The University of Chicago

Office of the Comptroller

Returned 11/29/51

5750 ELLIS AVENUE
TELEPHONE: MIDWAY 0800

November 26, 1951

Mr. Leo Szilard
Institute of Radiology and Biology

Dear Mr. Szilard:

Under date of September 19, 1951 we wrote you relative to the increase in your annuity premium because of the change in salary effective with your new appointment. Attached to our letter was a Salary Deduction Agreement blank to give effect to this change in premium, which we asked that you sign in duplicate and return both copies to this office.

Inasmuch as the signed form has not been returned, we are enclosing a duplicate form and shall appreciate your signing and returning both copies to this office at once. If we do not hear from you within ten days, we will assume you do not wish to increase your annuity at this time.

Yours very truly,

John S. Kirkpatrick
Comptroller

gb

FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA 14, MARYLAND

Mr. W. B. Harrell
Business Manager
The University of Chicago
5801 Ellis Avenue
Chicago 37, Illinois

Dear Mr. Harrell:

GRANT NO.	E 144
GRANTEE:	University of Chicago
INVESTIGATOR:	Dr. Leo Szilard

Based on your request dated November 23, 1951, funds available for expenditures under the above-designated grant have been reallocated to budget categories as shown below and are available for obligation for the period December 1, 1950, through November 30, 1951, inclusive.

CATEGORY	ORIGINAL ALLOCATION	LAST REVISED ALLOCATION	CHANGE APPROVED	CURRENTLY APPROVED ALLOCATION
PERSONNEL	$ 6,400	$	$ - 50	$ 6,350
PERMANENT EQUIPMENT	---			---
CONSUMABLE SUPPLIES	500			500
TRAVEL	300		+ 50	350
OTHER EXPENSE	---			---
OVERHEAD	576			576
TOTAL	$ 7,776	$	$	$ 7,776

REMARKS:

DATE November 29, 1951

APPROVED: L. A. Lowe Jr.
Chief Budget Officer
Division of Research Grants ~~and Fellowships~~

Expenditures of funds within each category of the budget may be made at the discretion of the grantee.

Transfers into "Personnel" from any other category or into "Consumable Supplies" from any other category may be made at the discretion of the grantee unless the total of all transfers between categories exceeds 25% of the approved budget, in which case prior approval must be secured from the Public Health Service. No transfers may be made into "Permanent Equipment", "Travel", "Other", or "Overhead" without prior approval of the Public Health Service.

This form should be made a part of the official file of this grant so that it will be available to Government auditors at the time the account is audited.

cc: Dr. Szilard
EB

PHS-1483(NIH)
6-50

THE UNIVERSITY OF CHICAGO

DATE December 3, 1951

TO Mr. J. I. Kirkpatrick DEPARTMENT Comptroller

FROM W. B. Harrell DEPARTMENT Business Manager

IN RE: Grant No. E 144, Public Health Service
Dr. Leo Szilard

Attached is copy of letter from C. A. Lowe, Chief Budget Officer, Division of Research Grants, PHS, which is in reply to our letter dated November 23, 1951 regarding transfer within the budget under Grant No. E 144.

Also attached is budget transfer covering transfer in the amount of $50.00 as follows:

From:	Personnel	$50.00
To:	Travel	$50.00

enclosures

cc: Dr. L. Szilard
Dr. Coggeshall
Miss Bergstrom

THE UNIVERSITY OF CHICAGO
CHICAGO 37 · ILLINOIS

BUSINESS MANAGER · SPECIAL PROJECTS
5801 ELLIS AVENUE

November 23, 1951

Re: Grant No. E 144

Mr. C. A. Lowe
Operations Officer
Division of Research Grants
National Institutes of Health
Bethesda 14, Maryland

Dear Mr. Lowe:

Approval is requested of the following transfer within the budget originally approved under the above-referenced grant:

From:	Personnel	$50.00
To:	Travel	$50.00

This transfer is requested to pay partial travel expenses for Dr. Szilard (Principal Investigator) while attending Cold Spring Harbor Symposium in New York. It represents approximately less than one per cent of the total amount of the grant, $7776.00.

Your favorable consideration will be appreciated.

Very truly yours,

W. B. Harrell
Business Manager

cc: Dr. L. Szilard
Dr. Coggeshall
Mr. Kirkpatrick
Miss Berkstrom

THE UNIVERSITY OF CHICAGO
OFFICE OF THE COMPTROLLER
FORM NO. 34

MANUAL OF ACCOUNTS
ACCOUNT INFORMATION SHEET

QUADRUPLICATE
Department

Name of Account:

Medical Research No. 185
Salaries
Travel
Consumable Supplies
Other Expenses
Overhead

Account Code			
L	Account	Sub	Fund
3	3250	-	1623
3	3250	20	1623
3	3250	34	1623
3	3250	35	1623
3	3250	36	1623
3	3250	90	1623

In Charge of:

Mr. Leo Szilard

Departmental Classification:
Biological Sciences Division
Institute of Radiobiology & Biophysics

Purpose of Account:

To set up appropriations from the Medical Research No. 185 Fund and record expenditures against the appropriations in accordance with the terms of the U.S.P.H.S. grant E-144(c).

Source of Funds: Donor Federal Security Agency, Public Health Service

Amount $ Period 12/1/51 - 11/30/52

Payable 50% at once; balance on acceptance of final report on preceding grant, Medical Res. No. 149. Subject to refund.

Account to be debited with:

Expenditures approved by the responsible investigator or his authorized representative and subject to the specific limitations as set forth in the grant and regulations governing U.S.P.H.S. grants.

Account to be credited with:

Disposition of Balance:

For balance sheet purposes, the unexpended balance of this appropriation account is combined with the unappropriated balance of the fund and classified as "Deferred Income".

Bookkeeper:
Restricted Expendable Bookkeeper
Government Accounts Division

Statements to:
Mr. Leo Szilard
Dean of Biological Sciences Division

TABULATING HEADING CARDS

Name of Account:	Card Code	L	Account	Sub	Fund	Cards Punched
Medical Res. No. 185 Salaries	1	3	3250	20	1623	
Medical Res. No. 185 Travel	1	3	3250	34	1623	
Medical Res. No. 185 Consumbl. Sup.	1	3	3250	35	1623	
Medical Res. No. 185 Other Exp.	1	3	3250	36	1623	
Medical Res. No. 185 Overhead	1	3	3250	90	1623	
Medical Res. No. 185	2	3	3250		1623	
Salaries	2	3	3250	20	1623	
Travel	2	3	3250	34	1623	
Consumable Supplies	2	3	3250	35	1623	

(OVER)

Date Established 11/8/51
Date Revised
Date Discontinued

Prepared by R.R.G.
Approved by S.B.L. E. H.
Entered Code Rack

Medical Res. No. 185 (Cont.)					
Other Expense	2	3	3250	36	1623
Overhead	2	3	3250	90	1623

11/8/51

R.R.G.
S.B.L. E.H.

FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA 14, MARYLAND

Mr. W. B. Hafrell
Business Manager
The University of Chicago
5801 Ellis Avenue
Chicago 37, Illinois

Grant No. E 144
Grantee University of Chicago
Investigator: Dr. Leo Szilard

Dear Mr. Harrell:

Based on your request dated November 23, 1951 funds available for expenditure under the above-designated grant have been reallocated to budget categories as shown below and are available for obligation for the period December 1, 1950, through November 30, 1951, inclusive.

CATEGORY	ORIGINAL ALLOCATION	LAST REVISED ALLOCATION	CHANGE APPROVED	CURRENTLY APPROVED ALLOCATION
PERSONNEL	$6,400	$	$ - 50	$ 6,350
PERMANENT EQUIPMENT	----			----
CONSUMABLE SUPPLIES	500			500
TRAVEL	300		+ 50	350
OTHER EXPENSE	----			----
OVERHEAD	576			576
TOTAL	$7,776			$ 7,776

Remarks:

Date November 29, 1951

Approved /s/ C. A. Lowe
Chief Budget Officer
Division of Research Grants

Expenditures of funds within each category of the budget may be made at the discretion of the grantee.

Transfers into "Personnel" from any other category or into "Consumable Supplies" from any other category may be made at the discretion of the grantee unless the total of all transfers between categories exceeds 25% of the approved budget, in which case prior approval must be secured from the Public Health Service. No transfers may be made into "Permanent Equipment", "Travel", "Other", or "Overhead" without prior approval of the Public Health Service.

This form should be made a part of the official file of this grant so that it will be available to Government auditors at the time the account is audited.

cc: Dr. Szilard

PHS-1483(NIH)
6-50

Szilard, Leo	University of Chicago	E-144
First Investigator listed on application	Grantee Institution	Grant No.

BIBLIOGRAPHY 1/ of publications to be credited in whole or in part to this grant
(If necessary add continuation sheets)

Date	Signature of Investigator

1/ Please use abbreviations for periodicals found in the Quarterly Cumulative Index Medicus, e.g.: Stone, P.W., and Miller, W.B., Jr.: Mobilization of radioactive sodium from the gastrocnemius muscle of the dog, Proc. Soc. Exper. Biol. & Med. 71:529 (Aug.) 1949.

THE UNIVERSITY OF CHICAGO
COMPTROLLER FORM NO. 40R
5M-10-52

REQUEST FOR BUDGET TRANSFERS
(ENTRY CODE O)

Triplicate
For Other Adm. Officer

INSTRUCTIONS FOR PREPARATION: This form is to be used in requesting transfers to or from Budget Accounts (including regular budget appropriations, restricted expendable appropriations, and budget income estimates). It should be prepared in triplicate by the Dean or other appropriate administrative officer, and all copies forwarded to the Central Administration for approval, where necessary, otherwise directly to the Comptroller's Office, where they will be numbered and the copies returned to the appropriate offices as notification that the request has been approved. If disapproved, the appropriate officer will be notified by the Central Administration or the Comptroller.

Decreases in appropriations or increases in budget income estimates and negative appropriations shall be entered under the "Debit" section; increases in appropriations or decreases in budget income estimates and negative appropriations shall be entered under the "Credit" section.

This form is also to be used for making and adjusting appropriations from Restricted Expendable Funds and Unexpended Plant Funds.

(Give Full Account Name)	Entry Code	Account Code L	Account	Sub	Fund	Amount
DEBIT: (Decreases in Appropriations or Increases in Budget Income Estimates and Negative Appropriations)						
Medical Research No. 185 - Salaries & Wages	3	3	3250	20	1623	313 77
- Annuities				33		68
- Travel				34		~~234.28~~ 267.14
- Consumable Supplies				35		200 38
CREDIT: (Increases in Appropriations or Decreases in Budget Income Estimates and Negative Appropriations)						
Medical Research No. 214 - Fund	3	3	3250	00	1658	~~749.11~~ 781.97

REASONS FOR REQUEST:

To cancel balances of appropriations remaining after submitting final report under USPHS Grant No. E. 144 (C 1)

Amount of Grant	$ 7776.00
Total Expenditures(report)	6994.03
Balance Remaining	~~749.11~~ 781.97

REQUESTED—Dean or Other Adm. Officer L.T. Coggeshall	DATE 4-7-53		DATE
APPROVED—Central Administration R.W. Harrison	DATE 4-7-53	FUNDS AVAILABLE—Comptroller John T. Wilyatich	DATE JUN 10 1953
CHECKED FOR PROPRIETY OF ENTRY By _____		CODING VERIFIED BY	COMPTROLLER'S NO. 11392

FEDERAL SECURITY AGENCY • Public Health Service
NATIONAL INSTITUTES OF HEALTH • Bethesda 14, Md.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTE OF DENTAL RESEARCH
NATIONAL HEART INSTITUTE
NATIONAL INSTITUTE OF MENTAL HEALTH
NATIONAL MICROBIOLOGICAL INSTITUTE
NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS
THE CLINICAL CENTER
DIVISION OF RESEARCH GRANTS

October 26, 1951

In reply refer
to our E-144(C)

Dr. Leo Szilard
Professor of Biophysics
Institute of Radiobiology
and Biophysics
The University of Chicago
Chicago 37, Illinois

Dear Doctor Szilard:

Upon recommendation of the National Advisory Health Council on October 19, 1951, the Surgeon General has approved your application for research grant, E-144(C). The amount, terms, and period of the grant are specified on the enclosed Statement of Research Grant Award. You may obligate these funds at any time after the beginning date shown on the Award Statement even though check in payment of the grant may be delayed several weeks.

I trust that these funds will permit proper conduct of your research project and that if we may be of further service, you will not hesitate to let us know.

Sincerely yours,

Leonard Karel

Leonard Karel, Ph.D.
Chief, Extramural Programs
National Microbiological Institute

Enclosure

CC: Dean L. T. Coggeshall
Mr. W. B. Harrell
Business Office

PHS-1533(RG)
9-50

FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA 14, MARYLAND

STATEMENT OF RESEARCH GRANT AWARD

GRANT NO. E-144(C)	AMOUNT: $ 7,776
GRANTEE-INSTITUTION: The University of Chicago	FIRST PAYMENT: $ 3,888
INVESTIGATOR(S): Dr. Leo Szilard	FUTURE COMMITMENT: IF SCIENTIFIC PROGRESS JUSTIFIES CONTINUATION AND NECESSARY FUNDS ARE APPROPRIATED, SUPPORT WILL BE GIVEN AS FOLLOWS: 1st additional year - $7,776* 2nd additional year - None
PERIOD December 1, 1951 - November 30, 1952	*Including any overhead requested.

BUDGET CATEGORIES

The funds available for expenditure under this grant have been allocated to budget categories as shown below and are available for obligation only for the period shown.

TRANSFER OF FUNDS BETWEEN CATEGORIES	CATEGORY	AMOUNT
Expenditures of funds within each category may be made at the discretion of the grantee. Transfers into "Personnel" or into "Consumable Supplies" from any other category may be made at the discretion of the grantee unless the total of all transfers between categories exceeds 25% of the approved budget, in which case prior approval must be secured from the Public Health Service. No transfers may be made into "Permanent Equipment", "Travel", "Other Expenses" or "Overhead" without prior approval of the Public Health Service. *(For other budgetary rulings see Section VIII of the [redacted] Statement of Policy.)*	PERSONNEL	$ 6,300
	PERMANENT EQUIPMENT	---
	CONSUMABLE SUPPLIES	500
	TRAVEL	300
	OTHER EXPENSES	100
	OVERHEAD	576
	TOTAL	$ 7,776

REMARKS:

October 19, 1951
DATE RECOMMENDED BY THE NATIONAL ADVISORY HEALTH COUNCIL

October 26, 1951
DATE APPROVED BY THE SURGEON GENERAL, PHS

Leonard Karel
SIGNATURE

Leonard Karel, Ph.D.
Chief, Extramural Programs
TITLE
National Microbiological Institute

Division of Research Grants June 1951

EXPLANATION OF TERMS OF STATEMENT OF RESEARCH GRANT AWARD

I. ACTIVATION OF GRANT: Research grants may be activated on the initial date of the period shown in the Statement of Grant Award or an agreed-upon subsequent date. Expenditures on new grants and on continuation grants may not be made before the effective beginning date so established.

II. PAYMENTS: For all new grants payment of the full amount will be made in one installment at the beginning of the grant period. For all continuation grants payment will be made in two installments, an initial payment of one-half of the total approved and a second payment reduced by the amount of the unobligated balance shown on the financial report as carried forward from the current grant. No unobligated balances may be carried over as amount additional for a renewal period, the total amount to be made available having been recommended in the renewal grant.

III. REDUCED BUDGETS: Where the amount approved by the Surgeon General is less than the amount requested, the budget category allocations are not completed on the Statement of Research Grant Award which is transmitted to the investigator. Upon completion by the institution, one copy of the Statement must be returned to the Division of Research Grants before the grant may be vouchered. Overhead must be adjusted to an amount not in excess of 8% of the total of the other categories, all categories including overhead to equal the amount of the reduced budget recommended.

IV. FUTURE COMMITMENT: The Statement of Research Grant Award indicates to the investigator all future commitment that has been recommended in his behalf, all future commitment being contingent upon evidence of satisfactory scientific progress and upon appropriation of necessary funds by the Congress. If no future commitment is indicated, it must be realized by the investigator that any renewal application for this project will be required to compete for funds available at that time.

THE UNIVERSITY OF CHICAGO

Date: November 12, 1951

To: Mr. Leo Szilard
Department: Institute of Radiobiology and Biophysics

From: Arthur Lincicome
Department: Assistant Comptroller

In Re: Medical Research No. 185 - Acct. No. 3-3250-00-1623

In accord with instructions from Mr. Harrell, we have opened the above-referenced account to cover Grant No. E-144(C) from the U. S. Public Health Service for the period Dec. 1, 1951 to Nov. 30, 1952. The budget has been allocated as follows:

3-3250-00-1623	Medical Research No. 185	
-20-	Salaries	$6,300
-28-	Fees for Volunteers	
-32-	Permanent equipment	
-34-	Travel	300
-35-	Consumable Supplies	500
-36-	Other Expense	100
-90-	Overhead	576
-96-	Contingency	
	Total	$7,776

This grant is a continuation of the project carried under Acct. No. 3-3250-00-1683. Care should be taken that all charges for services rendered and materials received after Nov. 30, 1951 are made against the new account, and similarly, that those before Dec. 1, 1951 are made against the old account.

The amounts shown (if any) for sub-accounts 32, 34, and 36 may not be increased except by prior written approval of the USPHS, which approval you should ask the Business Manager to get as necessary.

The "Overhead" amount may not be expended by you. Also, if an amount is shown above for "Contingency", such amount may not be expended from that subaccount. Any amounts needed for expenditure from the "Contingency" item must be transferred to the proper subaccount before expenditure.

The regular commitment and expenditure procedures of the University may be followed for this account except that each "Purchase Request" (Form 100R) must bear the note "Government contract - invoice in duplicate."

If you have any question regarding the administration of this account, please advise.

Arthur Lincicome

AL:NR
cc-Mr. Harrell
Mr. Watson
Mr. Cotton
Dean Coggeshall
Mr. Hogness
Central Administration

Mr. Cotton:
When payment is received credit Account No. 0-0271-73-1623.

A. L.

FEDERAL SECURITY AGENCY • Public Health Service

NATIONAL INSTITUTES OF HEALTH • Bethesda 14, Md.

April 4, 1952

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTE OF DENTAL RESEARCH
NATIONAL HEART INSTITUTE
NATIONAL INSTITUTE OF MENTAL HEALTH
NATIONAL MICROBIOLOGICAL INSTITUTE
NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS
THE CLINICAL CENTER
DIVISION OF RESEARCH GRANTS

In reply refer to
Grant # E-144(C)
(Period Covered)

12/1/51 to 11/30/52

Business Manager, Special Projects
The University of Chicago
5801 Ellis Avenue
Chicago 37, Illinois

Dear Sir:

A voucher representing final payment due on the above Public Health Service grant-in-aid has been processed and check should reach your office within three to four weeks. The amount due was determined as follows:

Initial payment	$ 3,888.00
Transfer of unexpended balance from previous grant	21.25
Other transfers (if any).	
Final payment	3,866.75
Total approved and made available . .	7,776.00

Sincerely yours,

C. A. Lowe

C. A. Lowe, Operations Officer
Division of Research Grants

cc:

Dr. Leo Szilard
Inst. of Radiobiology & Biophysics
The University of Chicago
Chicago 37, Illinois

146

THE UNIVERSITY OF CHICAGO
OFFICE OF THE COMPTROLLER
FORM NO. 34

MANUAL OF ACCOUNTS

ACCOUNT INFORMATION SHEET

REVISED

QUADRUPLICATE
Department

Name of Account:	Account Code L	Account	Sub	Fund
Medical Research No. 185				
Salaries	3	3250	20	1623
Annuities	3	3250	33	1623
Travel	3	3250	34	1623
Consumable Supplies (OVER)	3	3250	35	1623

In Charge of:
Mr. Leo Szilard

Departmental Classification:
Biological Sciences Division
Institute of Radiobiology & Biophysics

Purpose of Account:
To set up appropriations from the Medical Research No. 185 Fund and record expenditures against the appropriations in accordance with the terms of the U.S.P.H.S. grant E-144(C).

Source of Funds: Donor Federal Security Agency, Public Health Service

Amount $ Period 12/1/51 - 11/30/52

Payable 50% at once; balance on acceptance of final report on preceding grant, Medical Res. No. 149. Subject to refund.

Account to be debited with:
Expenditures approved by the responsible investigator or his authorized representative and subject to the specific limitations as set forth in the grant and regulations governing U.S.P.H.S. grants.

Account to be credited with:

Disposition of Balance:
For balance sheet purposes, the unexpended balance of this appropriation account is combined with the unappropriated balance of the fund and classified as "Deferred Income."

Bookkeeper:
Restricted Expendable Bookkeeper
Government Accounts Division

Statements to:
Mr. Leo Szilard
Dean of Biological Sciences Division

TABULATING HEADING CARDS

Name of Account:	Card Code	L	Account	Sub	Fund	Cards Punched
Medical Res. No. 185 Salaries	1	3	3250	20	1623	
Medical Res. No. 185 Annuities	1	3	3250	33	1623	
Medical Res. No. 185 Travel	1	3	3250	34	1623	
Medical Res. No. 185 Consumbl. Sup.	1	3	3250	35	1623	
Medical Res. No. 185 Other Exp.	1	3	3250	36	1623	
Medical Res. No. 185 Overhead	1	3	3250	90	1623	
Medical Res. No. 185	2	3	3250	—	1623	
Salaries	2	3	3250	20	1623	
Annuities (OVER)	2	3	3250	33	1623	

Date Established 11/8/51
Date Revised 2/1/52
Date Discontinued

Prepared by RRG
Approved by SEL E. H.
Entered Code Rack

171 A

Medical Research No. 185 (Cont.)

Other Expenses	3	3250	36	1623
Overhead	3	3250	90	1623

Medical Res. No. 185 (Cont.)

Travel	2	3	3250	34	1623
Consumable Supplies	2	3	3250	35	1623
Other Expense	2	3	3250	36	1623
Overhead	2	3	3250	90	1623

KARL PRESSER, M. D.
101 EAST 74TH STREET
NEW YORK 21, N. Y.
BUTTERFIELD 8-8535

January 4, 1952

Dr. Leo Szilard
1155 East 57th Street
Chicago 37, Illinois

FOR PROFESSIONAL SERVICES

$35.00

Paid Feb 29/52

X CLUB MEETING

Time: Thursday, January 17, 1952 - 6:30 P.M.

Place: Private Dining Room - Quadrangle Club

SPEAKER: Dr. Walter L. Palmer, Department of Medicine

Subject: Problems of Ulcerative Colitis

Please indicate on the enclosed card whether or not you will attend and return to:

L. T. Coggeshall, M.D.
Billings S144
Faculty Exchange

INVOICE

The John Crerar Library

SCIENCE • TECHNOLOGY • MEDICINE

86 EAST RANDOLPH STREET • CHICAGO 1, ILLINOIS
TELEPHONE ANdover 3-6660

232

Institute of Radiobiology & Biophysics
University of Chicago
5650 Ellis
Chicago 37, Illinois

Attn: Dr. L. Tallard

INVOICE NO.: 6355 DATE: 1-17-52 YOUR ORDER NO.:

Photostats: One article (11 pages)	$ 2.50

Invoice sent to Proc. Off. for payment 1/18/52. sdo.

THE UNIVERSITY OF CHICAGO
OFFICE OF THE COMPTROLLER
FORM NO. 34

MANUAL OF ACCOUNTS

ACCOUNT INFORMATION SHEET

QUADRUPLICATE
Department

Name of Account:
Navy Bacterial Virus Research
Salaries
Annuities
Travel
Consumable Supplies
Overhead

Account Code			
L	Account	Sub	Fund
3	3250		1746
3	3250	20	1746
3	3250	33	1746
3	3250	34	1746
3	3250	35	1746
3	3250	90	1746

In Charge of: Leo Szilard

Departmental Classification:
Biological Sciences Division
Inst. Radiobiology & Biophysics

Purpose of Account: To set up appropriations from the Navy Bacterial Virus Research Fund and record expenditures against the appropriations in accordance with the terms of Contract No. N6ori 02038 for research, development, and services.

Source of Funds: Donor U.S. Government, Department of the Navy

Amount $8,834.00 Period 1/1/52 - 12/31/52

Payable As cost invoices are submitted

Account to be debited with:
Expenditures approved by the project director or his authorized representative and subject to the specific limitations as set forth in the contract.

Account to be credited with:

Disposition of Balance:
For balance sheet purposes, the unexpended balance of the appropriation account is combined with the balance of the fund account and the net amount transferred to Accounts Receivable - U. S. Government (0-0128-99-1000).

Bookkeeper:
Restricted Expendable Bookkeeper
Government Accounts Division

Statements to:
Leo Szilard ✓
Dean of Biological Sciences Division

TABULATING HEADING CARDS

Name of Account:	Card Code	L	Account	Sub	Fund	Cards Punched
Navy Bacteria Virus Res Salaries	1	3	3250	20	1746	
Navy Bacteria Virus Res Annuity	1	3	3250	33	1746	
Navy Bacteria Virus Res Travel	1	3	3250	34	1746	
Navy Bacteria Virus Res Con Sup	1	3	3250	35	1746	
Navy Bacteria Virus Res Overhead	1	3	3250	90	1746	
Navy Bact Virus Res	2	3	3250		1746	
Salaries	2	3	3250	20	1746	
Annuity	2	3	3250	33	1746	
Travel	2	3	3250	34	1746	

Date Established 2/14/52 (over)
Date Revised
Date Discontinued

Prepared by TH KRG SBL EH 2/18/52
Approved by
Entered Code Rack

171

Navy Bact Virus Res (Cont.)	2	3	3250		1746
Consumable Supplies	2	3	3250	35	1746
Overhead	2	3	3250	90	1746

Bursar's Form #250A

THE UNIVERSITY OF CHICAGO

OFFICE OF THE BURSAR

5801 ELLIS AVENUE

FEB 21 1952

Dr. Leo Szilard

Inst. - Radiobiology

Research Institutes-308

MAKE CHECKS PAYABLE TO THE UNIVERSITY OF CHICAGO—REMIT TO THE BURSAR

Telephone Charge		
# 213	3	63
241	4	00
550	3	19
1311	2	69
	13	51

PAST DUE
MAY WE HAVE YOUR
REMITTANCE PROMPTLY

THE UNIVERSITY OF CHICAGO
PAID
MAR 3 1952
RECEIPT #
OFFICE OF THE BURSAR No. 1

Please bring or send this notice with your remittance to Window No. 1

THE UNIVERSITY OF CHICAGO
Comptroller's Form 64R

TRAVEL EXPENSE VOUCHER

Prepare in
DUPLICATE—for General Travel
TRIPLICATE—for B.S.D. Travel
QUADRUPLICATE—for Government Contract Travel

Date April 3, 1952

Name Leo Szilard, Institute of Radiobiology and Biophysics, RI 308
(Address)

For travel expenses incurred while engaged on University business as follows:

Destination Madison, Wisconsin Travel Authorization Number

Purpose Visit to the American Foundation for the Study of Genetics

I certify that the amounts given herein represent actual expenses of the above travel and are fair charges against The University of Chicago.

Date of Departure 3/29/52 *Hour 8:15 pm
Date of Return 3/30/52 *Hour 6:40 pm
*Contract No. USPHS Grant # E-144 (C)

Signature of Traveler

Travel advances (if any)	$	$	$
Expenditures:			
Transportation (Attach receipts for air travel)			
From Chicago To Madison Carrier Wisc. Central Airlines			$8.63
From Madison To Chicago Carrier "			8.63
From To Carrier			
Pullman, extra fares, etc. (Attach receipts or Pullman ticket stubs for each charge)			
From To Space Used (Lower, upper, etc)			
From To Space Used			
From To Space Used			
*Reason for space more expensive than lower berth			
Hotels (Attach receipts for each) Dates 3/29/52 Name The Edgewater - Madison			9.60
Dates Name			
Dates Name			
Meals			
Taxi fares To and from airports in Chicago and Madison (Attach receipts when such are available)			6.00
Miscellaneous (Attach such receipts as are issued in the regular course of business; explain unusual items)			
Total Expenditures:			
Charge Med. Res. #185, Travel (Account Name) 3 | 3250 | 34 | 1623 (Account Code)			$32.86
Balance of advance (if any) to be deposited with the Bursar			
Excess of expenses over advances received			

*Use only for travel to be charged against Government Contracts

INSTRUCTIONS:
For General Travel—This form is to be prepared in duplicate and approved with the authorized signature of the Department. The original should be forwarded to the Comptroller. The duplicate should be retained by the Department.
If a travel advance was made, any unused balance must be deposited with the Bursar to be credited to your personal advance account, with the travel authorization number given as a reference.
If expenses exceed the sum advanced, or if no advance was made, a check will be issued promptly.
For Biological Sciences Division Travel (except when traveling under Government Contracts) the original and duplicate copies of this form should be forwarded to the Comptroller through the Biological Sciences Division Accounting Office and cash deposited with the Hospital Cashier, rather than with the Bursar.
For Government Contract Travel—three copies of this form should be forwarded to the Comptroller and cash deposited with the Bursar.

Approved: ORIGINAL SIGNED BY T. H. DAVIES

Authorized signature

Charge:

DO NOT WRITE BELOW THIS LINE

Account Code L	Account	Sub	Fund	Entry Code	Authorization Number	Type of Charge	Amount of Authorization Cancelled	Amount of Charge

Audited

for Comptroller Date

Coding Verified

Tabulating Department

Comptroller's Voucher Number

Credit:

Account Code L	Account	Sub	Fund	Entry Code	Advance Number	Authorization Number	Amount of Credit
0	014	04	1000	41			

148

Leo Szilard
Rotchschild

THE UNIVERSITY OF CHICAGO
COMPTROLLER FORM NO. 40R
5M-6-51

REQUEST FOR BUDGET TRANSFERS
(ENTRY CODE O)

Triplicate
For Other Adm. Officer

INSTRUCTIONS FOR PREPARATION: This form is to be used in requesting transfers to or from Budget Accounts (including regular budget appropriations, restricted expendable appropriations, and budget income estimates). It should be prepared in triplicate by the Dean or other appropriate administrative officer, and all copies forwarded to the Central Administration for approval, where necessary, otherwise directly to the Comptroller's Office, where they will be numbered and the copies returned to the appropriate offices as notification that the request has been approved. If disapproved, the appropriate officer will be notified by the Central Administration or the Comptroller.

Decreases in appropriations or increases in budget income estimates and negative appropriations shall be entered under the "Debit" section; increases in appropriations or decreases in budget income estimates and negative appropriations shall be entered under the "Credit" section.

This form is also to be used for making and adjusting appropriations from Restricted Expendable Funds and Unexpended Plant Funds.

(Give Full Account Name)	Entry Code	Account Code L	Account	Sub	Fund	Amount
DEBIT: (Decreases in Appropriations or Increases in Budget Income Estimates and Negative Appropriations)						
Navy Bacterial Virus Res. Fund	03	0	0275	93	1746	8,834 00
CREDIT: (Increases in Appropriations or Decreases in Budget Income Estimates and Negative Appropriations)						
Navy Bacterial Virus Research						
Salaries	03	3	3250	20	1746	5,400 00
Annuities				33		150 00
Travel				34		300 00
Consumable Supplies				35		500 00
Overhead				90		2,484 00

REASONS FOR REQUEST: To set up appropriations from funds provided by Contract No. N6ori-02038 for the period 1/1/52 thru 12/31/52 in accordance with Mr. Harrell's letter dated 2/5/52.

Mr. Leo Szilard

REQUESTED—Dean or Other Adm. Officer	DATE		DATE
L.T. Coggeshall	2/14/52		
APPROVED—Central Administration	DATE	FUNDS AVAILABLE—Comptroller	DATE
R.W. Harrison	2/14/52	John T. Wilcox	FEB 12 1952
CHECKED FOR PROPRIETY OF ENTRY		CODING VERIFIED BY	COMPTROLLER'S NO.
By _____			10874

170

Humphreys,
Physics of the Air.

Dr. Szilard

AMERICAN FOUNDATION FOR THE STUDY OF GENETICS

Route 5
RESEARCH LABORATORY: ~~P. O. Box 208~~, MADISON, WISCONSIN
Telephone ~~Gifford 7010~~ 4-0748

Chicago Office: ~~134 NORTH LA SALLE STREET~~, CHICAGO ~~2~~, ILLINOIS
~~Telephone AN dover 3-3938~~
325 No Wells St
Superior 7-9756

Abba Lerner

A. W. Phillips

Economica Aug 50

London School of Econ.

Yorkshire Bulletin of Economic and Social Res.

Vol 2 No 2 July 1950

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A PERSONAL LETTER

to a

FELLOW LIBERAL

in a time of crisis

* *)(* *

"Liberals should be getting off their posteriors and shaking them for all they are worth to get the nomination for Justice Douglas."

Lincoln's Birthday, 1952

AN OPEN PERSONAL LETTER TO A FELLOW LIBERAL

IN A TIME OF CRISIS

Lincoln's Birthday, 1952
411 Washington Street
Fremont, Ohio

Dear Lewis Mumford:

As a Democrat in the liberal tradition of Jefferson, Altgeld and Roosevelt, I agree wholehartedly with your letter in the New York Times Magazine, January 27, 1952; in which you say concerning Justice William O. Douglas' article the previous fortnight, "The Black Silence of Fear":

> "Justice Douglas' article convinces me that despite his recent announcement that he will not run, he is the only possible Democratic Presidential candidate capable of putting the life-and-death issues that confront our democracy before the electorate. No one else has pointed out with such clarity the shameful inroads on our freedom and our power of choice, made by both the Democratic and Republican parties. No one has better understood the hatred our present military and foreign policies have awakened in East -- and West.
>
> "Our leaders in both parties have talked peace and prepared for war; they have talked freedom and abetted totalitarian compulsion; they have talked security and by putting their faith in 'magic weapons,' they have promoted insecurity.
>
> "By reasons of his character and convictions, Douglas today looms like another Lincoln. Shall we recognize his gifts in time to put them to work? -- What we need now is a courageous leader who stands both for our old native tradition and our new promise. William O. Douglas is such a leader, it seems to me, and, unless he has compelling personal reasons for keeping to his original decision, his nomination as Democratic candidate is still in order."

To paraphrase your letter, no one else has pointed out with such clarity the proper choice for President in 1952 by liberal Democrats, if they are true to the liberal tradition and to their professed ideals.

It is all very well, after the fact of nomination, if the machine politicians have their way, for liberals to support some estimable men like Estes Kefauver or Adlai Stevenson. But their first choice ought to be Justice Douglas. At this stage, until the nomination is a fact, liberals should be getting off their posteriors and shaking them for all they

are worth to get the nomination for Justice Douglas. I am convinced that it can be done, the politicos notwithstanding. But it will take work -- right now -- by all who call themselves liberals.

I have talked with and corresponded with dozens of liberals in all parts of the country about Justice Douglas; started doing so ever since his address on December 30, 1947 at the Chicago dinner in observance of the 100th anniversary of the birth of John Peter Altgeld. In that address (Vital Speeches, February 1, 1948), Justice Douglas set forth an American liberal philosophy from which he has not deviated apropos the world crisis.

He warned then that we cannot win the battle for democracy in the world if we adopt totalitarian methods and if we support fascist and feudal regimes. He warned then that we cannot stem the tide of communism with dollars or bullets -- that we must win the hearts of the masses of the people by supporting their aspirations for independence, freedom and national pride. He warned then -- in 1947, just when the present witch hunt, the "revival of heresy" (to use Carey McWilliams' phrase) was getting started -- that in sacrificing our ideals of civil liberties and civil rights, all in the name of so-called "security", we would be traveling down the road to totalitarianism.

Ever since, in other public addresses, in his books, in his articles in Look Magazine, in Life Magazine, in the New York Times Magazine, he has fearlessly developed these same themes. Like Lincoln (as you suggest), Like Jefferson, like Altgeld, like Franklin D. Roosevelt in his prime, William O. Douglas has been holding high and bright the ideals and the principles and the professions without which America has no meaning.

As you suggest, he is the only public figure in high place in America today who has come forward fearlessly, and in the way of the finest American tradition, with a program that would both stem the tide of communism and also make possible the survival of America and the Western world as homelands of freedom. All of the liberals with whom I have talked and corresponded admit all this. They all say, as you have said, that William O. Douglas ought to be the Democratic candidate for President. But nothing much has been done by us to get him as the candidate. I write this because I believe something ought to be done -- and at once. For liberals now to sit on their hands, to settle for lesser men, is to betray the cause of liberalism. For liberals to play the game of "practical politics", as some are doing, and go along with certain candidacies because these certain candidacies have the backing of machine politicians, or of powerful newspapers and magazines, is also betraying the cause of liberalism. Better by far, I believe, to go down to defeat behind a true liberal, behind William O. Douglas, than to play a game that sells out both liberalism and the ultimate security of America itself as we have known it.

What is needed more than anything else in the coming presidential election is a real debate on the one issue that is important. This is the issue of foreign policy. If the Republicans nominate Senator Taft (as I think they will), or General Eisenhower, and if the Democrats nominate President Truman or Senator Kefauver, or somebody handpicked by President Truman, there will be no real debate on foreign policy. The truth is

that not even Senator Taft offers any real alternative to the Truman foreign policy, notwithstanding his supposed criticism of it. Taft would simply go along with the Truman program, only not so far and not so fast voluntarily. A careful analysis will show that Taft comes forward with the present foreign policy merely diluted and dehydrated. If Truman or his choice is elected, or on the Republican side, Taft or Eisenhower, the nation would be committed to following the present Truman doctrines, at the end of which, in my opinion, is only bankruptcy, moral and economic, with Soviet communism more dominant than ever in the world, especially in Asia and the Near East, which is the real battle ground. As for Senator Kefauver, the New York Times in an editorial January 25, said: "Senator Kefauver is a strong supporter of the Administration's foreign policy." As for Senator Paul H. Douglas, who is still being boomed in certain circles, his foreign policy is even worse than the Administration's, for remember that he favored (University of Chicago Round Table, December 3, 1950), using the atomic bomb in Korea and in China, and he has called for our making common cause with totalitarian dictators such as Chiang kai-shek and Franco.

Only William O. Douglas, among public leaders of eminence, represents an alternative. Only William O. Douglas offers the people any real choice at all for a foreign policy. All of the other men mentioned are Me-toeers. This juncture of crisis has been able to produce only one transcendent figure to give the people a choice in the one field -- foreign policy -- which is the one issue that ought to be debated in the presidential campaign. Yet this is indisputably the fact.

To me, it is clear that liberals in this time of crisis must call for the nomination of Justice Douglas or forfeit the right to call themselves liberals. I am aware that Justice Douglas has not approved and may not affirmatively approve any such call in advance of a nomination. I am aware that he is reported to have said that he is not available. But I am convinced that all this should be ignored. No man who was ever seriously demanded by the people for President has ever refused to accept their call. No man has a right to refuse to accept such a call. It goes with citizenship. Moreover, as The Nation magazine has pointed out, there are definite indications that Justice Douglas is available, that he will accept a call from the people. It is inconceivable that he would present a program to the people, as he has been doing in a magnificent manner, and then refuse to give the leadership for carrying out his program.

But there has to be a call. Five months remain to sound the call before the Democratic national convention. It makes no difference what President Truman decides to do. Liberals all over America must go to work.

Two immediate steps are necessary.

First, the formation of a committee, big or small, for raising some funds and for establishing some kind of headquarters, for the receiving and sending of mail.

Second, this committee should immediately send out copies of Justice Douglas' speeches and articles. These should go out at once to every labor union official, to every newspaper editor, to every women's club leader, to everybody listed in "Who's Who", to every college professor -- in short to all the key people in America. In primaries, they should be urged to write Justice Douglas' name in.

I am satisfied that the rest will follow -- the local committees, the state committees, the pressure on the politicians and the delegates to the convention, and the raising of the money for a real campaign of education. The money can be had. I know of one multimillionaire who is for William O. Douglas heart and soul. He only has to be convinced that a serious drive is on and that Justice Douglas will accept the call for contributing and getting other to contribute what is needed. But the main reliance should be and can be in the little people. They have to have leadership.

It is no excuse to say that we have no time for this effort. Of course we have no time. I am working on a new book. Probably you are too. All liberals are busy making a living, if nothing else. But we must make time. You ask: "Shall we recognize his gifts in time to put them to work?" The answer is up to you and to me and others to whom I am sending a copy of this letter. There is at stake what we say we believe in -- also the lives of our children. For them we can make time, or we must hide our heads in shame and sit back, trembling like cowards, prigs and poltroons, to wait for the dark night of reaction and disaster to come.

Sincerely yours,

Harry Barnard

Harry Barnard,
Author of "Eagle Forgotten", the
Life of John Peter Altgeld.

Lewis Mumford, Esq.
c/o Harcourt Brace & Co.
Publishers,
New York 17, New York

Copies to:

Irving Dillard, Herbert H. Lehman, William Benton, Thurman Arnold, Freda Kirchwey, Abe Fortas, Paul Porter, Leon Henderson, Joseph P. Kennedy, Carey McWilliams, Adlai E. Stevenson, Marshall Field, Stephen A. Mitchell, Sidney Yates, Adolph Sabath, Edward Keating, Dorothy Thompson, Doris Fleeson, Thomas L. Stokes, Marquis Childs, Walter Lippman, James Loeb Junior, Thomas Mann, Louis L. Mann, Abba Hillel Silver, Spencer Irwin, Herbert Brucker, Robert Morss Lovett, Curtis MacDougall, Arthur E. Morgan, Hans Morgenthau, Louis Wirth, Herbert Finer, Malcoln Sharp, Robert M. Hutchins, Pearl Buck, Katherine Arnett, A. N. Spanel, Ted Thackrey, Arthur W. Olsen,

Albert Deutsch, Max Lerner, Bishop G. Bromley Oxnam, Al Billstein, Drew Pearson, Leon Pearson, Irving Stone, Phil Kerby, Bertram B. Moss, Albert Lepawsky, Alfred Kamin, Emily Balch, Russell W. Ballard, George Stoddard, Harold Taylor, Gordon K. Chalmers, Ed. C. Johnson, Paul Hutchinson, Carl Sandburg, Cyril Bath, Henry Busch, James A. Cunningham, John J. deBoer, Dorothy W. Douglas, Guy Nunn, Frank Edwards, Francis Biddle, Arthur Schlesinger Sr., Arthur Schlesinger Jr., Louis Bromfield, Harry Schneiderman, C. E. Israel, Angus Cameron, Emanuel Celler, James Henie, James T. Farrell, Frazier Reams, Mrs. Eleanor Roosevelt, Ed. A. Lahey, Prof. J. G. Randall, E. T. Randall, C. Vann Woodward, Henry A. Wallace, James P. Warburg, Colston E. Warne, Willard Uphaus, John Carroll, Ben Cherrington, Philip Hornbein, Odell Shepard, Robert J. Havighurst, Michael Straight, Franklin D. Roosevelt Jr., Art Wetle, Owen Lattimore, Claude Pepper, William Langer, Henry Steele Commager, Max Ascoli, Henry Pringle, Quintin Reynolds, Irving Pflaum, Frederick L. Allen, Jacob M. Arvey, V. Y. Dallman, Gardner Cowles, Carroll Binder, Rexford G. Tugwell, Aubrey Williams, Nicholas John Matsoukas, Ben Abramson, Meyer Kestnbaum, Leo Lerner, John Fischer, William L. Shirer, Raymond Swing, Glen H. Taylor, Mrs. Harold Ickes, Elliott Roosevelt, James Roosevelt, John K. Fairbank, Walter Reuther, John L. Lewis, William Green, Philip Murray, Arthur Miller, Arthur J. Goldberg, Darryl Zanuck, Milburn P. Akers, John A. Lapp, Bishop Bernard J. Sheil, M. H. Rubin, William H. Holly, Arthur Garfield Hays, Marquis James, D. R. Fitzpatrick, Ellis Arnall, William C. Menninger, Roger Baldwin, Richard J. Finnegan, Oliver Loud, Louis Filler, Frederick Schuman, Waldo R. Browne, Archibald MacLeish, Lillian Hellman, Bill Mauldin, Norman Thomas, Helen Gahagan Douglas, T. S. Matthews, Joseph Edelman, G. Mennen Williams, Blair Moody, Henry Morgenthau Jr., Joseph E. Davies, Milton Meyer, Kermit Eby, Homer A. Jack, Herman Weiner, Robert W. Kenny, Richard Hofstadter,, Richard Rovere, Olin Downes, A. J. Leibling, E. B. White, I. F. Stone, James Wechsler, Chester Bowles, Claude G. Bowers, Dorothy Schiff Thackrey, Charles Clayton Morrison, Eliot Janeway, Norman Cousins, Norman Corwin, Orson Welles, Ernest T. Weir, Prentiss Brown, Irving Brant, Bruce Cabot, Harry Elmer Barnes, Edward Lamb, Matthew Josephson, Walter White, Bernard DeVoto, Walter Prescott Webb, Walter Johnson, Dumas Malone, Ralph J. Bunche, Bernard Baruch, Upton Sinclair, Henry J. Kaiser.

ENCLOSURE A

Research proposal submitted to the Office of Naval Research, United States Navy, by Leo Szilard, Professor of Biophysics in the Institute of Radiobiology and Biophysics of the University of Chicago, through and with the approval of Dr. Lowell T. Coggeshall, Dean of the Division of Biological Sciences.

Problem: Study of the growth, adaptation, and mutation of bacteria and bacterial viruses, carried out with new biophysical methods.

Background: Up to now, studies of growth, adaptation, and mutation of bacteria were invariably carried out in cultures which grew from a small inoculum up to a certain concentration of bacteria at which further growth was limited either by the exhaustion of the nutrient or by insufficient supply of oxygen. For a number of problems this conventional method of study is inadequate, and preliminary experiments which we carried out (unpublished) show that these problems are capable of a solution if a different method is adopted.

Significance: The new method permits us to study these phenomena while the bacteria are being kept indefinitely in the growth phase and to vary independently the growth rate and concentration of the bacteria. Thus a number of the previously unmanageable problems become open to experimental attack.

Plan: Several lines of investigation to be listed below will be carried out by means of an apparatus called the "Chemostat" which we have developed. This apparatus permits us to maintain a bacterial population in the growth phase over long periods of time (in excess of ten days). It permits varying the growth rate at constant temperature by automatically maintaining the concentration of one of the growth factors required by the bacterial strain at such a low level that the growth rate is depressed to any desired degree. In preliminary experiments carried out with a tryptophane requiring strain of coli, we found, for instance, that we could vary the growth rate between the normal growth rate and a growth rate about ten times lower by maintaining tryptophane concentrations ranging

from 3×10^{-9} grams per cc. to 3×10^{-10} grams per cc. The following is a selection from the investigations which will be carried out with the chemostat:

1) The number of mutants (resistant to some bacterial virus) which establish themselves in the bacterial population will be determined for different growth rates. The results should show whether at a given temperature the mutation rate is determined by the number of cell divisions or rather the time that the bacteria spend in the growth phase.

2) The ratio of mutation rates for different mutations will be studied in order to determine whether this ratio depends, for one and the same organism, on the particular growth factor which is used for depressing the growth rate.

3) Bacterial metabolism will be studied:

a) It will be determined whether oxygen consumption varies at a given temperature with the growth rate; and

b) It will be determined whether, at depressed growth rates, the bacterial population pours out, at an increased rate, intermediate metabolites into the nutrient liquid.

4) The growth rate will be determined for bacterial strains requiring various growth factors as a function of the growth factor concentration. These functions will be determined for two temperatures differing by about ten degrees, in the hope of obtaining relevant information on the chemical kinetics of bacterial growth.

Requirements: Space, general laboratory facilities, and most of the necessary special apparatus are available in the new Institutes Building of the University of Chicago. I have had considerable experience with the methods that are to be used, and Dr. Aaron Novick is well qualified to apply those methods to the problems under consideration. The proposed program requires also substantial fractions of the time of a qualified Research Associate and a Technician, both of whom would be available from the candidates in sight. Though it seems wise to plan this program on a two year basis, it is believed that some significant results can be obtained within the first year.

Proposed budget for 1 July, 1950, through 30 June, 1951

Personnel		
4/5 time of one Assistant Professor (Novick)	$4,000	
3/4 time of one Research Assistant	2,600	
3/4 time of one technician	1,800	
	8,400	$8,400
Overhead (~~45~~ 46% of above)	3,780	3,780
Annuities (5%, Novick)	200	200
Equipment, etc.		
Apparatus and installation	1,600	
Expendables (glassware, chemicals, etc.)	500	
	2,100	2,100
Travel	300	300
Total for one year		$14,780

Submitted by Leon B. Novick

Professor of Biophysics

ENCLOSURE A - 11

Research proposal submitted to the Office of Naval Research, United States Navy, by Leo Szilard, Professor of Biophysics in the Institute of Radiobiology and Biophysics of the University of Chicago, through and with the approval of Dr. Lowell T. Coggeshall, Dean of the Division of Biological Sciences.

Problem: Study of the relationship between chemical structure and mutagenic action.

Background: We have developed a technique that makes possible for the first time precise measurement of the mutation rate of bacteria (see enclosed reprints). This method permits us to determine whether a given substance can increase the spontaneous mutation rate of a microorganism and is not disturbed by the question of selection.

Significance: Techniques available up to the present have confined mutagenic studies to the very powerful reagents that kill very extensively, i.e. ultraviolet radiation, x-rays, the nitrogen mustards, etc. This new method because of its great sensitivity permits us to detect the mutagenic action of substances that are only slightly mutagenic and do not kill the organism. In addition, it allows us to measure the dependence of mutagenic activity on concentration of the chemical substances. Through studies on the kinds of substances that are mutagenic and their kinetics we hope to be able to understand considerably more than is known at present about the biochemical nature of a mutation and the mechanism of its induction.

Plan: In some preliminary experiments we have found that we can increase the spontaneous mutation rate in E coli twenty-fold through the use of a relatively low concentration of caffeine. Other methylxanthines behave similarly. In addition, we have found that adenine itself is mutagenic but much less so than the methylxanthines. First we would like to see whether the mutagenic activity of these compounds is due to some antagonism of normal purine synthesis and utilization. Furthermore, we plan to continue these experiments using other purine analogues, pyrimidines and their analogues, and compounds biochemically interesting for other reasons. In addition, we plan to examine what kinds of chemical inhibition can be found for such mutagens. Finally, we will study the dependence of the mutagenic effect on the concentration of the mutagen. Through these studies we hope to be able to develop some concept of the relationship between chemical structure and mutagenic activity.

Requirements: Space, general laboratory facilities, and most of the necessary special apparatus are available in the new Institutes Building of the University of Chicago. I have had considerable experience with the methods that are to be used, and Dr. Aaron Novick is well qualified to apply those methods to the problems under consideration. The proposed program requires also substantial fractions of the time of a qualified Research Associate and a Technician, both of whom would be available from the candidates in sight. Though it seems wise to plan this program on a two year basis, it is believed that some significant results can be obtained within the first year.

Problem: ~~We would like~~ To determine the relationships ~~exist~~ between chemical structure and mutagenic activity.

Background: In the past the chemical mutagens studied have always been reagents that in addition to producing mutations caused very extensive killing. This was due to the lack of a technique for measuring mutation rates accurately. We have developed a device, called the chemostat, which permits percise measurements of the mutation rate. (See enclosed reprints.) With the chemostat we can readily determine whether a compound has even a very slight mutagenic effect.

Significance: With this technique we will be able to study compounds of biochemical interest. For example, some preliminary experiments on E coli with this method have shown caffeine (trimethylxanthine) to cause a large increase in the mutation rate even at low concentrations. The dimethylxanthines behave similarly. Even adenine itself is slightly mutagenic. Studies of this kind--what types of chemical structure are associated with mutagenic activity--and what are the kinetics of these phenomena--should furnish the kind of information needed for understanding genetic phenomena at the biochemical level.

Plan: First we would like to see whether other purines and pyrimidines and their analogues possess mutagenic activity. This work will then be extended to amino acids and their analogues as well as other compounds of biochemical interest. Moreover studies will be made on what types of chemical inhibition or antagonism can be found for such reagents. Furthermore we plan to study the dependence of the mutagenic effect on the concentration of the mutagen.

PROGRESS REPORT

United States Public Health Service Research Grant E-144(C)

Study of the Growth, Adaptation, and Mutation of Bacteria and Bacterial Viruses, Carried Out with New Biophysical Methods

Leo Szilard
Institute of Radiobiology and Biophysics
The University of Chicago

December 1, 1950 - June 12, 1952

A. Summary Statement:

Work on this project has largely been concerned with a study of mutations in bacteria. In addition, some progress is reported on the mechanism of biosynthetic regulation in bacteria.

The work on mutations has demonstrated that the spontaneous mutations studied occur at a rate which is time dependent rather than generation dependent. In addition, a method has been developed for observing "evolution" in bacteria.

A study has been made of the effect of mild chemical reagents on the mutation rate, and it was discovered that purines and purine analogues have the property of increasing the mutation rate without killing the organisms. No other class of compounds studied displayed this character. Very recently it was discovered that certain purine derivatives have the unusual property of decreasing the mutation rate.

An attempt has been made to learn something about the nature of the regulatory mechanisms employed by a bacterium to regulate the rates of syntheses of its amino acids. This study has been largely concerned with the investigation of the rate of synthesis of a tryptophane-like substance produced by a biochemical mutant incapable of synthesizing tryptophane. The rate of formation of this compound was observed under a variety of conditions in a bacterial population growing in the Chemostat. This work was extended to include a study of the rate of arginine synthesis by a bacterium capable of synthesizing its own arginine. It was found that arginine synthesis is suppressed by an exceedingly low concentration of arginine in the medium.

B. Full Statement of Progress:

A new model of the Chemostat has been constructed and has been employed for a variety of studies. The Chemostat permits the maintenance of a population of bacteria of constant size growing at an arbitrary but fixed growth rate. All of the work has been done with the B strain of E. coli and mutants derived from it.

Bacterial mutations: In a population of bacteria in a Chemostat, mutants resistant to phage T5, for example, should increase linearly in frequency in time providing that the mutant grows at the same rate as the wild type. Such a straight line increase, when observed, furnishes from its slope the mutation rate; and at the same time, rules out selection for or against this mutant. This technique permits for the first time precision in the measurement of mutation rates. Using this method, it has been possible to show that the rate of mutation to phage T5 resistance is a constant per unit time, independent of the generation time. This rate has a value of 1.25×10^{-8}/hour/bacterium at 37° C. for a population of bacteria growing under tryptophane control. Decreasing the temperature by 10° reduces the rate about a factor 2.

In the course of these studies on mutation rates, sudden falls in the frequency of phage resistant mutants were observed. These falls, it was possible to show, resulted from the appearance of a strain by mutation that can grow faster than the original strain under the conditions prevailing in the Chemostat. This faster strain displaces the original strain and all of the phage resistant mutants accumulated in it. One Chemostat was run for 600 generations, during which some 10 "evolutionary steps" were observed.

The precision furnished by the Chemostat for the measurement of mutation rates makes possible the detection of mutagenic character on the part of mild chemical reagents--reagents that do not, like those employed in the past, kill a large fraction of the population. A large number of compounds were tested. Mutagenic activity was found only in the class of purines and purine analogues. Caffeine, a trimethylxanthine, for example, at a concentration of 150 mg/l, gives a more than 10 fold increase over the spontaneous mutation rate. Even adenine is mutagenic, but much less so than caffeine. No pyrimidine or pyrimidine analogue tested displayed any such mutagenic character.

An investigation of the purine ribosides has led to the discovery of a new phenomenon--the decrease in the mutation rate. Guanosine, inosine, and adenosine, for example, can completely eliminate the mutagenic effect of theophylline. This antimutagenic action seems to lead to a value even less than the normal spontaneous rate.

Regulatory activities: Studies were made of the manner in which a bacterium controls the rates of syntheses of the various amino acids so that no excess is produced even under conditions in which the rate of protein synthesis has been reduced by a factor of 10 through the feeding of a required amino acid at a very low concentration. This study has been concerned with the rate of production of a tryptophane-like substance by a mutant incapable of making tryptophane. This compound is produced at a constant rate, independently of the growth rate, between generation times of $3\frac{1}{2}$ hours and 14 hours. If protein synthesis is stopped by withholding tryptophane, the compound continues to be produced from ammonia and lactate at a high rate for more than 8 hours. The

bacterium can synthesize this compound at a rate four times as fast as it would have to make tryptophane if it were to grow at its maximum growth rate in the absence of tryptophane. At short generation times the compound is produced at a low rate. The rate of the production of the compound, at generation times which are long enough to permit it to proceed at full blast, increases from 25° to 37° by about a factor of 2 and decreases from 37° to 43° by about a factor of 0.75. If the generation time is switched from a low value, at which the compound is made at a low rate, to a longer generation, at which it is made at a high rate, the response in the production rate of the compound to the change in generation time appears to be immediate, i.e. if there is a lag it is less than 30 minutes. If the bacterial population in a stationary state is pouring out the compound, and if the concentration of tryptophane is suddenly raised, the production rate of the compound falls to less than one-third of its previous value, and if there is a lag it is less than 10 minutes.

Some studies on the rate of arginine synthesis by a bacterium that can synthesize arginine have shown that arginine synthesis can be suppressed by external arginine even at an exceedingly low concentration of arginine. This suppression of the rate of synthesis of an amino acid by an increased concentration of that amino acid is proposed as a possible mechanism for the regulation of the rate of amino acid synthesis.

Papers published during this period include the following:

Aaron Novick and Leo Szilard, Science 112, 715 (1950).
Aaron Novick and Leo Szilard, Proc. Nat. Acad. Sci. 36, 708 (1950).
Aaron Novick and Leo Szilard, Science 113, 34 (1951).
Aaron Novick and Leo Szilard, Cold Spring Harbor Symp. Quant. Biol. XVI, 337 (1951).
Aaron Novick and Leo Szilard, Growth, in press.

C. Significant Accomplishments:

The following facts have been established relating to a tryptophane-requiring strain of E. coli when grown with tryptophane as the controlling growth factor in the Chemostat:

1. The rate of mutations to resistance to the virus T5 has a value of about 1.25×10^{-8}/hour and does not depend on how fast the bacterium grows within the limits of a generation time of 2 hours and 12 hours.

2. There is a class of compounds which are chemically not very reactive but, when employed in low concentrations in which there is no appreciable killing, will increase the rate of mutation 3 to 17 fold. This has been established so far for the following substances: caffeine (17 - 150), theophylline (10.8 - 150), paraxanthine (8.4 - 150), theobromine (7.5 - 150), tetramethyl uric acid (7.6 - 150), 8-chloro caffeine (4.3 - 150), 8-methoxy caffeine (5.2 - 150), 8-azaguanine (3.4 - 150), adenine (5.2 - 500). The mutation rates per hour per 10^8 bacteria and the concentrations used in milligrams per liter are indicated in the brackets.

3. It was found that guanosine, adenosine, or inosine, will completely counteract the mutagenic effect of theophylline.

D. Plans for Next Year:

It is proposed to put the main emphasis on the study of the relationship of mutagenic action, antimutagenic action, and chemical constitution. In addition, we plan to continue our study of the regulation of biosynthetic processes.

Project

Chicago, Illinois MAY 27 1952

The University of Chicago
Attn: The Bursar
5801 Ellis Avenue, Chicago 37, Illinois
3-3250-00-1746 Inv. No. 1

net

N6ori-02038	Jan. thru April, 1952	Reimbursable costs incurred for research and development and services specified in contract.

(See Contractor's Statement for Certificate)

N6ori-02038 1/1/52

The University of Chicago
5801 Ellis Avenue
Chicago 37, Illinois Project

Contract No. N6ori-02038
Estimated Cost: $ 8,834.00
Account Code: 3-3250-35-1746

CONTRACTOR'S STATEMENT OF COST INCURRED thru April 30, 1951

	11/1 - 4/30/52	Period to Date
Labor	1,605.00	1,605.00
Overhead	738.30	738.30
Annuities	37.50	37.50
Materials & Services: Purchases	57.91	57.91
: Withdrawals from Stores		
Equipment: Purchases		
: Withdrawals from Stores		
Travel Expense		
Communications		
Total Cost	2,438.71	2,438.71
Deduct: Payments Received thru 4/30/52		-0-
Net Amount of this Invoice No. 1.	2,438.71	2,438.71

CERTIFICATE OF CONTRACTOR

We certify that the above bill is correct and just and that payment therefor has not been received.

We further certify that the personal services and the supplies, equipment, materials, etc., listed hereon were required by and were used in the performance of the work under the contract referred to on this voucher and that payments have been made of all amounts for which reimbursements are hereby claimed; that the amounts claimed for personal services involving part time work, determined from a distribution of wages for the period indicated to be directly chargeable to the United States under the provisions of the contract referred to on this voucher, are true and correct and that payments of these amounts have been made to all employees whose wages are included in the distribution; that payrolls. procurement records, invoices and requisitions concerned will be kept for a period of five years after final settlement under this Task Order, subject to inspection upon request by authorized representatives of the United States Government; and that no individual items costing $50 or more have been included in the subtotals and totals of charges for which no itemizations or evidentiary substantiations are furnished; and that the research provided for in said contract has been conducted in accordance with the terms thereof during that part of the period specified therein to which the costs stated in this voucher are applicable.

THE UNIVERSITY OF CHICAGO

By /s/ W. E. Thaggard, Assistant Comptroller

By /s/ W. B. Harrell, Business Manager

Project

THE UNIVERSITY OF CHICAGO

EXPENDITURES UNDER CONTRACT NO. N6ori-02038

FOR THE MONTH(S) OF Jan. 1 THRU April, 1952

SALARIES & WAGES:

1-1

	NAME	TITLE	CHECK NO.	PERIOD OF SERVICE FROM	THRU	RATE	UNITS WORKED	PREMIUM TIME	AMOUNT	TOTAL FOR PERIOD	✓
50%	Aaron Novick	Ass't. Prof	88577	3/1	3/31/52	250 00	1 Mo.			250 00	✓
55%	Hugo T. Victoreen	Biologist	86624	"	"	151 25	1			151 25	✓
50%	Aaron Novick	Ass't Prof	91277	4/1	4/30/52	250 00	1			250 00	✓
55%	Hugo T. Victoreen	Biologist	89372	"	"	151 25	1			151 25	✓
50%	Aaron Novick	Ass't Prof	83094	1/1	1/31/52	250 00	1			250 00	✓
"	"	"	85825	2/1	2/29/52	250 00	1			250 00	✓
55%	Hugo Victoreen	Biologist	81215	1/1	1/31/52	151 25	1			151 25	✓
"	"	"	83882	2/1	2/29/52	151 25	1			151 25	✓
							Total Salaries			1605 00	

ALLOWANCE FOR OVERHEAD Forty Six per cent (46%) of SALARIES: $1,605 00 @46% 738 30

ANNUITY PREMIUMS

Aaron Novick	2/1 - 2/29/52		12 50
" "	1/1 - 1/31/52		12 50
	3/1 - 3/31/52		12 50
		Total Annuities	37 50

Project

THE UNIVERSITY OF CHICAGO

EXPENDITURES UNDER CONTRACT NO. W-60-1-02035
FOR THE MONTH(S) OF June 1 THRU April 30 1952

1-2

DATE	QUANTITY OR P.O. No.	UNIT	CHECK NO.	DESCRIPTION OR VENDORS NAME	UNIT PRICE	AMOUNT	TOTAL	
				Purchases from Outside Vendors - each listed item supported by a certified true copy of Vendor's Invoice				
4/10/52	21693		71493	Nutritional Biochemicals Corporation				
				Total Materials & Services			52 91	
				Total amount of this invoice as shown on page 1-2			2438 71	

Task Order 38
Contract N6ori-20

Request for Renewal for the Period January 1, 1953 through December 31, 1953, Submitted by Leo Szilard, Professor of Biophysics in the Institute of Radiobiology and Biophysics of the University of Chicago, through and with the approval of Dr. Lowell T. Coggeshall, Dean of the Division of Biological Sciences.

Problem: To determine the relationships between chemical structure and mutagenic activity.

Background: In the course of the work on this project a search has been made for compounds possessing mutagenic activity without killing the organisms. We have used a device called the Chemostat which permits precise measurements of the mutation rate (see enclosed reprints). We have studied mutations in the bacterium E. coli.

The only compounds possessing the above properties that we can find are either purines or purine derivatives. No pyrimidine or pyrimidine analogues tested showed such activity.

Recently we have found that certain purine ribosides (nucleosides) possess the unusual property of reducing the mutation rate. This is the first time that any such behavior has been observed.

Significance: The discovery in our laboratory of antimutagenic activity on the part of the nucleosides offers great promise as a lead to the understanding of the nature of the mutation. Since very much is being learned in other laboratories about the metabolism of nucleic acid derivatives, these findings of ours may very well be integrated with this knowledge. This may give us for the first time an understanding of genetic phenomena at the biochemical level.

Plan: We plan to continue our search for compounds that have mutagenic activity. We will, however, expend our major effort in an attempt to understand the nature of the antimutagenic activity that we have recently found. We would like to know whether these compounds act through a simple competition with normally occurring compounds in the cell or whether there is some more deep-seated stabilization of the genetic system by the nucleosides.

Requirements: The space, general laboratory facilities, and most of the necessary special apparatus have been available to us in the Research Institutes Building of the University of Chicago. The proposed program requires, in addition to my time, that of Dr. Aaron Novick and substantial fractions of the time of a qualified research associate and a technician.

Proposed Budget:

Personnel		
Assistant Professor (A. Novick), 6/13 time	$3,000	
Secretary, part time	600	
Research assistant, 9/16 time	1,800	
		$5,400
Overhead (46% of above)		2,484
Annuity (5%, Novick)		150
Expendable Supplies (glassware, chemicals, etc.)		500
Travel		300
TOTAL		$8,834

Submitted by_____

Leo Szilard
Professor of Biophysics

THE UNIVERSITY OF CHICAGO

DATE July 18, 1952

TO Dr. Leo Szilard

DEPARTMENT Institute of Radiobiology and Biophysics

FROM W. B. Harrell

DEPARTMENT Business Manager

IN RE: Renewal Proposal
Task Order 38
Contract N6ori-20

This will confirm statements made to you concerning application for renewal of Task Order 38, Contract N6ori-20. The situation is as follows:

1. The present expiration date of Task Order 38 is, as you know, December 31, 1952.

2. Said Task Order is covered under a basic contract (N6ori-20) between the University and the Office of Naval Research.

3. Your project is one of twenty-four (24) currently covered by Task Orders under the basic contract.

4. A standard overhead rate equal to 46 per cent of direct Salaries and Wages applies uniformly to all of the Task Orders under the basic agreement.

5. The uniform overhead rate of 46 per cent of direct Salaries and Wages has also been negotiated with other divisions of the Department of Defense (Army and Air Force).

The University could not accept a different overhead rate for your Task Order without reopening the overhead rate question for all contracts the University has with the Department of Defense (Army, Navy and Air Force).

In preparing the budget to accompany the proposal for renewal of your Task Order beyond December 31, 1952, will you, therefore, please compute the overhead at 46 per cent of the estimated direct Salaries and Wages to be reimbursed under the Task Order.

When the renewal proposal is completed twelve (12) copies (including the budget) should be forwarded to this office through the Office of the Dean of the Division of the Biological Sciences (Dr. LeRoy) for transmittal to the Office of Naval Research.

Your cooperation and assistance in this respect is much appreciated.

WBH:F:ab
cc: Dr. G. V. LeRoy
Dr. T. H. Davies

February 20, 1953

Dr. Elizabeth K. Kelly
Head, Biophysic Section
Physiology Branch
Department of the Navy
Office of Naval Research
Washington 25. D.C.

Dear Mrs. Kelly,

Enclosed you will find nine copies of the semi-annual Progress Report which Dr. M. T. Jones informs us was due in January.

I wish to apologize for the delay.

Very sincerely yours,

Enclosure

Leo Szilard

LS/llt

February 26, 1953

Dr. M. T. Jones
Chicago Branch of the ONR
John Crerar Library - 10th floor
86 East Randolph Str.
Chicago, Illinois

Dear Dr. Jones,

Enclosed is a copy of our Progress Report. I have sent nine copies to Mrs. Kelly in Washington.

Very sincerely yours,

Leo Szilard

PROGRESS REPORT

Contract N6ori - 02038

Leo Szilard
Institute of Radiobiology and Biophysics
The University of Chicago

July 1, 1952 - December 31, 1952

During the period between July 1st, and December 31st, 1952 we continued our program of studying mutations in bacteria using the Chemostat to obtain precise values of mutation rates. We concentrated our attention on the study of the Anti-mutagenic action of the purine ribosides.

We had earlier found that certain purines increase the rate of mutation to bacteriophage resistance in the B strain of E coli. The methylated xanthines, caffeine and theophylline, at concentrations of about 100 mg/l increase the rate ten to twenty fold over the spontaneous rate for mutation to T5 resistance. No pyrimidines have any effect on the mutation rate, nor do any of the purines contained in nucleic acid counteract the mutagenic effect of the purines used. On the contrary adenine itself is mildly mutagenic.

We further found that we can antagonize the mutagenic effect of these purines with certain purine ribosides. Adenosine, guanosine and inosine are effective in this respect, while xanthosine has no effect. Not only do these compounds counteract the effect of the above mutagens but in addition they reduce the "spontaneous mutation rate". Although these nucleosides reverse the effect of the mutagenic purines to less than 10%, they only reduce the spontaneous rate to 40 to 50%.

We determinated what concentrations of ribosides are required to counteract the mutagenic effects of the purines. With theophylline at a concentration of 150 mg per liter the mutation rate to T5 resistance increases from its spontaneous value of 1.3×10^{-8} per bacterium per hour to a value of 11×10^{-8}. The concentration of riboside required to reduce this to one half is about 0.4 mg per liter for adenosine and 2 mg per liter for guanosine or inosine. 10 mg per liter of any of these ribosides reduces the mutagenic effect of theophylline to a point where it is no longer detectable.

A study of the precise dependence of the mutation rate on the concentrations of guanosine at a fixed concentration of theophylline has provided data that are consistent with the notion of competitive inhibition of theophylline by guanosine. However, other models can be constructed that are equally consistent.

The antagonism of the mutagenic effect of the purines by the ribosides was quite complete in every case except one. The compound tetramethyl uric acid which gives a mutation rate of 7×10^{-8} at a concentration of 150 mg per liter is only weakly antagonized; high concentrations of ribosides depress the rate only to about 5×10^{-8}.

Several purine nucleotides were tested for antimutagenic activity but in every case they are much less effective than the corresponding nucleosides. This lower effectiveness might be due to a lower permeability of the bacterial cell wall for the nucleotides.

A study of the mutagenic effect of x-rays has been started. The x-rays obtained from a cobalt source are used at a very low intensity (100r per hour) where there is no detectable killing. At this intensity

the mutagenic effect of the x-rays is similar to that of theophylline at a concentration of 150 mg per liter. However, in the case of x-rays there is no reduction in the mutation rate by even high concentrations of nucleosides.

Leo Szilard
Professor of Biophysics

PROGRESS REPORT

Contract N6ori - 02038

Leo Szilard
Institute of Radiobiology and Biophysics
The University of Chicago

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Leo Szilard
Professor of Biophysics

PHS-421(RG)
Rev. 4-51

FEDERAL SECURITY AGENCY
Public Health Service
Division of Research Grants

EXPENDITURES REPORT

Type of Report	Period (From)	Period (To)	Grant No.
Preliminary X Final	12/1/51-	11/30/52	E-144(C)

1. Amount of Grant Funds Received		7,776 00
2. Interest Earned (if any)		- 0 -
EXPENDITURES		
3. Total Expenditures covered by this report (per schedules A,B,C,D, and E attached)	6,994 03	
4. Total amount previously reported	- 0 -	
5. Total Expenditures to Date (line 3 plus line 4)		6,994 03
6. Cash Balance (line 1 minus line 5)		781 97
7. Less (Encumbrances outstanding)		
A. Personnel Salaries and Wages		
B. Travel		
C. Permanent Equipment		
D. Consumable Supplies		
E. Other	- 0 -	
8. Total Obligations Outstanding		
9. Free or Unobligated Balance (line 6 minus line 8)		781 97

I hereby certify that the foregoing report is true in all respects and that the expenditures and obligations have been made solely for the purposes set forth in the application for the grant recommended by the National Advisory Councils.

The University of Chicago — (Institution)

5801 S Ellis Avenue — (Address)

W. L. THAGGARD — (Please type name of person signing report)

Assistant Comptroller — (Title of person signing report)

AUG 5 1953 — (Date)

/s/ W. L. Thaggard — (Signature)

I hereby certify that the above expenditures and obligations listed on this report were made with my approval.

L. SLICHTER — (Investigator)

SUPPLEMENTAL SCHEDULES

A-1. Expenditures for Personnel: Salaries and Wages

Name	Position	Number of Months Employed	Amount Paid
E. Statsingn	Tech.	11/19-11/30/52	11 80
I. Marcus	Tech.	10/25-11/30/52	381 00
Howard H. Lee	Biologist	12/51-9/52	2,750 00
Hugo J. Vietoreen	Biologist	12/51 10/52	825 83
Aaron Novick	Asst. Prof.	12/51-11/52	1,987 60
Aaron Novick(annuity)	Asst. Prof.	12/51-11/52	99 32
TOTAL			6,085 55

B. Expenditures for Travel

Date	Name of Traveler and Destination	Transportation Charges	Other Travel Allowances	Total
3/29-3/30/52	~~Leo Szilard chgo to Madison~~ Wis, and returd	1726	15 60	32 86
TOTAL				32 86

C. EXPENDITURES FOR PERMANENT EQUIPMENT

Itemize All Purchases Over $10

TOTAL

D. EXPENDITURES FOR CONSUMABLE SUPPLIES

Itemize all Purchases over $5

Total of Items under $50 Ea. 299 62

TOTAL

TOTAL 29962

To be used for continuation of Item C or D (Specify)

TOTAL

E. EXPENDITURES FOR ALL OTHER (Itemize all Other Purchases)

TOTAL

F. OVERHEAD 576 00

Dr. Szilard's copy

FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

APPLICATION FOR RESEARCH GRANT

(LEAVE BLANK)

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

Date June 12, 1952

Application is hereby made for a grant in the amount of $ 7,776.00 for the period

from December (Month) 1, (Day) 1952 (Year) through November (Month) 30, (Day) 1953 (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: Study of the growth, adaptation, and mutation of bacteria and bacterial viruses, carried out with new biophysical methods

NAME OF PRINCIPAL INVESTIGATOR	TITLE OF PRINCIPAL INVESTIGATOR
Leo Szilard	Professor of Biophysics

ADDRESS OF PRINCIPAL INVESTIGATOR

Institute of Radiobiology and Biophysics
The University of Chicago, Chicago 37, Illinois

NAME OF FINANCIAL OFFICER TO WHOM CHECK SHOULD BE MAILED	TITLE OF FINANCIAL OFFICER
W. B. Harrell	Business Manager, Special Projects

ADDRESS OF FINANCIAL OFFICER

The University of Chicago
5801 Ellis Avenue, Chicago 37, Illinois

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: The University of Chicago

NAME AND TITLE OF OFFICIAL AUTHORIZED TO SIGN FOR INSTITUTION *(Please Type)*: George V. Le Roy, M. D., Associate Dean, Division of Biological Sciences

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

PHS-398
Rev. 8-51

Form Approved
Budget Bureau No. 68-R249.4

APPLICANT'S COPY

(LEAVE BLANK)

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

BUDGET PROPOSED FOR THE YEAR December 1, 1952 through November 30, 1953

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.)*		
Professor of Biophysics (L. Szilard), full time		$10,500
Assistant Professor (A. Novick), full time	$2,000	4,500
Research Assistant, full time	2,200	1,100
Research Assistant, full time	2,100	1,200
PERMANENT EQUIPMENT *(Itemize)*		
Apparatus and installation		3,000
CONSUMABLE SUPPLIES *(Itemize)*		
Glassware, chemicals, etc.	500	2,000
TRAVEL *(State purpose)*		
For exchange of information with others working on related subjects and for presenting results at other universities or research institutions.	300	300
OTHER EXPENSE *(Itemize)*		
Annuities: L. Szilard		525
A. Novick	100	225
SUBTOTAL	$7,200	
OVERHEAD	576	
TOTAL FOR THE YEAR	$7,776	$23,350

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 _____

2 _____

3 _____

4 _____

PHS-398
Rev. 8-51

Study of the growth, adaptation, and mutation of bacteria and bacterial viruses, carried out with new biophysical methods

Leo Szilard, Professor of Biophysics, Institute of Radiobiology & Biophysics
Aaron Novick, Assistant Professor, Institute of Radiobiology & Biophysics

Institute of Radiobiology and Biophysics, Division of the Biological Sciences, The University of Chicago, Chicago 37, Illinois

The study of the effect of mild chemical reagents on the mutation rate in bacteria by means of the Chemostat will be continued. Work done in the past year has shown that many purines and purine analogues have the property of increasing the mutation rate without killing the organisms. No other class of compounds tested showed this property. It is hoped that by continued study of these mutagens, some relation between the chemical properties of the various purines and their mutagenic effect may be found. During the course of this work it was discovered that certain purine derivatives have the property of being able to decrease the mutation rate. The main emphasis of the research planned for the coming year will be placed on an attempt to understand this very important phenomenon. In addition, work on the mechanism of the regulation of biosynthetic activity in bacteria will be continued.

PROGRESS REPORT

United States Public Health Service Research Grant E-144(C)

Study of the Growth, Adaptation, and Mutation of Bacteria and Bacterial Viruses, Carried Out with New Biophysical Methods

Leo Szilard
Institute of Radiobiology and Biophysics
The University of Chicago

December 1, 1950 - June 12, 1952

A. Summary Statement:

Work on this project has largely been concerned with a study of mutations in bacteria. In addition, some progress is reported on the mechanism of biosynthetic regulation in bacteria.

The work on mutations has demonstrated that the spontaneous mutations studied occur at a rate which is time dependent rather than generation dependent. In addition, a method has been developed for observing "evolution" in bacteria.

A study has been made of the effect of mild chemical reagents on the mutation rate, and it was discovered that purines and purine analogues have the property of increasing the mutation rate without killing the organisms. No other class of compounds studied displayed this character. Very recently it was discovered that certain purine derivatives have the unusual property of decreasing the mutation rate.

An attempt has been made to learn something about the nature of the regulatory mechanisms employed by a bacterium to regulate the rates of syntheses of its amino acids. This study has been largely concerned with the investigation of the rate of synthesis of a tryptophane-like substance produced by a biochemical mutant incapable of synthesizing tryptophane. The rate of formation of this compound was observed under a variety of conditions in a bacterial population growing in the Chemostat. This work was extended to include a study of the rate of arginine synthesis by a bacterium capable of synthesizing its own arginine. It was found that arginine synthesis is suppressed by an exceedingly low concentration of arginine in the medium.

B. Full Statement of Progress:

A new model of the Chemostat has been constructed and has been employed for a variety of studies. The Chemostat permits the maintenance of a population of bacteria of constant size growing at an arbitrary but fixed growth rate. All of the work has been done with the B strain of E. coli and mutants derived from it.

Bacterial mutations: In a population of bacteria in a Chemostat, mutants resistant to phage T5, for example, should increase linearly in frequency in time providing that the mutant grows at the same rate as the wild type. Such a straight line increase, when observed, furnishes from its slope the mutation rate; and at the same time, rules out selection for or against this mutant. This technique permits for the first time precision in the measurement of mutation rates. Using this method, it has been possible to show that the rate of mutation to phage T5 resistance is a constant per unit time, independent of the generation time. This rate has a value of 1.25×10^{-8}/hour/bacterium at 37° C. for a population of bacteria growing under tryptophane control. Decreasing the temperature by 10° reduces the rate about a factor 2.

In the course of these studies on mutation rates, sudden falls in the frequency of phage resistant mutants were observed. These falls, it was possible to show, resulted from the appearance of a strain by mutation that can grow faster than the original strain under the conditions prevailing in the Chemostat. This faster strain displaces the original strain and all of the phage resistant mutants accumulated in it. One Chemostat was run for 600 generations, during which some 10 "evolutionary steps" were observed.

The precision furnished by the Chemostat for the measurement of mutation rates makes possible the detection of mutagenic character on the part of mild chemical reagents--reagents that do not, like those employed in the past, kill a large fraction of the population. A large number of compounds were tested. Mutagenic activity was found only in the class of purines and purine analogues. Caffeine, a trimethylxanthine, for example, at a concentration of 150 mg/l, gives a more than 10 fold increase over the spontaneous mutation rate. Even adenine is mutagenic, but much less so than caffeine. No pyrimidine or pyrimidine analogue tested displayed any such mutagenic character.

An investigation of the purine ribosides has led to the discovery of a new phenomenon--the decrease in the mutation rate. Guanosine, inosine, and adenosine, for example, can completely eliminate the mutagenic effect of theophylline. This antimutagenic action seems to lead to a value even less than the normal spontaneous rate.

Regulatory activities: Studies were made of the manner in which a bacterium controls the rates of syntheses of the various amino acids so that no excess is produced even under conditions in which the rate of protein synthesis has been reduced by a factor of 10 through the feeding of a required amino acid at a very low concentration. This study has been concerned with the rate of production of a tryptophane-like substance by a mutant incapable of making tryptophane. This compound is produced at a constant rate, independently of the growth rate, between generation times of $3\frac{1}{2}$ hours and 14 hours. If protein synthesis is stopped by withholding tryptophane, the compound continues to be produced from ammonia and lactate at a high rate for more than 8 hours. The

bacterium can synthesize this compound at a rate four times as fast as it would have to make tryptophane if it were to grow at its maximum growth rate in the absence of tryptophane. At short generation times the compound is produced at a low rate. The rate of the production of the compound, at generation times which are long enough to permit it to proceed at full blast, increases from 25° to 37° by about a factor of 2 and decreases from 37° to 43° by about a factor of 0.75. If the generation time is switched from a low value, at which the compound is made at a low rate, to a longer generation, at which it is made at a high rate, the response in the production rate of the compound to the change in generation time appears to be immediate, i.e. if there is a lag it is less than 30 minutes. If the bacterial population in a stationary state is pouring out the compound, and if the concentration of tryptophane is suddenly raised, the production rate of the compound falls to less than one-third of its previous value, and if there is a lag it is less than 10 minutes.

Some studies on the rate of arginine synthesis by a bacterium that can synthesize arginine have shown that arginine synthesis can be suppressed by external arginine even at an exceedingly low concentration of arginine. This suppression of the rate of synthesis of an amino acid by an increased concentration of that amino acid is proposed as a possible mechanism for the regulation of the rate of amino acid synthesis.

Papers published during this period include the following:

Aaron Novick and Leo Szilard, Science 112, 715 (1950).
Aaron Novick and Leo Szilard, Proc. Nat. Acad. Sci. 36, 708 (1950).
Aaron Novick and Leo Szilard, Science 113, 34 (1951).
Aaron Novick and Leo Szilard, Cold Spring Harbor Symp. Quant. Biol. XVI, 337 (1951).
Aaron Novick and Leo Szilard, Growth, in press.

C. Significant Accomplishments:

The following facts have been established relating to a tryptophane-requiring strain of E. coli when grown with tryptophane as the controlling growth factor in the Chemostat:

1. The rate of mutations to resistance to the virus T5 has a value of about 1.25×10^{-8}/hour and does not depend on how fast the bacterium grows within the limits of a generation time of 2 hours and 12 hours.

2. There is a class of compounds which are chemically not very reactive but, when employed in low concentrations in which there is no appreciable killing, will increase the rate of mutation 3 to 17 fold. This has been established so far for the following substances: caffeine (17 - 150), theophylline (10.8 - 150), paraxanthine (8.4 - 150), theobromine (7.5 - 150), tetramethyl uric acid (7.6 - 150), 8-chloro caffeine (4.3 - 150), 8-methoxy caffeine (5.2 - 150), 8-azaguanine (3.4 - 150), adenine (5.2 - 500). The mutation rates per hour per 10^8 bacteria and the concentrations used in milligrams per liter are indicated in the brackets.

3. It was found that guanosine, adenosine, or inosine, will completely counteract the mutagenic effect of theophylline.

D. Plans for Next Year:

It is proposed to put the main emphasis on the study of the relationship of mutagenic action, antimutagenic action, and chemical constitution. In addition, we plan to continue our study of the regulation of biosynthetic processes.