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

APPLICATION FOR RESEARCH GRANT
(A PRIVILEGED COMMUNICATION)

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No.
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Formerly

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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: $ 25,850.00 (Same as total of itemized budget, page 2, item A8.)

B. PERIOD DATES: 9 (Mo.) 1 (Day) 60 (Year) thru 8 (Mo.) 31 (Day) 61 (Year) (Normally 12 months. See instructions.)

C. TITLE OF RESEARCH PROPOSAL (Do not exceed 53 typewriter spaces)
THE RELATION OF TREATMENT TO DIABETIC COMPLICATIONS

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

E. PRINCIPAL INVESTIGATOR:
Name Christian R. Klimt, M.D., Dr.P.H. Telephone No. FE 9-7311 Extension 2459
Title Associate Professor Department or Service Epidemiology
Mailing address of Research office 1158 Mayo, University of Minnesota, Minneapolis 14, Minn.
Institution University of Minnesota Major Sub Division College of Medical Sciences

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

G. INSTITUTION SPONSORING REQUEST
Name University of Minnesota
Mail address Minneapolis 14, Minnesota
Name & title of official authorized to sign application on behalf of institution
Clinton T. Johnson, Comptroller

H. NAME, TITLE, AND ADDRESS OF FINANCIAL OFFICER:
Clinton T. Johnson
Comptroller
University of Minnesota
Minneapolis 14, Minnesota
Manner in which check(s) should be drawn:
University of Minnesota

I. 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.

J. PERSONAL SIGNATURES (in ink)
(1) Principal Investigator _____ (Same as shown in "E" above) _____ (date)
(2) Authorized official of applicant institution _____ (Same as shown in "G" above) _____ (date)

Approved
L. M. Schuman, M.D.
L. M. Schuman, M. D.
Professor of Epidemiology

Gaylord W. Anderson, M.D.
Director, School of Public Health

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

Robert Howard, Dean
College of Medical Sciences

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

(1) 1. PERSONNEL List all positions, including Principal and Co-investigator. Amounts requested must not exceed proportion of total salary computed from % of time spent.	(2) % time on this project	(3) Requested from PHS (omit cents)
Christian R. Klimt	25 %	$ --------
Curtis L. Meinert, Research Assoc. in Statistics	100 %	7,400
Secretarial Assistance (one full-time, short-term as needed)	100 %	4,600
Jacob E. Bearman, Prof. of Biostatistics, Consultant	10 %	1,000
Insurance and retirement, workmens' compensation	%	672
	%	
	%	
2. PERMANENT EQUIPMENT, itemize (see instructions)		
Office equipment (typewriters, calculators, dictaphone, filing cabinets, office furniture, photocopy machine, etc.)		$ 3,000
Books, journals, etc.		See
3. CONSUMABLE SUPPLIES, itemize (see instructions)		
Office supplies (printed study forms, stationery, IBM cards, etc.)		$ 1,000
Books, journals, etc.		306
4. TRAVEL, itemize (see instructions)		
Between Project Sites: Minneapolis, Cleveland, Cincinnati, Boston, New York, and Baltimore for principal investigator and statistician and one professional meeting for each of them annually.		$ 3,000
5. OTHER EXPENSE, itemize (see instructions)		
Telephone (long distance between project sites)		$ 500
IBM services		1,000
6. TOTAL DIRECT COST REQUIREMENTS		$22,478
7. INDIRECT COST ALLOWANCE (The administrative official signing this application may request an amount for indirect costs. Review detailed instructions) (Round to low dollar)		$ 3,372
8. TOTAL BUDGET (Same as amount shown in item A, page 1)		$25,850

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
$14,500	$1,850	$ 1,000	$3,000	$2,500	$ 22,850	$ 3,428	$ 26,278

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

3. $ 27,000 4. $ 28,500 5. $ 30,000 6. $ 31,500 7. $ 33,000

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:

GRANT NUMBER	TITLE OF PROJECT	AMOUNT	PERIOD OF SUPPORT
(1) Active or approved:	Research contract No. SAph 73736, Bureau of State Services, Chronic Disease Program, USPHS "A Controlled Family Study of the Aggregation of Prediabetes"	$3,000	February to August 1960
(2) Applications submitted, awaiting decision:			

B. ALL OTHER RESEARCH SUPPORT:

SOURCE	TITLE OF PROJECT	AMOUNT	PERIOD OF SUPPORT
(1) Active or approved:			
(2) Applications 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) immediately following Principal Investigator, then other professional personnel, lettered consecutively.

A. Principal Investigator: Christian R. Klimt, M. D., Dr.P.H., Assoc. Prof. of Epidemiology
(Name and title)

1. Date of birth: [redacted]; Place of birth: Vienna, Austria;
Present nationality: Austrian; Male ☒; Female ☐.

2. Educational experience:

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

DEGREE	INSTITUTION CONFERRING	FIELD(S)	YEAR
M.D.	University of Vienna	Medicine	1944
M.P.H.	Johns Hopkins School of Hygiene	Public Health	1952
Dr.P.H.	Johns Hopkins School of Hygiene	Epidemiology	1959

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

WHERE	NATURE	YEAR
Austria, Switzerland, Egypt, Iraq in employ of WHO, Johns Hopkins Sch. of P.H.	Public Health, Epidemiology, Virus and Tropical Diseases, Heredity of Prediabetes	1949-1958

3. Fields of present major scientific interest, in order of choice:
Diabetes, Epidemiology of Hereditary Mechanisms

4. Supplemental information:

Detailed curriculum vitae submitted previously

B. Curtis L. Meinert, M.S., Research Associate
(Name and title)

1. Date of birth: [redacted]; Place of birth: Sleepy Eye, Minnesota;
Present nationality: U.S.A.; Male ☒; Female ☐.

2. Educational experience:

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

DEGREE	INSTITUTION CONFERRING	FIELD(S)	YEAR
B.A.	University of Minnesota	Psychology	1956
M.S.	University of Minnesota	Biostatistics	1959

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

WHERE	NATURE	YEAR
University of Minnesota	Cerebral Palsy, Drug Evaluation, in animals and human patients.	1957-1960

3. Fields of present major scientific interest, in order of choice:
Statistical aspects of clinical trials in treatment of chronic disease

4. Supplemental information:
Part-time teaching experience in biostatistics from 1956 to 1960.

RESEARCH PLAN AND SUPPORTING DATA

Details of the proposed plan and other necessary data should be typed (single spaced) in accord with the outline below, which is suggestive only. See instructions. Please continue numbering pages in sequence for entire application. Additional continuation sheets, if needed, may be requested from the Division of Research Grants.

1. **RESEARCH PLAN**
   - A. **Specific Aims** - Provide a concise statement of the aims of the work immediately proposed, and relate these to your long-term goal.
   - B. **Method of Procedure** - Give details of your research plan, including how results will be analyzed. For each specific aim mentioned in "A" show how your plan is expected to fulfill the aim.
   - C. **Significance of this Research** - Explain why the results of the proposed work may be important.
   - D. **Facilities Available** - Describe the general facilities at your disposal. List the major items of permanent equipment.
2. **SUPPORTING DATA**
   - A. **Previous Work Done on this Project** - Describe briefly any work you have done to date that is particularly pertinent.
   - B. **Results Obtained by Others** - Summarize important results to date obtained by others on this problem, citing publications. Select no more than five.
   - C. **Personal Publications** - Cite your most important publications on this or closely related work. List no more than five.
   - D. **Justification of Budget** - Defend itemized budget for the initial period (A, page 2) where you feel it necessary, and delineate reasoning basic to budget estimates for continuation years.

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1. **RESEARCH PLAN**
   - A. **Specific Aims** —

The aim of the proposed study is to determine the relative effectiveness of four treatment schedules (e.g. standard diet plus placebo tablets, standard diet plus a standard tolbutamide dose, standard diet plus a standard insulin dose, and standard diet plus insulin in varying amounts dosed to maintain normoglycemia) to prevent the principal late complications (retinopathy, cardiovascular disease, nephropathy, and neuropathy) of diabetes mellitus. Incidental to this objective there will have to be developed standardized diagnostic procedures, record systems, and clinical definitions.

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METHODS OF PROCEDURE:

This specific grant request is to cover activities of the "Coordination Center" (C.C.) for a multiclinic study at six University clinics. Five of the clinics are grantees of the N.I.H. for the same project and have in their application outlined procedures, still largely flexible at this stage, applicable to the selection of patients and to their follow-up over the proposed study period of ten years. Patients diagnosed not more than six months before, will be observed for a period of one month while only on a standard ADA diet for development of acidosis and other objective signs as well as subjective symptoms indicative of decompensated diabetes. If they remain free of such signs and symptoms, they become eligible for entering the study.

The reports of such eligible cases will be forwarded to the C.C. and from a list of random numbers, one of the four treatments will be selected for application to each. In the case of the placebo and the tolbutamide groups, a double blind study design could be employed which, for ethical reasons, would not be possible for the insulin groups. The patient will be allocated a permanent serial number and will be registered in at least three separate filing systems , by name, by number, and by recall date. He will be recalled at three-monthly intervals, at which time the status of his diabetes will be evaluated by prescribed uniform techniques and one of the four specialized examinations (eye, heart, and vascular system, kidney and nervous system) will be performed. These examinations will as much as possible be simple, reproducible, based on a permanent record (fundus photograph, x-ray, E.K.G., kidney function test, etc.) and blind so far as the treatment group of the patient is concerned. In this way, at annual intervals, but staggered for reasons of practicality, all the necessary follow-up examinations will be performed.

It will be the function of the C.C. to watch for the completeness of the periodic examinations, to produce, in co-operation with the clinical investigators, a set of standard record forms, a complete study protocol, and to conduct ancillary studies intended to foster standardization of diagnostic techniques. At intervals the results will be evaluated and progress reports prepared. For purposes of analysis, the following points in a patient's history can be utilized:

1. Treatment failure, either permanent or temporary due to decompensation of the patient's diabetes.
2. Onset of a late complication (retinopathy, Kimmelstiel-Wilson's nephropathy, cardiovascular disease and diabetic neuropathy)
3. Progression in severity of a late complication
4. Death

During the first year, or a portion thereof, the study will constitute a pilot phase, during which the necessary procedures, administrative and technical, will have to be developed. Following this, a more realistic appraisal of expected numbers of patients will be possible. In view of the presumably uneven, but not well known, distribution of onsets of late complications, likely to vary not only with duration of the disease, but also with age at first diagnosis, sex, and possibly also with group specific environmental and hereditary factors, a good estimate of required numbers to obtain statistically significant results may not be possible even after completion of the pilot phase.

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It will be one of the tasks of the C.C. to attempt to follow patients lost to observation in order at least to determine whether they were alive or dead at a specified time. This will require recording, on admission to the study, of addresses of relatives and of friends, of such identifying marks as social security numbers, driver's license, Blue Cross number, etc.

It will also be a paramount task of the C.C. to assure the completeness of records and the adherence to standards by all investigators once agreement has been reached among a majority. This will be done through frequent personal checks, discussions with clinical and clerical personnel at all study centers, and through interchange of permanent diagnostic records among the investigators and again to the same investigator in coded form.

SIGNIFICANCE OF THIS RESEARCH:

Over the years many studies have been made, which appear to demonstrate that the rate of development of late complications is inversely correlated to the degree of normoglycemia maintained. On the other hand, even in well-controlled diabetics specific complications continue to occur and the less specific cardiovascular complications have an incidence in excess of what would be expected for a non-diabetic group of similar age and sex composition. Only from a prospective type of study, as the one proposed, can come the definitive answer as to the best treatment schedule available for the prevention of late complications of diabetes mellitus, a disease where the acute life-endangering signs can be controlled since the advent of insulin in 1922, and where the enhanced risk of infectious complications has within recent years been normalized by the use of antibiotics.

Incidental to this study, it is expected that progress will be made in standardizing clinical definitions, diagnostic procedures, and specific record-keeping systems, which should influence clinical practice and administrative procedure throughout the country.

FACILITIES AVAILABLE:

The Coordination Center will be located strategically in the Epidemiology Department of the School of Public Health, in the Mayo Building and Hospital of the University of Minnesota. There have been allocated two rooms to this study for the location of the center. One floor above in the Biostatistical Department, there are available a complete set of IBM machines for mechanical card analysis. Dr. Bearman, Professor of Biostatistics and principal statistical consultant to the project, is located there. On the third floor of the same building, the In and Out-patient diabetes clinic is located, as is the office of Dr. F. Goetz, principal clinical investigator from the University of Minnesota. Other statistical services, including electronic computers are available from the University.

PREVIOUS WORK DONE ON THIS PROJECT:

The group of six principal clinical investigators and varying junior associates have met on five occasions for one to two day meetings, during which much of the work of planning was accomplished. The epidemiologist has attended the last three of these meetings in Cleveland, New York, and Boston, respectively. He has also consulted with a number of senior research workers with experience in multiclinic and therapeutic studies on the problematic areas of the study design, administration, and methods of analysis.

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The senior investigator has been engaged in research work on the heredity of prediabetes for the last year and a half, conducted under a research contract of the USPHS, where part of the results and some of the field experience are directly applicable to the present study.

RESULTS OBTAINED BY OTHERS:

These have been presented by the clinical investigators in their grant applications and little could be added but the conclusion that results have been contradictory. In this country, it was found that chemical control (e.g., "normal" blood sugar levels) have tended to delay the onset of late complications, while studies from abroad yielded no significant correlation. None of these studies were prospective, nor did they feature random treatment allocation, and none had a negative as well as a positive control group (diet plus placebo and diet plus insulin in needed amounts). None of them was on a scale where statistically significant results might have been hoped for.

PERSONAL PUBLICATIONS:

A list of publications has been submitted with the curriculum vitae. However, the following two should be added:

1. Modification for Field Use and Calibration of the Cortisone-Glucose Tolerance Test in Human Volunteers. C.R. Klimt, F.W. Wolff, C. Silverman, J. Conant, submitted for publication to "Diabetes".
2. A Population-based Study of Diabetic and Control Families for Aggregation of Prediabetes. C.R. Klimt, H. Beard, C. Silverman, F.W. Wolff, manuscript in preparation.

JUSTIFICATION OF BUDGET:

Personnel: The full-time participation of a statistician and of a secretary is believed to be adequate but essential for the handling of the routine functions of the "Coordinating Center". An estimate of workload is difficult at this stage. Assuming that every clinic contributes 100 new cases per year, six hundred patients will accrue to the study annually. Examinations will be done at quarterly intervals, or approximately 1200 during the first year, assuming even admission rates to the study. Much time will be necessary to produce and introduce to each participating clinic the necessary record system and to maintain the master file at the Center itself. During subsequent years the number of patient records will increase by about 1200 a year. On the other hand, it is expected that much of the procedure will have become routine both at the Center and at the clinics and will require less time. Ancillary studies may have to be conducted, such as a calibration study of eye fundus photographs for retinopathy, the natural history of specific diabetic complications with respect to expectancy by age, sex, and duration of the disease, the adaptation of the life table technique to the study of chronic disease with uneven expectation of onset per unit time, etc.

Equipment and Supplies: These are limited to the needs of an epidemiological and statistical research office.

Travel: Much of the success of a multi-clinic study as the one envisaged (necessitated by the need for adequate numbers of cases and for variability in clinic material) depends on effective coordination through repeated personal contact and on repeated checks for reliability of adherence to agreed standards. This function must be accomplished by frequent travel of the principal investigator and his

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statistician to the outlying clinical centers.
Telephone: Much business, such as allocation of treatment group to new patients, will be handled most efficiently by long-distance telephone.

Prepared for the Bio-Sciences Information Exchange.
Not for publication or publication reference.

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

NOTICE OF RESEARCH PROJECT

PROJECT NO. (Do not use this space)

SUBMITTED TO: Public Health Service, National Institutes of Health, Division of Research Grants, Bethesda 14, Md.

TITLE OF PROJECT:

The Relation of Treatment to Diabetic Complications

Give names, departments, and official titles of PRINCIPAL INVESTIGATORS and ALL OTHER PROFESSIONAL PERSONNEL engaged on the project.

C.R. Klimt, M.D., Dr.P.H., Associate Professor of Epidemiology, Graduate School of Public Health, University of Minnesota, Minneapolis, Minn.

F.C. Goetz, M.D., Assistant Professor of Medicine, University Hospital, University of Minnesota

For rest of personnel see page one.

NAME AND ADDRESS OF APPLICANT INSTITUTION:

University of Minnesota, Minneapolis 14, Minnesota

SUMMARY OF PROPOSED WORK — (200 words or less — Omit Confidential data.)

In the Bio-Sciences Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Recently diagnosed cases of diabetes, who remain free of acidosis and other diabetic signs while on diet alone for the period of one month will be allocated at random to four treatment groups: diet plus placebo tablets, diet plus a standard dose of tolbutamide (+/- 1.5 gms), diet plus a standard dose of insulin (10-15 units/day) and diet plus insulin in amounts necessary for the maintenance of normal blood glucose levels. The patients will be seen at three monthly intervals, the adherence to prescribed treatment and the control of the diabetic state investigated and one of the following groups of late complications studied at each recall: retinopathy, cardio-vascular disease, nephropathy and neuropathy. Evaluation will be made on the basis of treatment failure, onset and progression in severity of late complications of diabetes and finally death. The study is intended to take ten years to accomplish its purpose and will be a cooperative effort of the following institutions: University of Minnesota, Western Reserve University, University of Cincinnati, Johns Hopkins University, Massachusetts General Hospital and the State University of New York.

SIGNATURE OF PRINCIPAL INVESTIGATOR C.R.Klimt

Identify the Professional School (medical, dental, public health, graduate, or other) with which this project should be identified:

SCHOOL Graduate School of Public Health, U. of Minn.

INVESTIGATOR — DO NOT USE THIS SPACE

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REV. 1-60

Form Approved
Budget Bureau No. 105-R002

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Continuation of list of personnel

R. A. Field, M.D., Assistant Physician, Massachusetts General Hospital, Boston, Mass.

M. G. Goldner, M.D., F.A.C.P., Clinical Professor of Medicine, State University of New York, Downtown Medical Center, Brooklyn, N. Y.

T. E. Prout, M.D., Assistant Professor of Medicine, The Johns Hopkins Hospital, Baltimore, Md.

H. C. Knowles, Jr., M.D., Associate Professor of Medicine, Cincinnati General Hospital, Cincinnati, Ohio.

Max Miller, M.D., Associate Professor of Medicine, Western Reserve University, Cleveland, Ohio.

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