PHS-1533
Rev. 12-58

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service
National Institutes of Health DATF August 7, 1962
Bethesda 14, Maryland

NOTIFICATION AND STATEMENT OF GRANT AWARD

In reply refer to our: HE 07410-01

Dr. Ivan D. Frantz, Jr. (SRC)
Department of Medicine and Physiological Chemistry Formerly HP-7410
University of Minnesota Medical School •
Minneapolis 14, Minnesota

Dear Dr. Frantz:

Upon recommendation of the appropriate National Advisory Council, the Surgeon General has approved the Public Health Service grant described below.

The attached explanation outlines Public Health Service policy relative to the payment and management of grant funds, as well as to the scientific and budget freedom afforded grantees in their work.

STATEMENT OP GRANT AWARD MADE UNDER THE PUBLIC HEALTH SERVICE ACT

SECTION OF ACT: 301(d)
TYPE OF AWARD: Research
NATIONAL ADVISORY COUNCIL: Heart
GRANT PERIOD: 6/25/62 - 5/31/63
ABBREVIATED TITLE OF PROJECT OR PROGRAM: HE 07410-01 Pilot Study: Diet and Heart Disease
GRANTEE INSTITUTION: University of Minnesota
PAYEE (CHECK WILL BE DRAWN AS FOLLOWS) 641394
PRINCIPAL INVESTIGATOR(S) OR PROJECT DIRECTORS: Dr. Ivan D. Frantz, Jr. et al

Assistant Vice President, Business Admin©
University of Minnesota
Administration Building, Room 303
Minneapolis 14, Minnesota

FUTURE SUPPORT (Provided Funds Are Appropriated-See Attached Sheet Concerning Continuation)
X Amounts Include Indirect Costs
1st Additional Year (02) $96,345
2nd Additional Year None
3rd Additional Year
4th Additional Year

BUDGET ALLOCATION	AMOUNT
DIRECT COSTS (EXCLUSIVE OF TRAINEE STIPENDS)	121,681
TRAINEE STIPENDS	
INDIRECT COST ALLOWANCE (OVERHEAD)	10 539
TOTAL GRANT	$ 132,220
AMOUNT OF FIRST PAYMENT	$ 22,700
BALANCE DUE	109,520

• Approved for Support for_ -Additional Years Ending_____, e mun s o e
Determined Annually.

Signature

Name and Title J. Franklin Yeager
Associate Director
For Extramural Programs
National Heart Institute

LIST NUMBER
ALLOTMENT NUMBER 7520372 - 24001 -01

cc: Co-investigators
Financial Officer
Signer of Application
Public Relations Officer

REMARKS * This award is made with the conditions that (l) the actual total amount of the grant will be determined by negotiation within the celling stated, and (2) the study will be conducted using only the double blind procedure. These conditions also apply with respect to the first additional year of the grant. No further payments will be scheduled until after the total amount of the grant has been negotiated.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
National Institutes of Health

EXPLANATION OP STATEMENT OF RESEARCH GRANT AWARD - Revised July 1, 1961

I. PUBLIC HEALTH SERVICE POLICY REQUIREMENTS:* The grantee institution is obligated to administer any Public Health Service grant or award in accordance with the policies governing the Grant and Award Programs of the Public Health Service.

II. PERIOD OF GRANT; The Statement of Grant Award indicates the period for which the grant is being made and the number of additional years for which support has been recommended, Funds may be obligated or expended only within the approved period of the grant. If, during the period of the grant, the principal investigator wishes to extend the ending date without additional funds, an extension may be approved if requested by letter at least 60 days before the termination date shown.

III. PAYMENT OF GRANT: Payment of this grant will be made in full if the total approved amount is $5,000 or less. If it is in excess of $5,000, it will normally be paid in four installments. FUNDS MAY NOT BE OBLIGATED OR EXPENDED PRIOR TO THE BEGINNING DATE OR SUB-SEQUENT TO THE TERMINATION DATE SHOWN ON THE STATEMENT OF GRANT AWARD. If Public Health Service support for this project is continued, any unexpended balance up to $5,000 or one half of the amount of the continuation grant, whichever is less, will be transferred to and remain available for expenditure during the period of the continuation grant. DEFICITS MAY NOT BE TRANSFERRED to the continuation grant or to any other Public Health Service account.

IV. REBUDGETING OF FUNDS: Expenditures for direct costs may generally be made at the dis-cretion of the investigator, within the over-all policies of the grantee institution and without regard to the category distribution proposed in the application. Exceptions include, for example, (1) payments of any kind to Federal employees, (2) construction of buildings, (3) consultant fees to employees of the grantee institution, and (4) charges for entertainment, meals, and refreshment. Funds awarded to support conferences may not be rebudgeted without prior approval of the Public Health Service.

V. EQUIPMENT PURCHASED WITH GRANT FUNDS: Title to equipment purchased with grant funds resides with the grantee institution during and after the termination of a grant project, without further obligation to the Public Health Service; except that the Public Health Service may request the grantee institution to make available highly specialized or very expensive equipment to other institutions by loan or transfer of title if the property is no longer required for the research program at the grantee institution.

Title to equipment purchased with funds from a grant awarded to an individual or to a profit-making institution resides with the Public Health Service. The individual or the profit-making institution will be advised concerning the disposition of the equipment after the termination of PHS support of the research project involved.

VI. SCIENTIFIC FREEDOM: The investigator is not required to follow the specific details of the project submitted for review, particularly if he finds promising leads that in his opinion are likely to be more productive than those outlined in the original proposal,

VII. CONTINUATION OF PROJECT: The Statement of Grant Award indicates in the column entitled "FUTURE SUPPORT" the maximum dollar amounts of support for any additional years that have been recommended for this project, provided the Congress appropriates the necessary funds. Forms on which to request this support will be sent to the principal investigator approximately four months before the termination date of the current grant. If no future support is indicated, an application for continuation support must compete with other applications for available funds. Necessary forms and instructions will be sent to the principal investigator approximately two months In advance of the deadline for submittal of this type of application.

* REFERENCE: For further information on specific details applicable to general policies on Research Grants, see "Grant and Award Programs of the Public Health Service, Volume I - Policy and Information Statement on Research Grants - 1959."

(Leave Blank)

R'cd date 2/28/62

Council Mar 62

Action

. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

APPLICATION FOR RESEARCH GRANT
(A PRIVILEGED COMMUNICATION)

(Leave Blank)

No. HP 7410

ss SRC (1)

Formerly

NRP-Yes

Application is hereby made for a grant in the amount and for the period stated, for the purpose of conducting research as described herein, in accord with the Agreement signed below.

A. AMOUNT REQUESTED: $ 99,800 (Same as total of itemized budget, page 2, item A)

B. PERIOD DATES: July 1 (Mo. Day) Year -thru- June 30, 1963 (Mo. Day Year). (Normally 12 months. See instructions.)

a TITLE OF RESEARCH PROPOSAL (Do not exceed 53 typewriter spaces)

Feasibility Study; Diet and Heart Disease

D. TYPE OF APPLICATION (please check one only, and add No. if applicable): X New Project Proposal- or • Revision of, • Supplement to, or Renewal of PHS application or grant No

E. PRINCIPAL INVESTIGATOR:

Name Ivan D. Frantz, Jr

Title- Research Professor

Mailing address of Research office Dept, of Medicine

University of Minnesota, Minneapolis 14, Minn.

-Telephone No F c 9 — 7311 -Extension 2294-

-Department or Service Medicine and Physiological Chemistry

Institution- University of Minnesota

Major

Subdivision The Medical School

F. CO-PRINCIPAL INVESTIGATOR, if any. (Name and title only)

Ancel Keys, Ph.D., Professor and Director Laboratory of Physiological Hygien
Edward Engberg, Superintendent, Faribault State Hospital

G. INSTITUTION SPONSORING REQUEST

Name

Mail address University of Minnesota, Minneapolis 14, Minnesota

Name & title of official authorized to sign application an behalf of institution

C.T. Johnson Assistant Vice Pres.

H. NAME, TITLE, AND ADDRESS OF FINANCIAL OFFICER:

C.T. Johnson
Assistant Vice President
University of Minnesota
Minneapolis 14, Minnesota

Manner in which check(s) should be drawn: (645448)
University of Minnesota

AGREEMENT: It is understood and agreed by the undersigned that any grant received as a result of this application is subject to the following terms. (1) Funds granted as a result of this request are to be expended for research or related purposes as governed by Public Health Service and grantee institution policies; (2) the grant may be revoked in whole or in part at any time by the Surgeon General of the Public Health Service, provided that a revocation shall not include any amount obligated previous to the effective date of the revocation if such obligations were made solely for the purposes of research; (3). all reports of original investigations supported by the grant shall acknowledge such support; (4) if any invention arises or is developed in the course of the work aided by the grant, the undersigned will either (a) refer to the Surgeon General for determination, or (b) determine in accordance with grantee institution's own policies as formally stipulated in a separate supplementary agreement entered into between the Surgeon General and the grantee institution, whether patent protection on such invention shall be sought and how the rights in the invention, including rights under any patent issued thereon, shall be disposed of and administered, in order to protect the public interest

PERSONAL SIGNATURES (in ink)

(1) Principal Investigator 3 * (darts)
(Same as shown in "E" above)

(2) Authorized official of applicant institution. FEB 23 1962 (date)
(Same as shown in "G" above)

Mail completed application to:
Division of Research Grants
National Institutes of Health
Bethesda 14, Md.

>M

A. BUDGET REQUEST (for the period shown on page 1)

(1)	(2)	
1. PERSONNEL List all positions, including Principal and Co-investigator. Amounts requested must not exceed proportion of total salary computed from % of time spent.	% time on this project	Requested from PHS (omit cents)
IVAN D. FRANTZ, JR., Principal Investigator	20 %	00
Ancel Keys, Ph.D., Coinvestigatorg a t o r %		-OO-
-Edward J. Engberg, C o i n v e s t i g a t o r	OO	
*Assistant S c i e n t i f i c Director	30 %	-OO
• Part time physicians - 600 hours at $10-		6,000
Junior Scientist	100 %	5,196
Senior dietician,	100 %	7,000
2. PERMANENT EQUIPMENT, itemize (see instructions)		
2 cooks at $3.64S	100	.7,296
0ASI--SERA, Workmen's Comp. (<		
**Automatic liquid s c i n t i l l a t i o n counter		12,500
3. CONSUMABLE SUPPLIES, itemize (see instructions?		
paper,—chemicals-		4,000
ons for 365 days		14\,600
4. TRAVEL, itemize (see instructions)		
-50-round t r i p s , Minneapolis to F a r i b a u l t		
O t h e r t r a v e l for— p r o f e s s i o n a l personnel		1,000-
5. OTHER EXPENSE, itemize (see instructions)		
****Renovatlen -of—kitchens-		20t000
B. TOTAL DIRECT COST REQUIREMENTS		S0,261
INDIRECT COST ALLOWANCE (The administrative official signing this application may request an amount for indirect costs. Review detailed instructions) (Round to low dollar) ($ 1 0 , 0 0 0 of permament equipment o m i t t e d)		10,539
TOTAL BUDGTEATL BUDs GMETO(Sat ms hee a ws n in item A, p a g e 1)		90,800,

B. ESTIMATE OF SUPPORT REQUESTED FOR THE YEAR FOLLOWING THE BUDGET PERIOD ITEMIZED ABOVE. Applicants for 1-year grants should type the word "None" in space for TOTAL BUDGET shown below.

Personnel	Equipment	Supplies	Travel	Other	Total Direct Cost	Indirect Cost	TOTAL BUDGET
				idy			
							#See
				$	$	$	
786	0	4,000	l , 3 7 5	14,600	4 7 , 7 6 1	7164	54,925 foot-
							#5

C. ADDITIONAL YEARS OF SUPPORT, beyond the 2 years covered above, if requested. Please show TOTAL AMOUNTS required for each such additional year, including indirect cost allowance.

3. $. -4. $ None 5. $ .6 $

Rev.10-60 *See f o o t n o t e #1 ***See f o o t n o t e #3 #See f o o t n o t e #5
**See f o o t n o t e #2 ****See footnote#4

Footnotes

*Footnote #1.

An Assistant Scientific Director, on active duty with Public Health Service, will be named later.

**Footnote #2.

Our laboratory is now in possession of quite adequate equipment for gas-liquid chromatography. We have a preparative ultracentrifuge, spectrophotometers, scalers with various types of detectors, a vibrating reed electrometer, and all minor equipment which will be needed. An electrocardiograph now on hand at Faribault will be available for the project. The Autotechnicon to be provided in the Laboratory of Physiological Hygiene will be used for the cholesterol measurements. We have a home-built, manually-operated, coincidence-type liquid scintillation counter which is reasonably adequate for our present needs. An automatic unit will both facilitate our other work and relieve the excess load which this project will impose. It will pay for itself in technicians' time saved. In our previous work on the analysis of stools for C^{14}, we have used ionization chamber techniques. These methods have been extremely time-consuming, and have been the main difficulty in the way of collection of adequate data. We hope to shift over to liquid scintillation counting for the analysis of all of our samples of carbon dioxide derived from the combustion of fractions from stools.

***Footnote #3.

This estimate is subject to revision. At present we cannot tell what the cost will be for the packaged foods which will be provided by the food industry. During the first year, the special diets will not be started until after the initial examinations have been completed. On the other hand, it may be necessary to feed the special diet to a few patients not in the study who will be housed in the buildings with the experimental subjects.

****Footnote #4.

The buildings in which the experimental subjects are to be housed have fairly well equipped kitchens, but they are currently being used only to serve food which is cooked in a single, large, central kitchen. It will be desirable to cook for the experimental groups in separate kitchens. This change will necessitate some rearrangement of facilities, the installation of larger ranges and hoods, and the purchase of some large kettles. The amount budgeted for this purpose was arrived at after consultation with the state advisory architect, who inspected the site. It is subject to revision after more detailed study.

#Footnote #5.

The request for a second year of support is based on the supposition that the study will continue, and that the original subjects will remain on the same regimens. If a decision should be reached to terminate the study after one year, the budget for the second year can be revised downward. In that event, only the collation of data and perhaps a few analyses will remain to be done during the latter part of the second year.

RESEARCH SUPPORT

List all other research support of the Principal Investigator, including that from own institution, and applications that are pending. Use continuation page if necessary. See instructions.

A. PUBLIC HEALTH SERVICE SUPPORT:

NUMBER	TITLE OF PROJECT	AMOUNT	PERIOD OF SUPPORT
(1) Active or approved:			
H-1875(C)	Intermediary metabolism of cholesterol	$14,573	4/l/61-3/31/62
H-1875(C7)	Intermediary metabolism of cholesterol	$24,258	4/1/62-3/31/63
	(Future commitment at same level through 3/31/67)		

(2) Applications submitted, awaiting decision:

B. ALL OTHER RESEARCH SUPPORT:

SOURCE	TITLE OF PROJECT	AMOUNT	PERIOD OF SUPPORT
(1) Active or approved:			
Life Insurance Medical Research Fund	Regulatory Mechanisms in Human Cholesterol Metabolism	$9,900 per year	7/1/61-6/30/63
Graduate School Univ. of Minn	Cholesterol Metabolism in relation to arteriosclerosis	500	7/1/61-6/30/62

(2) Implications submitted, awaiting decision:

BIOGRAPHICAL SKETCHES

Provide brief sketches for professional personnel already selected who are to be actively engaged in this project. The following format should be used for each person, with Co-investigator (if any) immediate following Principal Investigator, then other professional personnel, lettered consecutively.

A. Principal Investigator: Ivan D, Frantz, Jr., Research Professor -
(Name and title)

1. Date of birth: Jan. 16, 1916 — _; Place of birth: Smithville, W.Va, U. S. A. • ; Male X; Female •.
Present nationality:

2. Educational experience:

a. Degrees conferred (Begin with baccalaureate degree. Identify honorary degrees under field.):

DEGREE	INSTITUTION CONFERRING	FIELD(S)	YEAR
	Duke University	Major:—Chemistry	1937
	Harvard Medical School		

b. Other research training and experience, especially that establishing research qualifications in area covered by this application:

WHERE	NATURE	YEAR
	! Clinical and Research Fellow	1946
-Mass. cal—Hospital		
rd_University	' later Associate in Medicine	1954
-and]	and Assistant Physician	

3. Fields of present major scientific est, in order of choice:
relationship of lipides to atherosclerosis

4. Supplementary information:
Since 1954 George S. Clark Research Professor, Depts. of Medicine and Physiological Chemistry, Univ. of Minn,; and Director, Cardiovascular Research Laboratory, Dept. of Medicine, Variety Club Heart Hospital, Minneapolis.

B. Ancel Keys, Ph,D., Professor and Director, Lab. of Physiol, Hygiene
(Name and title)

1. Date of birth: Jan, 26, 1904 _• Place of birth: Colorado Springs, Colorado
Present nationality: U. S. ; Male X Female

2. Educational experience:

a. Degrees conferred (Begin with baccalaureate degree. Identify honorary degrees under held.):

DEGREE	INSTITUTION CONFERRING	FIELD(S)	YEAR
	University of California, Berkeley	Economics	1925
M.A,		Zoology	1928
Ph.D.		Oceanography	1930

b. Other research training and experience, especially that establishing research qualifications in area covered by this
University of Cambridge, England - Fellow (with Joseph Barcroft) 1932-3

WHERE	NATURE	YEAR
Ph.D. Cambridge, England-	Physiology major, Riochem. minor	1936_
National	Resi	1930-31
Oxford, England	Senior Fullbright fellow research	1951,52

3. Fields of present major scientific interest, in order of choice: Human physiol. epidemiology fat and cholesterol metabolism - ol - J Betaboligs ! and -coronary-heart—d-i.s&as-e„

4. Supplemented information:
Directed medical research programs in Chile, Mexico, England, Italy, Spain, So. Africa, Japan, Hawaii, Finland, Greece, Jugoslavia, Netherlands,

Biographical Sketches (cont.)

C. Edward John Engberg, M.D., Superintendent, Faribault State Hospital

1. Date of births Sept. 29, 1887 Place of births Minneapolis,Minn.

Nationality: U.S.

2. Educational experiences

M.D. University of Minnesota Medical School 1913

Internship Mounds Park Sanitarium, St. Paul, 1913-1914.

Private practice in neuropsychiatry in St. Paul from June, 1914 to July 1, 1937, except for 18 months service during World War I in Neuropsychiatric Units, U.S. Army, entering as 1st Lt. and honorably discharged as Captain.

Has filled present position as Medical Superintendent, Faribault State School and Hospital, since July 1, 1937.

Protocol for a Feasibility Study of the Effect of Diet on the Incidence of Manifestations of Atherosclerosis in a Closed Population.

It is recognized that the ultimate objective of this cooperative study is the demonstration of the effect of dietary alterations on the incidence of atherosclerotic cardiovascular disease in the free-living population. Use of institutionalized subjects carries the disadvantage that the conclusions drawn may not be directly applicable to the general population, either because of the peculiar characteristics of the institutional inmate, or because the experimental conditions cannot be reproduced outside the institution. On the other hand, the following advantages are apparent:

1) Diet can be more rigidly controlled - non-adherence will not be a factor.

2) A more nearly ideal diet can be enforced.

3) Drop-outs will be less numerous. Those drop-outs which do occur will be caused by factors unrelated to the experiment, will affect experimental and control groups alike, and will presumably be less likely to bias the results.

4) A statistically valid conclusion can probably be reached with a smaller number of subjects.

Because of these advantages, and because the feasibility of the experiment in the free-living population under present conditions is still in doubt, we believe that a preliminary study in an institution is desirable.

The Institution Chosen for the Study

Perusal of the populations of institutions of various types has led us to the conclusion that mental hospitals offer the best prospect for this research. The inmates of prisons are too young, and the turnover is too great. The population of individual monasteries is so small that an excessive number of separate units would be required. We propose that the feasibility study be carried out in the state hospital at Faribault, Minnesota, an institution with a current total population of 3,179 patients, 1,762 of whom arc males.

All of the patients at Faribault fall into the category of mental deficiency. We believe that patients with other types of mental illness could also be used, if this study were later to be expanded, but mental defectives are especially suitable. Their physiology is perhaps more nearly like that of the normal individual than is that of the schizophrenic,, More importantly, the institution is under no pressure to discharge them home.

Faribault now cares for male patients of an age suitable for this study as follows:

Age	Number of Men
	H p 7 4 1 0
40-44	131
45-54	215
55-59	84

As discussed below, we expect to divide our experimental subjects into three groups of equal size, one of which will be kept on the present institutional diet which closely resembles the diet of the average American. The subjects will be divided into cells and assigned to the three groups at random, in much the same fashion as in the open study. The two groups on the altered diets will be housed in two separate, identical modern buildings, with space for 110 men in each building.

Diets

Final decision as to the nature of the diets to be used should be made by the Executive Committee. We propose the following groups:

1. A control group, maintained on a diet as nearly as possible like that of the double-blind controls in the studies in the free-living population (GroupD of the free-living protocol).

2. A group to receive a reduced intake of saturated fat and increased intake of polyunsaturated fat. 40% of total calories to be derived from fat. Much of the food for this group will be obtained from the same source as the packaged foods for the open study. This group corresponds to Group C of the free-living protocol.

3. A group maintained on a diet as nearly as possible to the ideal. This diet should be similar in carbohydrate, fat, protein, vitamin, and mineral content to that of populations known to have the lowest incidence of atherosclerotic heart disease in the world.

Emphasis on this third group may be criticized on the grounds that it defeats the purpose of the study, which is to narrow the number of variables ,as much as possible. Our reply is that we would find it more palatable to be forced to repeat the experiment in order to determine which feature of the dietary change produced the successful outcome, than to repeat it because the first attempt had failed. The latter experiment might never be done. Although manipulation of the composition only of the fat in the diet involves fewer variables, it also involves more postulates which must prove correct if the experiment is to succeed. It is a source of concern that, on the basis of the best evidence now at hand, none of the diets to be used in the open study is likely to produce an average lowering of blood cholesterol much in excess of 15%. Considerable effort will be directed at making this third diet palatable. The object during the feasibility study will be to determine how closely the "ideal diet" can be approached without undue loss of cooperation from the subjects. A major feature of this diet will be that it should be acceptable to the general population under the more favorable conditions which may exist in the future. These would include full cooperation of the food industry, and solid scientific evidence of the effect of adherence on life expectancy.

If a large-scale closed study is organized (at a later date), it will be desirable to continue these same three groups, in order to obtain information concerning the degree of dietary change needed to obtain a satisfactory lowering in the incidence of coronary heart disease. If it should become apparent, however, that a marginal number of subjects will be available, I would prefer to omit Group 2. As I see it, the primary question to be answered by these studies is, "Can the incidence of coronary heart disease be significantly lowered by dietary manipulation?"If this question can be answered clearly in the affirmative, the finer details of the degree of dietary change needed can be worked out later. Group 3 appears to offer the greatest probability of providing this clear affirmative answer. If, on the other hand, the answer should be negative, it is highly unlikely that any of the other proposed diets would be successful, and they need not be tried.

Experimental Plan

The experimental plan will be similar to that agreed upon for the free-living population, with modifications appropriate to the type of subject. The most important modifications are:

1) "Pep talks" by dieticians and physicians will be unnecessary.

2) Evaluation of results must be entirely on the basis of objective evidence, primarily electrocardiography, transaminase in the case of acute events, and autopsy.

Eleven contacts are planned with each subject, as follows:

1) Initial. Complete physical examination, urinalysis, blood counts, electrocardiogram, chest film, cholesterol, 250 x 1 = 250 hours of physician's time.

2) 1 week. Weight, blood pressure, pulse, cholesterol
3) 2 weeks. Weight, blood pressure, pulse, cholesterol

Experimental diets will be initiated at this point. Follow-up examinations will be made as follows:

1) 2 weeks, Cholesterol
2) 4 weeks. Cholesterol
3) 8 weeks. Weight, blood pressure, pulse, cholesterol
4) 4 months. Weight, blood pressure, pulse, cholesterol
5) 6 months. Weight, blood pressure, pulse, cholesterol, electrocardiogram
6) 8 months. Weight, blood pressure, pulse, cholesterol
7) 10 months. Weight, blood pressure, pulse, cholesterol
8) 1 year. Repeat of initial examination

Whichever objective index of adherence is used in the free-living protocol (e.g., GLC analysis of adipose tissue) will also be used in this study.

The medical examinations will be carried out by physicians from the Faribault area, hired on an hourly basis. A dietician and two cooks will be needed to handle preparation of the diets. After the first four weeks one

technician will be able to collect the blood samples, determine the serum cholesterol concentrations, and record and mount the electrocardiograms. During the initial phase, personnel will be borrowed from other projects. The electrocardiograms will be read by electrocardiographers from University of Minnesota Hospitals. Criteria will coincide as closely as possible with those to be used in the open study.

A physician on active duty with the Public Health Service will serve as assistant scientific director of this project, as well as of the Minnesota open study.

Auxiliary Experiments

An important unsolved problem in this field is the question of the mechanisms by which dietary changes bring about alterations in the concentration of cholesterol in the blood. Our laboratory is now engaged in a small-scale study aimed at shedding light on this matter. Cholesterol synthesis, pool size, and excretion arc being investigated, using isotopic methods* The experimental and control groups at Faribault will provide ideal subjects for the extension of this work.

In collaboration with Dr. Keys' laboratory, we conducted an experiment in which we maintained five healthy volunteers on controlled diets which were switched back and forth between saturated and unsaturated fats. Each subject received cholesterol-C^{14} at the start of the study. The purpose was to try to account for the changes in blood cholesterol on the basis of alterations in the excretion of bile acids and unsaponifiable products in the feces. We are now about two-thirds of the way finished with the isotope analyses. The patients at Faribault will provide additional subjects for this study, which will probably be needed if the conclusion is to have statistical significance. We would like to carry out similar experiments on groups of individuals who show high and low blood cholesterols while on the same diet. Perhaps in this way we can identify the differences in metabolism which are responsible for the concentration of blood cholesterol characteristic of different people.

We believe that our present methods achieve clean separation of the unsapon ifiable excretion products of cholesterol from the bile acids. Neither fraction is contaminated to an appreciable extent with the other, and the recovery of both is quantitative. Thus, the relative importance of the two fundamentally different routes of cholesterol excretion in a given individual can be assessed.