repetition of the entire survey on all of the men after a period of about 5 years.

The first survey has been made or is in process in some of the areas: Crete (Greece), Calabria (Italy), Ascoli Piceno (Italy), Kurume (Japan), Dalmatia (Jugoslavia); some checking of details is needed for several of these areas. Preliminary surveys, excluding men known to be in poor health, have been made in two areas in Finland. In these, as in the others mentioned above, the feasibility of getting cooperation from practically all men of the area was demonstrated. It

is proposed that extension of the work in these areas be a part of the program. In the United States a study on railroad employees is now in progress. While it appears that not more than 75 per cent of the desired sample of 18 railroads will be obtained, the follow-up should be useful in comparison with findings to be obtained in the areas with more complete coverage. No costs of the work on the U. S. railroad employees is to be borne as a part of the currently proposed program.

It is proposed that the financing of the program be covered by funds both raised locally within each of the countries concerned and from the budget of the general program. It would seem appropriate to budget the costs for each area on a matching basis, so far as possible, and the budget offered here reflects this view. At least some local funds can be guaranteed from each of the countries concerned.

#### D. BASIC BATTERY OF OBSERVATIONS

The basic battery of observations proposed for all areas includes:

- 1) Record of age, occupation, family status, degree of habitual physical activity (1 to 4 from sedentary to very heavy),
- 2) Medical history and physical examination, including blood pressure, eye grounds, etc. (see forms),
- 3) Record of smoking habits,
- 4) Brief notes on personal dietary habits,
- 5) Anthropometric study (height, sitting height, weight, bi-acromial and bi-cristal diameters, skinfold thicknesses over the triceps and over the tip of the scapula, upper arm circumference,
- 6) 12-lead electrode ECG before and after a 2 1/2-minute step test,
- 7) Urine test for sugar and protein,
- 8) Blood sample for total cholesterol measurement,



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- 10) Detailed study of actual food consumed by representative households in the several seasons of the year, with both computation and direct chemical analyses for nutrients, including fatty acids (saturated, mono-enes, linoleic, other poly-ene
  - 10) Observations on actual work of members of the population.

To the foregoing would be added various other tests and measures according to the interests of the area teams and the availability of methods. Consideration would be given to the addition of items to the basic battery as new methods and concepts are developed. There is particular need for measures related to cerebrovascular function, to peripheral circulation, to pulmonary function and to emotional "stress".

#### E. ORGANIZATION

The whole program should comprise a Central Organization and Area Organizations for each area or country, these to be distinguished in the budgetary plan and responsibility for reports and accounting. The Central Organization would coordinate the whole program and would provide aid to all of the Area Organizations, in 1) Standardization of methods, recording forms, and analyses (chemical, anthropometric, clinical, statistical), 2) The provision of centralized analytical services for blood chemistry and food analyses, 3) Loan of survey equipment from a central pool, 4) Temporary provision of expert personnel to the areas during the periods of their most active operations, 5) Centralized statistical analysis of pooled data from the several areas.

The Central Organization would be directed by a Responsible Investigator, supervised by an Over-All Committee (including a cardiologist, a statistician and a public health expert) and advised by an Operating Committee composed of representatives of each of the areas. Each of the Area (or Country) Organizations would

be made up of a Responsible Investigator and an Advisory or Supervisory Committee for the Area. The Area Organization would be charged with the operation of the program within the Area and the provision of reports of progress and finances for the Area.

The budget proposed would reflect this scheme of organization and would be divided into a budget for the Central Organization and separate budgets for each of the Areas. Since the costs of operations within any particular area would vary from year to year, it is proposed that the area budgets allow for adjustment between year according to the practical requirements of conducting major initial and follow-up surveys with a five-year interim of less detailed follow-up. Similarly, it is proposed that the Central Organization be allowed considerable fluidity in assignment of funds to adjust most efficiently to changing needs and opportunities in the Areas.

Though not necessarily a part of the official organization, it seems desirable to develop active contact between this program and the other responsible organizations, notably the International Society of Cardiology and the World Health Organization. It is proposed to take steps to this effect.

#### F. CHARACTER OF THE AREAS AND POPULATIONS

Each area and population to be included in the program should have a potential contribution to the pooled data and analysis as well as have advantages because of the interests and abilities of local professional personnel, and cooperation to be expected at all levels. The areas noted below are selected on the basis of judgement in those regards based on personal knowledge and experience in surveys in the area.

Emphasis is on areas made up of small towns and villages in which infectious and parasitic diseases will not compromise the analysis of heart disease incidence and in which the populations are stable and adhere to common dietary patterns. On the whole, these populations are relatively comparable in physical activity but in

each area it is possible to find sizeable representations from relatively sedentary, from moderately active and from very active men. Urban populations of great cities are not included because of their relative instability in residence and occupation, the almost insuperable problem of sampling they represent, and the much smaller prospect of full cooperation from substantially all men in the samples selected. From recent experience we know that very high coverage of all men of given age (95 to 99+%) can be obtained in the relatively rural areas selected and these men can be easily followed up for years to come. Some features of the areas proposed for study are:

1) Kurume, Japan: Evidence that coronary heart disease is rare but hypertensive disease is common; diet low in both total and saturated fats but high in salt (sodium); highly stable, homogenous population giving excellent cooperation in surveys (99+% coverage); excellent population records; reputed high frequency of cerebrovascular hemorrhage but low frequency of all types of thrombosis; important data already collected in this and nearby areas in past three years.

2) Finland (two or more areas): High frequency of coronary heart disease among farmers and woodcutters as well as in the urban population; diet high in total fats and very high in saturated fats; excellent medical standards and services; indications of considerable differences in heart disease incidence between areas in East as contrasted with West Finland, but evidence that diets are not very dissimilar; suggested related regional differences in dietary iodine and thyroid function; active interest of Heart Association and other responsible organizations and officials in this international cooperative research program; excellent population cooperation demonstrated in recent surveys; extensive survey data already at hand but restricted to employed and ostensibly healthy populations.

3) Crete, Greece: Low frequency of coronary heart disease indicated in 1958 survey covering 97+% of all men aged 45-65 in 13 villages; diet high in total fat but almost all in form of olive oil, i. e. very high intake of mono-ene and low intake of saturated fatty acids; very stable and relatively homogenous population; good local contacts and follow-up prospects; important data at hand from 1957 survey; population cooperation shown by 657 respondees out of total roster of 674 men aged 45-65.

4) Italy (three areas): Stable and relatively homogenous populations with good population data; able professional workers experienced in surveys of the type proposed; excellent cooperation demonstrated in previous surveys; similar activity levels but distinctly different dietary habits in the several areas where local contacts already well established; indications of different frequencies of heart disease in the several areas with coronary heart disease indicated to be uncommon in the areas in Marche and Calabria.

a) Calabria (Nicotera): Diet low in total fats, especially low in saturated fats but high in mono-ene; cooperation demonstrated in 1957 survey when 598 men aged 45-65 out of a total roster of 622 were successfully examined; important data already at hand.

b) Marche (Ascoli Piceno): Diet lower in mono-ene but generally higher in other fats than in Nicotera; cooperation demonstrated in 1958 when 789 men aged 45-65 out of a total roster of 790 were successfully examined.

c) Emilia (near Bologna): Diet reputed to be much higher in saturated fats than in other areas of Italy; coronary heart disease much more prominent in hospitals than in hospitals in other areas of Italy; excellent cooperation demonstrate in rheumatic fever study five years ago; data indicate higher serum cholesterol than other areas in Italy.

5) Jugoslavia (two areas): Stable and relatively homogenous populations; reputed similar physical activity but major differences in diet and in the frequency of heart disease in the two areas; enthusiastic and able officials and professional personnel experienced in surveys; active and high quality dietary studies in operation; cooperation at all levels demonstrated in field work in 1958 (still in progress).

a) Dalmatia: Diet low in saturated fats but high in mono-ene; coronary and other heart disease rare in study of 1958; 727 men aged 40-59 out of total roster of 735 successfully examined in 1958.

b) Slavonia: Diet fat very different from that of Dalmatia with little olive oil but rather large amount of pork fat and appreciable dairy fats; indications of more heart disease than in Dalmatia; cooperation demonstrated in survey currently in progress.

6) Norway (2 areas ?): Reputed rather low but rapidly rising incidence of coronary heart disease; reputed large dietary differences between coastal and inland populations, inadequate information, however, on dietary details or about relative heart disease incidence by areas; excellent medical standards and services; good cooperation between health officials, university, hospital staffs and insurance officials, average national diet changed greatly since 1945; cooperative and stable population; high interest in international cooperative research program among key officials and organizations.

7) The Netherlands (two areas ?): Low reported mortality from heart disease (and all other causes of death) but reputed rather high and rising morbidity from coronary heart disease; diets greatly changed since 1945 (similar to Norway); excellent medical and social organization and services and cooperation between different branches of government and with medical scientists; stable and reputed cooperative population; interest in international program among key officials and organizations;

long active and able nutritional research.

8) Sweden and Denmark: Consideration of joining in the cooperative international research program proposed here is still in a preliminary phase in both Sweden and Denmark. In both countries there is great interest among some key officials, physicians and persons in academic medicine and both countries have much to offer because of their research leadership, stable and cooperative populations and recognition of the growing burden of heart disease. Able professional persons in both countries have participated in recent survey work and are anxious to develop programs. There may be significant regional differences within these countries but very little reliable information is at hand as yet (e. g. Jutland vs. Sjælland in Denmark; Skåne vs. the North in Sweden).

9) Hawaii: Important data were obtained in 1956 from selected samples of Japanese and Caucasians in Hawaii which showed major differences in diets and blood cholesterol values more or less paralleling differences in average autopsy findings and in heart disease representation in clinic patients. It would be desirable to include an area in Hawaii (Japanese with a sample of Caucasians for comparison) in this over-all program but there has been no on-the-spot discussion of this as yet. It is believed that the Hawaiian Heart Association is interested in the general problem

10) U. S. A.: In the United States there are currently several research programs that are similar in purpose and somewhat similar in design to the program offered here for areas abroad. Among these should be noted the Framingham (Mass.) Study, the Albany (N. Y.) Study, The Peoples Gas Co. Program (Chicago), and The Railroad Employees Study (Minneapolis). All of these promise to yield data that could be usefully compared with those from the presently proposed program and some of the data could well be pooled with those from all of the areas for certain analyses. It is believed that efforts should be made to provide for such cooperation.

In addition, it seems desirable to consider organizing at least one area in the U. S. to be more strictly comparable, i. e. a rural area with a full re-examination after five years. Such coverage and follow-up would be far more difficult and expensive to achieve in the U. S. than in the areas abroad. It is proposed, however, to begin efforts in this direction in Minnesota late in 1959 with a view towards conducting a full survey in 1960. It is proposed that the budget for this area should be included in the budget for the Central Organization because the work in the Minnesota area would be conducted by the Central Organization.

11) Other Areas: Research programs involving surveys and epidemiological concepts rather similar to those on which the present program is based are currently operating or planned in a number of countries besides those noted above - England, India, South Africa, Guatemala and Rumania. In other countries prominent medical scientists have expressed the desire to participate in such a program - Czechoslovakia, Mexico, Iran, Australia, Argentina, Chile, etc. It may prove feasible to effect coordination and cooperation with some of these groups as the presently proposed program develops but no specific provisions for this are incorporated in the present proposal. The budget for the Central Organization should allow the use of limited funds to help in the development of activities in other areas, but actual operations in any additional areas should be financed by specific budgets for the specific areas.

It is hoped that some coordination, guidance and more concrete help can be provided on a still wider basis by organizations that are peculiarly fitted to undertake such responsibilities, notably the World Health Organization and other U. N. organizations (F. A. O., UNESCO), The International Society of Cardiology, the U. S. Public Health Service.

## G. ROSTER, SURVEY TEAMS AND OPERATIONS

1) An accurate roster for each area of all men aged 40-59 (at first examination) is essential. In most areas the preliminary roster is established from tax, voting and other official lists; this must be corrected for clerical errors (age, name), emigration, and deaths. For a roster of true long-time inhabitants, all men are eliminated who have moved into the area from elsewhere within the previous 5 years. "Elsewhere" means distant places or nearby places that have a different mode of life. Finally, search must be made for true inhabitants who are not on the official lists. True inhabitants temporarily absent are included in the roster, noting where they are and why.

All of these points should be checked in the actual survey and the final report should show the numbers of the men in the preliminary roster and in each category of correction, the final true roster, the men actually examined in full and those whose examination was incomplete (e.g. invalids seen by a physician but not subjected to the full battery of observations). For men unwilling or unable to be examined, report as much information as possible, including occupation, current activity, reputed state of health.

2) While some local professional personnel may be engaged on a part-time basis for the active period of the survey, the team proper should be organized with fully qualified personnel on a loan or leave basis from their regular professional positions. In general this is practicable only for limited periods of time - one to (see page 16)



3 months at most - so the schedule is planned accordingly.

3) Most of the team should be made up of persons native to the country in which the area is situated but it is highly desirable to include a number of experts from other countries, some with experience in similar surveys in other areas. This assures standardization of methods and criteria, the counsel of specially qualified experts and is a powerful stimulus to team morale and local interest of the population. The contribution to international understanding and friendship, and the opportunities for adding to professional training, provided by such international team work at the "grass roots" level, should be recognized.

4) A supervisor and 4 native dietitians, selected for reliability and personality suited to field conditions which are often rough, make a good team which can study intensively about 16 families at a time. Since each family should have the diet measured for a week, and since several days are needed for preliminaries with a group of families, this means that such a team can cover about 48 families in 4 weeks. That number should be adequate to characterize an area, separated into several sub-areas or sub-populations, in which the dietary pattern is relatively uniform. Besides the measurements of amounts of foods, provisions should be made to collect the foods for analysis in representative menus for comparison of computed and chemically measured nutrients in them. A supervisor and 2 dietitians would require twice the time and a team of 9 could do the same job in less than 3 weeks. But if possible the dietary survey should be repeated in the same area at different seasons.

5) For the survey on all the men in an area in regard to all the other aspects - chemical, biochemical, anthropometric, etc. - an efficient team is made up of a general supervisor (preferably the responsible investigator for the area or country), 2 internists for history taking and physical examinations, an anthropometrist, a

biochemist or technician, a cardiologist, 2 technicians for ECG work, a physician or public health nurse to do interviews, a car driver and handy man, plus local help to round up subjects, fetch and carry, etc. With a cooperative population such a team can "process" from 150 to 200 men a week in the field, somewhat fewer when the field headquarters must be shifted several times a week from village to village. This means a total of 4 to 5 weeks of intensive work in the field to cover the average area containing 600 to almost 1000 men, so a schedule of 6 weeks allows enough time for rest and recreation as well as making a few repeats and rounding up missed appointments. This team and schedule does not cover chemical analytical work done on materials sent to a central laboratory, re-examination of ECGs and clinical records, tabulation and statistical analysis, all of which is done later at a home base laboratory.

6) A simple form should be provided for each subject on which the major clinical and ECG findings are remarked for the benefit of the local physician to whom the subject may have access. Maintenance of cooperation from the population requires that the subjects derive some personal benefit. With the most efficient team and scheduling the subject will lose more than a hour in the actual examination, plus time going and coming and waiting; this is cheerfully borne if the subjects are well treated and leave with some indication, such as a cryptic note to any physician who may be concerned, that he has been given individual consideration.

7) Besides the primary battery of items to be covered in the examinations, provision should be made in staffing and scheduling for additional items that should be covered if special facilities can be made available (e. g. chest X ray), or if there are special local medical problems or items of high interest to certain important members of the team. Among the latter might be special blood studies, estimation of habitual renal salt load, blood groups, etc.

8) The major follow-up survey, 5 years later, should be a duplicate of first and requires the same staffing and scheduling. In the interim there should be provision for an annual inquiry into changes in clinical status of the men in the survey, with clinical examination of those reported ill, etc. This will be greatly facilitated by prior arrangements with the local medical practitioners and should be accomplished in most areas by the responsible investigator for the area, accompanied by a visiting physician and/or nurse or other assistant, in one to two weeks.

H. INTERIM FOLLOW-UP

On the men in each area interim follow-up between the first survey and the re-survey five years later should be reported annually and should include at least the following points:

- 1) Deaths, with copy of the death certificates, autopsy protocol if available, interviews with the attending physician, members of the family and others who can supply information on the duration, character and circumstances of the final illness.
- 2) Major illnesses or injuries with information from the local physicians, the family and the man himself. Physical examinations and E. C. G. should be made when indicated.
- 3) Query as to major changes in occupation or the development of new complaints that may suggest possible cardiovascular involvement. Physical examination and E. C. G. when indicated.
- 4) Migration out of the area, with information on new address and the reason for migration.

Two visits a year to the area should suffice in most cases and a team of two persons (e. g. physician and public health nurse) and 1 to 2 weeks may suffice for

each visit. On these visits other interim activities may be included, e.g., re-check of serum cholesterol and/or E. C. G., etc., of men whose values recorded in the full survey were aberrant, special studies on sub-samples on salt intake, trials of new methods, etc.

#### I. COST AND BUDGET

This program will be budgeted for 8 years - first survey year, operations of follow-up, analysis and investigation of special problems in subsequent years, re-survey in the sixth year (5 years of follow-up) and 2 years for analysis of the data. An initial budget will be offered for 5 years, with the expectation that the whole program would be re-examined in the third year with a view to extension for an additional 5 years at that time.

In each area the cost in the first survey year and in the year of full re-survey ordinarily will be much more than in the intervening years. But precise budgeting for each year may be difficult; it is proposed that the budgets be given flexibility in the apportionment of the total long-time funds by individual years.

Costs differ in each of the areas so no single formula for budgets can be proposed. In several areas a major part of the first-year survey has already been completed, though some additional work is required (Crete, Kurume, 2 areas in Italy, 2 areas in Jugoslavia). It is proposed, therefore, that each area offer its own budget proposal and time table. In each area the maximum of local support will be secured so that the request for outside funds can be kept at a minimum.

Both the Area and the Central Organization budgets must reflect the provision whereby the Central Organization will take responsibility for serum cholesterol and food analyses for all areas. While in some areas it may be desired to perform these analyses locally, absolute comparability of the analytical data

demands central laboratory analyses on items that are suitable for this. This holds for serum total cholesterol and fatty acid analysis of foods. In order to economize on analytical costs and to take advantage of favorable conditions it is proposed that serum cholesterol analyses be centered in the Institute of Physiology in Naples. Provision for some subsidy from the Central budget is made but it is proposed that each Area also budget 90 cents, U. S., per cholesterol analysis.

The nutrient (especially fatty acid) analyses on diets from all of the Areas will be made by the Central Organization and the Areas will not be charged for these services. The Central Organization will maintain a pool of equipment for use in the Areas in periods of most active field work so as to eliminate unnecessary purchases of equipment for limited periods of use as well as to assure availability and standardization.

An important part of the Central Organization budget is devoted to salaries, travel and maintenance costs of expert personnel being attached temporarily to the operations of the several areas or being trained for the special requirements of particular operations. To assure identity of methods and criteria, it is important that each survey involve not only a local team but also a number of professional workers from other countries.