JUN 28 1963

FORM APPROVED; BUDGET BUREAU NO. 68-R249

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

APPLICATION FOR RESEARCH GRANT

(A PRIVILEGED COMMUNICATION)

Rec. 6-28-63

LEAVE BLANK		
TYPE: 1	PROGRAM: R01	GRANT NUMBER: HD 00045-01
REVIEW GROUP: HUE		FORMERLY:
COUNCIL: Nov. '63		
NOTICE OF RESEARCH PROJECT: ☒ YES ☐ NO		

A. TO BE COMPLETED BY PRINCIPAL INVESTIGATOR OR PROJECT DIRECTOR

1. TITLE OF RESEARCH PROPOSAL *(Limit to 55 letters and spaces)*
Kindred Patterns (Mentally Retarded; Control)

2. AMOUNT REQUESTED *(Same as item 9, page 2)*
$ 69,816

3. TYPE OF APPLICATION *(Check one):*
- ☒ NEW PROJECT
- ☐ REVISION OF PHS APPLICATION NO. _____
- ☐ RENEWAL OF PHS GRANT NO. _____
- ☐ SUPPLEMENT TO PHS GRANT NO. _____

4. DATES OF INITIAL PERIOD *(Usually 12 months):*
FROM: Jan: 1, 1964
THROUGH: Dec. 31, 1964

(LEAVE BLANK)

5. PRINCIPAL INVESTIGATOR OR PROJECT DIRECTOR *(Last name first)* — DEGREE
Lederberg, Joshua — Ph.D.

TITLE OF POSITION
Professor and Executive Head
Department of Genetics

MAILING ADDRESS
Stanford University Medical School
Palo Alto, California

TELEPHONE NUMBER: DA 1-1200 | AREA CODE: 415 | EXTENSION: 5049

DEPARTMENT OR SERVICE
Genetics Department

ADDRESS WHERE RESEARCH WILL BE CONDUCTED
Stanford University Medical School
Palo Alto, California

MAJOR SUBDIVISION (PROFESSIONAL SCHOOL, COLLEGE, ETC.)
Medical School

6. CO-PRINCIPAL INVESTIGATOR OR ASSOCIATE PROJECT DIRECTOR *(Last name first)* — DEGREE
Bodmer, Walter F. — Ph.D.

TITLE OF POSITION
Assistant Professor of Genetics

B. TO BE COMPLETED BY AN APPROPRIATE ADMINISTRATIVE OFFICIAL OF THE INSTITUTION

7. NAME OF INSTITUTION SUBMITTING APPLICATION
STANFORD UNIVERSITY

MAILING ADDRESS
Stanford, California

8. TYPE OF APPLICANT *(Check applicable items):*
- ☐ PUBLIC INSTITUTION
  - ☐ FEDERAL ☐ STATE ☐ LOCAL ☐ OTHER
- ☒ PRIVATE INSTITUTION
  - ☒ NONPROFIT, [redacted]
  - ☐ PROFIT
- ☐ INDIVIDUAL

9. NAME, TITLE, AND ADDRESS OF OFFICIAL TO WHOM CHECKS SHOULD BE MAILED
Mr. Kenneth D. Creighton, Controller
Encina Hall, Stanford University
Stanford, California

10. APPLICANT'S PHS ACCOUNT NO. *(Enter if known)*
458210

(LEAVE BLANK) TRANSACTION NO.

C. TERMS AND CONDITIONS: The undersigned understand and accept the terms and conditions set forth in the statement on the reverse of the original and applicant's retained copy of this page.
Sign original copy in ink. "Per" signatures are not acceptable.

11. PRINCIPAL INVESTIGATOR OR PROJECT DIRECTOR	*(Same as Item 5 above. Signature only)* Joshua Lederberg Joshua Lederberg	DATE: June 17, 1963
12. OFFICIAL AUTHORIZED TO SIGN FOR INSTITUTION	*(Type name and title below signature)* Albert H. Bowker Dean, Graduate Division	DATE: 6/25/63

PHS-398 (REV. 1-62)

HD 00045-01

A. DETAILED BUDGET FOR PERIOD SHOWN ON PAGE 1 (List all items in each category. Follow instructions)	TIME SPENT ON THIS PROJECT: HOURS PER WEEK	TIME SPENT ON THIS PROJECT: PERCENT OF TIME	AMOUNT REQUESTED FROM PHS (Omit cents)
1. PERSONNEL: Principal Investigator Joshua Lederberg, Professor			$ --
Walter Bodmer, Assistant Professor			--
Howard Cann (second year) Instructor in Pediatrics			--
Computer Programmer	[redacted]	100	8,000
Statistical Clerk	[redacted]	100	6,000
			14,000
Payroll costs at 7%			980
Total Personnel			14,980
2. MOVABLE EQUIPMENT:			
Desk Calculator			900
Files for data storage			300
			1,200
3. CONSUMABLE SUPPLIES:			
Office supplies			300
4. TRAVEL:			
Single trip to Washington, D. C. for data source consultation			400
5. OTHER EXPENSES ON WHICH INDIRECT COSTS ARE ALLOWED:			
Reference Materials			300
Communications			500
Photographic, illustration, printing			500
			1,300
6. SUB-TOTAL (Items 1 through 5)			$ 18,180
7. INDIRECT COST ALLOWANCE ON ABOVE ITEMS:			3,636
8. EXPENSES ON WHICH INDIRECT COSTS ARE NOT ALLOWED OR MUST BE NEGOTIATED:			
(1) Reimbursements to U. S. Census Bureau			10,000
(2) Reimbursements to U. S. Census Bureau			30,000
(3) Reimbursements to other California institutions			5,000
(4) Computer time (indirect costs already included)			3,000
			48,000
9. TOTAL BUDGET (Same amount as shown on Page 1)			$ 69,816

BUDGET - Continued

B. ESTIMATE OF TOTAL SUPPORT REQUESTED FOR THIS PROPOSED RESEARCH PROJECT — On Line 1, below, include category totals taken from the detailed budget on Page 2. Similar estimates for all succeeding years should be given, starting on Line 2. If support beyond the one year shown on Line 1 is not required, please enter word "None," on Line 2. **(NOTE: DO NOT USE** the lower part of each line which is prefixed **LB. This should be LEFT BLANK.**

	PERSONNEL	EQUIPMENT	SUPPLIES	TRAVEL	OTHER	SUBTOTAL DIRECT	INDIRECT COST	OTHER *(No indirect cost allowed)*	TOTAL
1.	14,980	1,200	300	400	1,300	18,180	3,636	48,000	69,816
LB									
2.	14,980	1,200	300	400	1,300	18,180	3,636	18,000	39,816
LB									
3.									
LB									
4.									
LB									
5.									
LB									
6.									
LB									
7.									
LB									

C. BUDGET JUSTIFICATION: *(Use continuation pages as necessary)*

The form of this application is partly conditioned by current policies of grant administration which prescribe the diversion of funds from other projects for pilot studies in a different field. The (hardly avoidable) lag between a research idea and the availability of funds to implement it also requires anticipation of developments. The investigators would prefer to complete preliminary studies before attempting to justify the further stages, but this would paralyze the work by interposing delays of many months at each step. Any constructive measures to solve this dilemma would be most helpful. Meanwhile, we can affirm that any decision to proceed with the study will be carefully reviewed at every stage; any reasonable mechanism of consultation would be welcomed. These considerations are especially pertinent to this application as the later stages are more data-assembling than hypothesis-testing research (at the present view, probably a transient one).

The principal budget items are:

A. 1. Personnel: Programmer and Statistical Clerk (self-explanatory)

A. 8. Expenses on which indirect costs are not allowed:

Item (1). Reimbursements to U.S. Census Bureau $10,000

This is referred to in attached correspondence, the utilization of existing data from the 8/59 and 3/62 samples. We have in mind a slightly more complex assembly than quoted therein, the generation of a collated source tape (by household, and by "ever-married females" therein).

Item (2). Reimbursements to U. S. Census Bureau $30,000

This would involve the inclusion of additional questions in new surveys. If Item (1) shows provocative interactions that need to be verified*, quite possibly part or all of these funds will have to be shifted to the second year. These funds will not be spent without consultation with other interested groups (e.g., Dr. R. Masland), but provision for this finding may be crucial to effective planning. (If objectionable this item should be severable from the rest of the proposal.)

*or retested, e.g.: to retrieve data on sex or viability of offspring, or longevity or fecundity of other relatives. Some questions and correlations are marginally reliable in the present survey (e.g. adoption, previous marriage, etc.)

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C. Budget justification (continued)

A. 8. Item (3). Reimbursements to other California institutions $5,000
Reimbursements to California establishments for clerical and computational costs in furnishing data files, e.g., on mentally retarded.

RESEARCH SUPPORT

List **All Other Research Support** of the Principal Investigator, and, separately, the Co-Principal Investigator, if he will be responsible for active direction of the project. **All Other Research Support** includes requests now being considered as well as any proposals which the Principal Investigator plans to submit to the Public Health Service or other granting agencies. Include support received from own institution. Amounts shown should reflect total funds awarded or pending over the entire grant periods indicated in the final column. Use blank continuation pages, if necessary, and follow the same format.

A. PUBLIC HEALTH SERVICE SUPPORT:

GRANT NO. (If designated)	TITLE OF PROJECT	PERCENT TIME ON PROJECT	TOTAL AMOUNT per annum	TOTAL PERIOD OF SUPPORT WITH DATES
(1) ACTIVE OR APPROVED:				
CA-04496	Genetics of Bacteria	40	$ 52,900	9/1/62 to 8/31/63
AI-5160	Genetics of Bacteria (cont. of above)	40	50,000	8/1/63 to 8/31/69
NB-04270	Molecular Neurobiology	30	110,500	12/1/62 to 11/30/67
5TI GM 295	Training Grant in Genetics	50	111,153	7/1/63 to 6/30/64
FR-00151-01	LINC Computer Evaluation	10	8,566	6/1/63 to 5/31/64
(2) APPLICATIONS PENDING DECISION OR PLANNED:				
2TI GM 295-06	Training Grant in Genetics (continuation)	50	246,000	7/1/64 to 6/31/69

B. ALL OTHER RESEARCH SUPPORT:

SOURCE AND PROJECT NO. (If designated)	TITLE OF PROJECT	PERCENT TIME ON PROJECT	TOTAL AMOUNT per annum	TOTAL PERIOD OF SUPPORT WITH DATES
(1) ACTIVE OR APPROVED:				
Nat. Science Foundation	Genetic Recombination in Bacteria	40	20,900	1/1/59 to 12/31/63
Kennedy Foundation	Molecular Neurobiology	30	25,000	1/31/63 --
NASA	Cytochemical Studies of Planetary Microorganisms; Medical Instrumentation	20	225,000	4/1/61 to 3/31/64
(2) APPLICATIONS PENDING DECISION OR PLANNED:				

HD 00045-01

(LEAVE BLANK)

Research Support of Co-Principal Investigator*

Public Health Service Support:

Grant No.	Title of Project	Total Amount	Total Period of Support
GM 10452-01A1	Stochastic Models in Medicine and Biology	$209,947	5/1/63 to 4/30/66

*Dr. Bodmer is Co-Principal Investigator on the above grant with Drs. Samuel Karlin and Dr. James L. McGregor.

BIOGRAPHICAL SKETCHES

Provide brief sketches for ALL professional personnel already selected who are to be actively engaged in this project. The same format should be used for each person, with Co-Investigator (if any) immediately following Principal Investigator, then other professional personnel, lettered consecutively. Use blank continuation pages as necessary.

A. PRINCIPAL INVESTIGATOR: *(Name and title)* Joshua Lederberg, Professor and Executive Head, Dept. of Genetics

1. DATE OF BIRTH May 23, 1925 CITY, AND STATE OR COUNTRY OF BIRTH New Jersey

PRESENT CITIZENSHIP U.S. SEX: ☒ 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.	Columbia College	Zoology	1944
Ph.D.	Yale University	Microbiology	1947

b. Other research training and experience, especially that establishing research qualifications in area covered by this application. Investigators should mention major professors and chiefs of service during research training comprising significant elements in their backgrounds, when appropriate. Include previous and present positions.

INSTITUTION	NATURE	YEAR
Univ. of Wisconsin	Asst. Prof., Assoc. Prof. and Prof. and Chairman of Medical Genetics Dept.	1947-59
Stanford University	Prof. and Exec. Head, Department of Genetics	1959--

3. FIELDS OF PRESENT MAJOR SCIENTIFIC INTEREST, IN ORDER OF CHOICE:
Genetics and evolution of microorganisms; neurobiology.

4. SUPPLEMENTAL INFORMATION: *(Be sure this is sufficient to provide an appreciation of your qualifications.)*

Member, National Academy of Sciences; Nobel Prize (1958) with G. Beadle and E. L. Tatum; Member, President's Panel on Mental Retardation; Director, Kennedy Laboratories for Molecular Medicine.

Co-Principal Investigator:

Walter F. Bodmer, Assistant Professor. Born Germany, January 10, 1936. British citizen.

B.A.	Clare College, Cambridge	Mathematics	1956
Ph.D.	Clare College, Cambridge	Population genetics	1959

Research Fellow, Clare College, Cambridge, 1958-50; Demonstrator 1960-61. Fellow, Visiting Assistant Professor 1961-62, Assistant Professor 1962--, Department of Genetics, Stanford University School of Medicine, Palo Alto, Calif.

Special fields of interest: chemical genetics, biometrical genetics.

See list of Dr. Bodmer's publications under "Supporting Data" section for a summary of his work in the field of biometrical genetics.

1. RESEARCH PLAN.

Introduction

There are three parts to the study as presently contemplated:

1. Reproduction patterns in kindreds of mentally retarded and contrasting samples.

2. Factors controlling and consequent to the seasonal variation of birth.

3. The analysis of U. S. Census data on family statistics to obtain national profiles of reproductive patterns.

The order is that of development of the problem. The first item shows the impetus for the study; the third is the most consequential.

Objectives

U. S. Census records contain much control data vitally important in genetic and epidemiological studies. The principal statistics sought now are detailed family patterns - the temporal clusters of cardinal dates (= ages): birth and marriage of the parents and birth of offspring.

Similar studies are under way for the kindreds of mentally retarded patients in California institutions, and data are being sought for other populations relevant to the epidemiology of mental performance and its hereditary distribution.

Present Status and Proposed Work

Census records have usually emphasized legal and economic units (households) rather than biological units (kindreds). However, certain data of great interest are available especially from current population samples. The August 1959 and March 1962 sample surveys notably collected family information as summarized in the attached correspondence from Dr. Brunsman. We propose a tabulation of these data that could show the temporal clusters for some 35,000 households (presumably about the same number of kindreds--some present households would comprise no ever-married females, others more than one). The most compact representation for each propositus female would be the monotonic sequence of cardinal dates: her birth, marriage, birth of first four and last offspring (if any). In addition we have number of offspring and husband's birthdate.

The dates are available to a precision of month and year. Unfortunately, sex of offspring is not, unless resident in the household.

For each household, cross-tabulation data would be available to indicate income level, educational progress, occupation, geographic and farm vs. nonfarm residence.

Specific subtabulations from such a file would include the distributions of season of birth, interval between marriage and ranks of children, fertility,and cross-correlations of these with each other, with age of parents, with the socio-economic factors, etc. It is especially pertinent that these figures come from a sample which is nominally representative of the entire United States for a variety of other demographic and statistical studies.

Special inquiries would be needed to establish the sex distribution of offspring, place of birth of parents, and perhaps most interesting, the reproductive patterns of each parent's family for tests of assortment.

At the present time, similar data are not available on any comprehensive basis. The utility of demographic data for genetic analysis has just begun to be recognized, but their exploitation is severely limited when only the means (contra the distributions) of such measures as fertility or parental age can be calculated.

With the cooperation of Dr. George Tarjan of the Pacific State Hospital at Pomona, California, and with several other institutions, similar files will be available on from 10,000 to 20,000 mentally retarded patients. Additional California control data will be available from the California Department of Public Health. These analyses should allow a more thorough characterization of the family patterns from which mentally retarded children arise, and (in some follow-up studies) the impact of a mentally retarded birth on further reproductive behavior of the family.

Significance

To appreciate the significance of the project one must assimilate the surprising lack of this rather simple information. If other means of answering these questions arise, the project might be suspended without further expenditure, and we intend to explore every reasonable alternative. However, at least the first stages appear to be a very economical exploitation of an existing file with regard to costs in money or effort, and further research would be expedited by leaving some room for manoeuver on the basis of the first results.

To illustrate the paucity of present information on family patterns, Slatis (1958), studying consanguinity in Chicago, needed a measure of the distribution of the interval from marriage to first and second births--he published on only about 100 kindreds, though these were especially pertinent to his study.

Our pathway to this problem was through a study of the seasonal distribution of births, among the general population and mentally retarded (cf. Knobloch and Pasamanick 1958). As in Ohio, the California samples show marked discrepancies. However, the interpretation of these findings is confounded by the demonstration of a strong occupational differential in the distribution (see attached note). Further consideration of these and other data showed how little we knew of the causes and consequences of these singularities. Furthermore, the occupational groupings can correspond only crudely to the social (viz. intrabreeding) strata of the population. For the cyclical peculiarities to show at all in these summaries, they must be much sharper and more significant from a general biological standpoint in the natural quasi-isolates. This could be determined by cross-correlations among spouses, and closer study of intra-family correlations.

In the field of mental retardation, maternal age is known to be an outstanding determinant, especially for the chromosome abnormalities. Less is known of other reproductive characteristics that might be pathognomic of a predisposition. Thus Benda (1960) remarks on the incidence of mongolism among children born after a long interval of infertility. The proposed study should help to clarify this issue by providing statistics both on the disease and, perhaps more crucially needed, some unselected controls. The significance of this issue for counseling to a large cohort of pre-menopausal women is obvious.

The chief limitation of this study is doubtless that it is not large enough, particularly to survive extensive dissection in cross-tabulation. It is, however, a start at using the most readily available existing data. Doubtless other comparable files exist among other population records (cf. Newcombe's Canadian record linkage studies). They can hardly be more cheaply accessible than data already taped in the U.S. Census and can never be as representative on a national scale. Hopefully, the national samples will serve as a standard for comparison of a substantial series of regional and group studies conducted for special purposes.

Family patterns should be sensitive to many of the same social and genetic parameters that would influence other epidemiological variables. As these statistics become better worked out, they could furnish indispensable criteria for the control of other studies. For example, in the relation of blood groups to gastric cancer and ulcer, or of smoking to lung cancer and cardio-vascular disease, the confounding of co-stratified variables is the most serious source of potential error. Intra-family comparisons would be a most powerful tool, but it is often not feasible or may be very expensive. As a ready expedient, one might ask that control vs. experimental groups be homogeneous or correctible in respect to critical parameters of the reproductive patterns. This is already well-understood with respect to age and sex, which are however not useful indicators of social stratification. For example, the seasonal distribution of the birthdates as a "signature" of parental variables should be homogeneous to test that "smokers" are otherwise equivalent to "non-smokers". More detailed study of the control kindreds as we now propose should suggest the most informative discriminants (i.e. the most variable to the other parameters). In relation to the cost of acquiring such data, utilitarian control standards could then be suggested.

These preliminary surveys may then be most useful in suggesting guidelines for future studies, including proposals for samples in the 1970 Census.

Methodology and Facilities

The optimum display of complex cross-tabulations is an unsolved problem, part and parcel of the proposed research. The development of a real-time computation system at Stanford (LINC (at Medical School, Genetics Department) - PDP1 - 7090 (at Computation Center)) alluded to in attachment 3, opens up the chance to investigate this for vital statistics data. In the Instrumentation Laboratory, and elsewhere at Stanford, we have many engineers experienced in display systems, e.g. military applications. It is time this kind of processing of complex data was used to advantage in biological investigation. The hardware costs of this program are being funded through the Instrumentation Laboratory and the Computation Center. The present application provides for the operating costs of acquiring the data, transferring them to magnetic tape (2×10^6 decimal characters per reel, which can be read in less than five minutes through the 7090, even faster after transfer to a disk file), and the connected programming work and computer time.

Prepared for the Science Information Exchange.

Not for publication or publication reference.

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

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Submit with completed Application to: Division of Research Grants, National Institutes of Health, Bethesda 14, Md.

TITLE OF PROJECT:

Kindred Patterns (Mentally Retarded; Control)

Give names, departments, and official titles of PRINCIPAL INVESTIGATORS or PROJECT DIRECTORS and ALL OTHER PROFESSIONAL PERSONNEL engaged on the project. Include day-month-year of birth of principal investigators.

Joshua Lederberg - Principal Investigator - May 23, 1925

Walter F. Bodmer - Co-Principal Investigator - January 10, 1936

Howard M. Cann

NAME AND ADDRESS OF APPLICANT INSTITUTION:

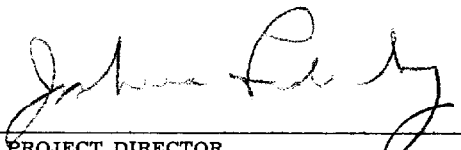
Stanford University, Stanford, California

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

In the Science 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.

Census data will be acquired and tabulated that will allow the statistical analysis of reproductive patterns-- the temporal distribution of birth, marriage and birth of offspring (and number of offspring) -- in relation to socio-economic variables. Similar data will be obtained on kindreds of mentally retarded patients in State institutions. Computer studies will be made to establish the optimum means of retrieval and presentation of complex data. Relationships to fertility, maternal age effects on infant performance, seasonal variations in birth incidence, and the extent of endogamous stratification in the samples of the U.S. population are expected.

SIGNATURE OF PRINCIPAL INVESTIGATOR or PROJECT DIRECTOR



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

SCHOOL **School of Medicine**

INVESTIGATOR — DO NOT USE THIS SPACE

PHS-166
REV. 12-61

FORM APPROVED
BUDGET BUREAU NO. 105-R002.