FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

APPLICATION FOR RESEARCH GRANT

(LEAVE BLANK)
E-72(C5)
M:I (2)

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH GRANTS
Bethesda 14, Maryland

Rec. 10-31-52

Date October 28, 1952

Feb. '53 Council

Application is hereby made for a grant in the amount of $ 9180.00 for the period

from September 1, 1953 through August 31, 1954
Month Day Year Month Day Year

inclusive *(not to exceed 1 year)* for the purpose of conducting a research project on the following subject:

(Give only brief descriptive title)

TITLE OF PROJECT: Genetics of Salmonella and Escherichia

NAME OF PRINCIPAL INVESTIGATOR	TITLE OF PRINCIPAL INVESTIGATOR
Joshua Lederberg	Associate Professor of Genetics

ADDRESS OF PRINCIPAL INVESTIGATOR
Department of Genetics
University of Wisconsin
Madison 6, Wisconsin

NAME OF FINANCIAL OFFICER TO WHOM CHECK SHOULD BE MAILED	TITLE OF FINANCIAL OFFICER
A. W. Peterson	Vice-President, Business & Finance

ADDRESS OF FINANCIAL OFFICER
Bascom Hall
University of Wisconsin
Madison 6, Wisconsin

AGREEMENT

It is understood and agreed by the applicant: (1) That funds granted as a result of this request are to be expended for the purposes set forth herein; (2) that the grant may be revoked in whole or 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 set forth in this application; (3) that all reports of original investigatons supported by any grant made as a result of this request shall acknowledge such support; (4) that if any patentable discoveries or inventions are made in the course of the work aided by any grant received as a result of this application, the applicant will, in consideration of such grant, refer to the Surgeon General of the Public Health Service, for determination, the question of whether such patentable discoveries or inventions shall be patented and the manner of obtaining and disposing of the proposed patents in order to protect the public interest.

NAME OF INSTITUTION: UNIVERSITY OF WISCONSIN

NAME AND TITLE OF OFFICIAL AUTHORIZED TO SIGN FOR INSTITUTION *(Please Type)*: A. W. Peterson, Vice President, Business & Finance

PERSONAL SIGNATURE
(This agreement must carry the actual signature of the official whose name appears on the line above.)

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Rev. 8-51

Form Approved
Budget Bureau No. 68-R249.4

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These dates to be the same as those given on page 1.

BUDGET PROPOSED FOR THE YEAR Sept. 1, 1953 through August 31, 1954

NOTE: Under column entitled "OTHER" indicate funds presently available or anticipated from other sources including own institution.

	BUDGET	
	REQUESTED FROM P.H.S.	OTHER
PERSONNEL *(Itemize all positions by indicating type; names of professional personnel, if selected.)*		
Principal Investigator (prorated for research only)		$ 6 000
Research Associate T. C. Nelson, Ph. D.	$ 3 600	
" " E. M. Lederberg, Ph. D. and)		
" " ——— Ph. D.)		7 500
Research Assistant full time —— M.A.	3 000	
3 Research assistants, 1/2 time grad. students		4 000
Hourly help (dishwashers)	500	1 000
PERMANENT EQUIPMENT *(Itemize)*		
CONSUMABLE SUPPLIES *(Itemize)*		
Glassware, chemicals and minor lab. apparatus	1 000	2 000
TRAVEL *(State purpose)*		
For consultations with other workers, including scientific meetings in the U. S.	200	100
OTHER EXPENSE *(Itemize)*		
Publication expenses	200	200
SUBTOTAL	8 500	
OVERHEAD	680	
TOTAL FOR THE YEAR	$ 9 180	

NOTE: The administrative official signing this application may add for overhead an amount not to exceed 8 percent of the operating costs, i.e. 8 percent of the subtotal.

ESTIMATE OF FUTURE REQUIREMENTS

Estimate of future requirements applies to funds needed from the Public Health Service for the years subsequent to the period proposed at the top of this page. The blanks at the right provide space for requesting four additional years of support; any amounts entered should include "overhead" if such is to be requested. Do not leave any of these spaces blank—enter one of the following as applicable: The amount needed, "not applicable," "unknown" or "none". FOR FURTHER INFORMATION: See detailed instructions accompanying application forms.

1 $ 9 180
2 9 180
3 9 180
4 unknown

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PUBLIC HEALTH SERVICE SUPPORT: Show previous and current Public Health Service grants supporting this project:

GRANT NUMBER	TITLE OF PROJECT	AMOUNT	PERIOD OF SUPPORT
PREVIOUS			
1445		$ 3 780	July 1948
1445-C	Genetics of Salmonella	3 780	
1445-C2		4 320	to
E-72-C3	Genetics of Bacteria	4 320	August 1952
CURRENT			
E-72-C4	Genetics of Bacteria	9 180	Sept. 1952 to August 1953

ALL OTHER SUPPORT: Excluding Public Health Service, but including that from own institution, list support from other sources for this project. If none, so indicate.

SOURCE	TITLE OF PROJECT	AMOUNT	PERIOD OF SUPPORT
CURRENT			
A.E.C.	Cytogenetic effects of radiations	$ 2 162	3/52 - 2/53
Chemical Corps	Recombination in bacteria	8 000 prer	1/52 - 9/53
Rockefeller	Immunogenetics of bacteria	8 000	1/52 - 8/53
U. of Wis.	Genetics of Bacteria	11 600*	7/52 - 6/53
PENDING			
U. of Wis.	Remodel building & new lab. furnishing	6 000 ±	ca. 1/53
U. of Wis.) Rockefeller)	not yet formulated, but expect to apply		53-54

*incl. research portion, investigator's salary

RESEARCH PLAN AND SUPPORTING DATA

On the continuation pages provided give details of the proposed plan and other necessary data in accordance with the outline below. Number each page, the first continuation page being page 4. Additional continuation pages, if needed, may be requested from the Division of Research Grants. See detailed instructions before preparing this portion of the application.

1. RESEARCH PLAN
   - A. Specific Aims—Provide a concise statement of the aims of the proposed work.
   - B. Method of Procedure—Give details of your plan of attack.
   - 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. PREVIOUS WORK DONE ON THIS PROJECT
   Describe briefly any work you have done to date that is particularly pertinent.
3. PERSONAL PUBLICATIONS
   Cite your most important publications on this or closely related work. List no more than five.
4. RESULTS OBTAINED BY OTHERS
   Summarize pertinent results to date obtained by others on this problem, citing publications deemed pertinent. Select no more than five.
5. BIOGRAPHICAL SKETCHES
   Provide brief sketches for ***All*** professional personnel selected who are to be actively engaged in this project.

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1. Research Plan

A. Specific Aims.
The long term objective is a deeper understanding of the mechanisms of bacterial heredity, and their relation to the evolutionary ecology of bacteria in their natural environments. More immediately, two distinctive mechanisms of variation, sexual recombination and genetic transduction, have been found in related bacterial groups, Escherichia coli and the Salmonellas. These mechanisms are to be studied more intensively to learn better how they work, and extensively to see the range of microorganisms to which they apply and the part they play in the evolution of new bacterial types. The problems which are being studied now, and which will engender the research topics for 1953-54, are summarized in the appended Progress Report, including the development of new serotypes in Salmonella, the mechanism of flagellar phase variation, the cytological basis of sexual recombination in E. coli and the genetic role of latent bacteriophage.

B. Method of Procedure
The procedures are inherent in the work in progress as outlined.

C. Significance of Research. The most immediate applications of this work concern the serological diagnosis of Salmonella types. The importance of a fuller knowledge of the biology of microbial pathogens requires no re-emphasis; some of the most potent approaches to this fundamental knowledge are through genetics and cytology. It is indispensable to epidemiology and to the long-term success of chemotherapy in the face of the development of drug-resistance.

D. Available Facilities: a well equipped microbiological research laboratory with chemical benches, incubators, refrigerator, cold room, freezer and fume hood. The equipment includes several centrifuges (including multispeed and chemical), Coleman spectrophotometer, analytical balance, shaking and pipetting machines, ultraviolet irradiation equipment, circular Warburg manometric apparatus, deFonbrune micromanipulator, lyophil apparatus, and a well appointed setup for critical microscopy (including darkfield and phase contrast) and photomicrography. It should be pointed out, however, that this type of work depends more on personal inspiration and dexterity than on special apparatus. For special purposes, the facilities of the Enzyme Research Institute and of other university departments have been made available and used from time to time.

2. Previous Work. (has been largely summarized in reference 1 below)

The mechanism of recombination of genetic factors in E. coli K-12, first discovered by Tatum and Lederberg in 1947, has been the subject of the larger part of previous research. It has been concluded that some sort of sexual process is involved, although the cytological aspects are still undemonstrated. The main evidence for this conclusion comes from the genetic analysis and the production of persistent diploid hybrids, and from the obligatory association of intact cells with the ability to exchange genetic factors. Throughout this period, Salmonella typhimurium was studied from a similar viewpoint, beginning with a nutritional survey of the Salmonella group. From 1948-52, Mr. N. Zinder was associated with this program as a graduate student, culminating in his dissertation for the Ph.D. (Wisconsin, 1952). (Dr. Zinder's interest in the program will continue under his appointment at the Rockefeller Institute). The transduction of genetic factors in Salmonella was discovered and developed during 1951-1952.

3. Personal publications.

1947 The nutrition of Salmonella. Arch. Biochem. 13:287-290

1951 Recombination analysis of bacterial heredity. Cold Spr. Harb. Symp. 16:413-443 (with E. M. Lederberg, N. D. Zinder and E. R. Lively; reviews earlier studies)

1952 Genetic exchange in Salmonella. J. Bact. 64: (Nov. '52) (with N. D. Zinder)

1952 Sex compatibility in Escherichia coli. Genetics 37:720-730 (with L. L. Cavalli and E. M. Lederberg)

1953 Genetic studies of lysogenicity in Escherichia coli. Genetics 38: (Jan. '53, with E. M. Lederberg)

4. Results obtained by others. The basic experimental findings of the work with E. coli have been confirmed and extended by several other laboratories as indicated in the following titles.

Cavalli, L.L. 1952 Genetics analysis of drug-resistance. World Health Org. Bull. 6: 185-206 [Istituto Sieroterapico Milanese]

Hayes, Wm. 1953 Observations on a transmissible agent determining sexual differentiation in Bacterium coli. J. Gen. Microbiol. In Press. [Postgr. Med. School London]

Rothfels, K. 1952 Gene linearity and negative interference in crosses of Escherichia coli. Genetics 37:297-311 [University of Toronto]

Nelson, T.C. 1951 Kinetics of genetic recombination in Escherichia coli. Genetics 36: 162-175 [Columbia University]

Newcombe, H.B. and Nyholm, M.H. 1950 Anomalous segregation in crosses of Escherichia coli. Amer. Nat. 84: 457-465
[Natl. Res. Council Canada]

5. Biographical sketches.

Principal Investigator:

Lederberg, Joshua. b. Montclair, N.J., 1925. B.A. Columbia 1944. Medical School, Columbia 1944-46; Ph. D. (microbiology) Yale 1947. Fellow, Jane Coffin Childs Fund for Medical Research, 1945-46; Public Health Service Fellow 1947 (resigned). University of WISCONSIN: Asst. Prof. Genetics, 1947-50; Assoc. Prof. 1950---. University of California, Berkeley: Visiting Assoc. Prof. Bact. 1950.

Affiliated Personnel (PHS funds):

Nelson, Thomas Clifford. b. Columbus, O., 1925. B.S. Queens College N.Y. 1946, M.A. 1946. Ph.D. (zoology-biophysics) Columbia 1951. Columbia U.: Lecturer in Biophysics 1947-49. California Inst. Tech.: Gosney Research Fellow 1950-51. Vanderbilt U. Asst. Prof. Biology, 1951-52. University of WISCONSIN: Project Associate 1952---.

Affiliated Personnel (other funds):

Lederberg, Esther M. (nee Zimmer) b. N.Y.City, 1922. B.A. Hunter 1942. M.A. Stanford 1946. Ph.D. Wisconsin (Genetics and bacteriology) 1950. Scholar N.Y. Bot. Gard. 1941-42. N.I.H.: Res. Asst. (Carnegie) 1942-43. Jr. Biologist 1943-44. University of WISCONSIN: PHS Predoctoral Research Fellow, NCI, 1947-49. University Fellow, 1949-50. Project Associate 1950---.

Skaar, P. David b. Mishawaka, Ind., 1923. B.A. Indiana 1947. Ph.D. (zoology) Indiana 1952. University of WISCONSIN: Project Assoc. 1951---.

Stocker, B.A.D.S. M.D.(Westminster) Dipl. Bact. (London). Sr. Lecturer, University of London, London School of Hygiene and Trop. Med. Commonwealth Fund travelling Fellow, 1952.

Spicer, C.C. M.B. Dipl. Bact. (London) Scientist, Standards Laboratory, Central Public Health Laboratory, Public Health Laboratory Service, London, Eng. Fellow, World Health Organization, 1952