ANALYSIS OF PROGRAM ACTIVITIES
NATIONAL INSTITUTES OF HEALTH
1956

NATIONAL HEART INSTITUTE

VOLUME I

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

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-87
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Pharmacodynamics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on Antiarrhythmic Drugs
PROJECT TITLE

7. Harriet M. Maling
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To screen drugs for antiarrhythmic activity.

Methods Employed: Selected drugs have been screened against petroleum ether-epinephrine induced arrhythmias in the anesthetized, vagotomized cat and against the "spontaneous" ectopic activity which is prominent in unanesthetized dogs the first day after ligation of the anterior descending coronary artery.

Major Findings: Dilantin has antiarrhythmic action in unanesthetized dogs against ventricular arrhythmia due to coronary artery ligation, but does not show artiarrhythmic action in anesthetized vagotomized cats against petroleum ether-epinephrine arrhythmias. This variability demonstrates the desirability of several types of tests.

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WIN 8568 (2-diethylaminoethyl 4-amino-2-hexoxybenzamide hydrochloride) shows antiarrhythmic activity against ligation-induced ectopic activity in a very low dose (0.32 mgm./kgm.). Antiarrhythmic activity of WIN 8568 has also been demonstrated by Grumbach (personal communication) in isolated rabbit hearts and against aconitine-induced auricular fibrillation in anesthetized dogs.

Significance to Heart Research: Two methods of testing drugs for antiarrhythmic activity have been developed. These methods can be used to determine whether new antiarrhythmic drugs deserve trial in human beings.

Proposed Course of Project: Occasional testing of drugs reported by others to have antiarrhythmic action will be done against the spontaneous ectopic activity occurring in unanesthetized dogs on the first day following coronary ligation.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-87
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,000	$2,046	$7,046	.3	.2	.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	0	0	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-87
SERIAL NUMBER

16. **LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:**

Sjoerdsma, A., Maling, H., Pratt, H.W., Axelrod, J., Kayden, H.J., and Terry, L.A. The antiarrhythmic action of Ambonestyl (2-diethylaminoethylisonicotinamide, MC-4112). New England Journal of Medicine, 255:213-216, 1956

17. **LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:**

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-28
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Pharmacology
SECTION OR SERVICE

5. Goldwater Memorial Hospital,
LOCATION (IF OTHER THAN BETHESDA)
New York, N. Y.

6. Studies with Muscular Relaxants
PROJECT TITLE

7. Bernard B. Brodie and John J. Burns
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To develop a long acting and effective muscular relaxant drug.

Methods Employed: Micro methods for drug analyzing, micro techniques for isolation of metabolites, clinical evaluation of the muscular relaxant effect of various drugs.

Major Findings: Recently Flexin (McNeil 485) has been introduced as a new drug for the treatment of multiple sclerosis, cerebral palsy, poliomyelitis and other conditions associated with peripheral muscular spasm. Studies of its physiological disposition show that the drug has one inherent disadvantage in being slowly and incompletely absorbed

when given orally. This property of Flexin explains some of the difficulty in controlling therapeutic response. Further studies have shown that the drug is metabolized in patients to a compound formed by the substitution of a hydroxyl group for the amino group in the molecule. This metabolite is as active a muscular relaxant as the parent drug and it has the added advantage of being rapidly and completely absorbed when given orally. These observations have initiated studies in several clinics to evaluate this metabolite as a new drug for the treatment of patients with spastic diseases.

Significance to HEART Research: A long acting and effective muscular relaxant drug would be of great value for the treatment of various spastic diseases.

Proposed course of project: No further study planned.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-88
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$9,300	$499	$9,799	.4	.7	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-88
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-89
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Pharmacodynamics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Relationships Among Ventricular Stroke Work, Contractile Force and Systemic Output
PROJECT TITLE

7. Marion deV. Cotten and Harriet M. Maling
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The objective of this project was to study the interrelationships which exist among the ventricular stroke work, contractile force and systemic output.

Methods Employed: The experiments were conducted in heart-lung preparations of the dog. The systemic output was measured with a Shipley-Wilson rotameter and the atrial pressures were controlled by a venous reservoir connected to the superior vena cava. The aortic resistance was controlled with a Starling resistance and the heart rate was maintained constant by keeping the temperature of the blood at 37° C. Atrial and aortic pressures were measured with electronic pressure transducers. Stroke work was calculated in the usual manner from the aortic pressures, left atrial pressures and stroke volume. The force of ventricular contraction was measured with a system of heart-levers which permitted measurements of contractile force at the initial diastolic fiber length existing at the time the measurements were made.

Major Findings: Increasing the left atrial pressure resulted in increases in the left ventricular stroke work, the left ventricular contractile force and the systemic output. There was a linear relationship between the increases in the stroke work and the increases in the contractile force, between the increases in stroke work and systemic output and between the contractile force and systemic output. Typical ventricular function curves resulted from plotting the stroke work against the atrial pressure. Increasing the aortic pressure resulted in increases in the left ventricular stroke work and contractile force which were related linearly. In the latter experiments, the systemic output diminished as the aortic pressure was elevated so that there was no linear relationship between the stroke work and systemic output or between the contractile force and the systemic output. The administration of norepinephrine produced a marked increase in the stroke work, contractile force and systemic output. As in the previous experiments in which the atrial and aortic pressures were increased, there was a linear relationship between the stroke work and contractile force. There was a linear relationship between the stroke work and systemic output and the contractile force and systemic output with norepinephrine.

Significance to HEART Research: Previously, there has been no definitive information available regarding the relationship which exists among the stroke work, contractile force and systemic output. These experiments provide such information and demonstrate that, under the conditions studied, changes in the stroke work of the heart are related linearly to concomitant changes in the ventricular contractile force while the systemic output is related linearly to these two functions only under certain circumstances.

Proposed Course of Project: These experiments are completed and no additional studies are planned.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-89
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$8,500	$3,533	$12,033	.4	.5	.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-89
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-90
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Pharmacodynamics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Comparison of Adrenergic Blocking Drugs in Inhibiting Cardiac Actions of Sympathomimetic Amines
PROJECT TITLE

7. Marion deV. Cotten
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: The objective of this project was to compare the effectiveness of five adrenergic blocking agents in inhibiting the increases in cardiac contractile force produced by epinephrine, norepinephrine and isoproterenol.

Methods Employed: The experiments were conducted in anesthetized, vagotomized dogs with intact circulatory systems. Blood pressure was measured in the usual manner with an electronic pressure transducer and the force of cardiac contraction was measured with a strain gauge arch.

Major Findings: Phentolamine and dibenzyline markedly inhibited the increases in cardiac contractile force produced by epinephrine, norepinephrine and isoproterenol. Phentolamine also produced a partial blockade of the increase in contractile force produced by electrical stimulation of the cardiac sympathetic nerve fibers. In addition to inhibiting the contractile force effects of the three sympathomimetic

amines, the phentolamine and dibenzyline also reversed the pressor response to epinephrine and virtually abolished the pressor response to norepinephrine. The blockade of the cardiac stimulant effects of the three sympathomimetic amines was not related to the development of hypotension produced by phentolamine and dibenzyline since the blockade was equally effective when the blood pressure was kept at control values by partial compression of the aorta. The blocking action also was not due to an insensitivity of the heart to all cardiac stimulant drugs since ouabain produced typical increments in cardiac contractile force after complete blockade of the cardiac stimulant effects of epinephrine, norepinephrine and isoproterenol. The blockade was also not related to a diminished effectiveness of the sympathomimetic amines with repeated injections since control experiments have shown that the responses to the amines are quantitatively unaltered with frequent repeated administrations. In contrast to the marked inhibition of the cardiac actions of the sympathomimetic amines by phentolamine and dibenzyline, three other adrenergic blocking drugs had only slight to moderate inhibiting effects. These three included hydergine, azapetine and piperoxan. The latter three blocking agents did, however, produce a reversal of the pressor response to epinephrine and a moderate reduction of the pressor response to norepinephrine.

Significance to HEART Research: Previous investigators, using isolated heart muscle preparations, had reported that the adrenergic blocking drugs did not inhibit the cardiac stimulant effects of epinephrine or norepinephrine. The present findings using intact animals show that two of these blocking drugs do effectively block the contractile force effects of epinephrine, norepinephrine and isoproterenol and illustrate the necessity for employing intact animals for such experiments.

Proposed Course of Project: The project is completed and no further experiments are planned.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-90
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$11,500	$4,835	$16,335	.3	1.2	1.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	2	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-90
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-91
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Pharmacodynamics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Contrast Between the Effects of Increased Cerebrospinal Fluid Pressure and Augmented Reflex Sympathetic Activity on the Cardiac Contractile Force
PROJECT TITLE

7. Marion deV. Cotten
PRINCIPAL INVESTIGATOR

8. Neil C. Moran
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The objective of this project was (1) to confirm results obtained previously in dogs on the effects of increased reflex sympathetic activity on the cardiac contractile force and blood pressure and (2) to compare the effects of increased reflex sympathetic activity in the cat with the effects of increased cerebrospinal fluid pressure.

Methods Employed: Anesthetized cats with intact circulatory systems were used. The force of ventricular contraction was measured with a strain gauge arch sutured directly to the ventricular muscle while the blood pressure was measured in the usual manner with an electronic pressure transducer. Increases in reflex sympathetic activity were produced by temporarily occluding the common carotid arteries and by electrically stimulating the cut central end of a sciatic nerve. Increased cerebrospinal fluid pressure was obtained by connecting a needle in the subdural space to a saline-containing pressure bottle connected to a mercury manometer.

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Major Findings: Increased reflex sympathetic activity produced a marked increase in the blood pressure with only a moderate direct increase in the cardiac contractile force. Thus, these results obtained in the cat are in agreement with similar findings in the dog. In contrast to the effects of increased reflex sympathetic activity, the administration of norepinephrine, in doses which produced increases in blood pressure comparable to those produced by reflex sympathetic stimulation, produced significantly greater direct increases in cardiac contractile force. Elevation of the cerebrospinal fluid pressure also provoked marked rises in the blood pressure associated with marked increases in the cardiac contractile force. The latter findings demonstrate that the sympathetic nervous system may be stimulated in such a fashion as to produce marked increases both in blood pressure and contractile force. In contrast, reflex sympathetic stimulation produces a marked increase in blood pressure, but only a moderate direct increase in cardiac contractile force.

Significance to HEART Research: These experiments represent an extension of a project aimed at studying the reflex control of the cardiac contractile force. There is relatively sparse information regarding the central and reflex sympathetic control of the contractility of the heart and it is anticipated that such experiments may provide data regarding these functions.

Proposed Course of Project: No additional experiments similar to those described above are planned. Other experiments will be conducted with cats along the lines described in the accompanying Individual Project Report for 1956 entitled "Reflex Control of Cardiac Contractile Force".

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-91
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,100	$2,232	$7,332	.3	.2	.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	0	0	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-91
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-92
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Pharmacodynamics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Reflex Control of Cardiac Contractile Force
PROJECT TITLE

7. Marion deV. Cotten
PRINCIPAL INVESTIGATOR

8. Neil C. Moran
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: The objective of this project was to study the extent to which reflex sympathetic nervous activity could influence the force of cardiac contraction and to compare the latter changes with concomitant changes in the blood pressure.

Methods Employed: Anesthetized dogs with intact circulatory systems were used in which direct measurements of the force of ventricular contraction were made with a strain gauge arch. Blood pressure was measured in the usual manner with an electronic pressure transducer. Changes in the size of the left ventricle were determined with a mercury-filled rubber-tube resistance attached to the left epicardial surface of the left ventricle. Increases in reflex sympathetic activity

were produced by temporary occlusion of the common carotid arteries and by electrical stimulation of the cut central ends of the vagus and sciatic nerves. Electrical stimulation of the postganglionic cardiac sympathetic fibers was also employed to compare these effects with those produced by reflex sympathetic stimulation.

Major Findings: Increased reflex sympathetic activity resulted in marked increases in the blood pressure but only moderate direct increases in the ventricular contractile force. Thus, the heart did not receive sufficient direct sympathetic stimulation during such maneuvers to allow it to operate against the increased blood pressure without moderate dilation. Administration of methoxamine, a vasoconstrictor amine lacking direct cardiac stimulant properties, produced a marked rise in blood pressure, no direct change in the contractile force and a marked increase in the size of the left ventricle. In contrast, the injection of l-norepinephrine, in doses which produced increases in contractile force comparable to those produced by reflex sympathetic stimulation, resulted in much smaller pressor responses and a small decrease in the size of the left ventricle. The latter changes indicated that sufficient direct cardiac stimulation had been supplied to allow the heart to operate against the increased blood pressure without increasing its fiber length. Larger doses of norepinephrine, which produced marked increases in cardiac contractile force and blood pressure, also produced a slight decrease in the size of the left ventricle. Electrical stimulation of the cardiac postganglionic sympathetic nerve fibers resulted in marked increases in contractile force, a small pressor response and a slight decrease in the size of the left ventricle, suggesting that the cardiac sympathetic nerve fibers are potentially capable of producing far greater increases in cardiac contractile force than are obtained following reflex sympathetic stimulation. The surgical removal of the cardiac sympathetic nerve fibers resulted in a moderate reduction in the contractile force response to reflex sympathetic stimulation while bilateral removal of the adrenal glands resulted in a more marked reduction. The concomitant removal of both the cardiac sympathetic fibers and the adrenal glands virtually abolished the moderate increase in contractile force produced by reflex sympathetic stimulation.

Significance to HEART Research: Little is known of the central and reflex sympathetic control of the cardiac contractile force. It is anticipated that experiments such as those described above will provide useful information regarding this important area of physiology.

Proposed Course of Project: These experiments will be extended to determine the mechanisms responsible for the striking disparity between the effects of increased reflex sympathetic activity on the blood pressure and cardiac contractile force. These experiments will be done in cats in which reflex sympathetic stimulation produces similar effects on the blood pressure and cardiac contractile force (see accompanying Individual Project Report for 1956 entitled "Contrast Between the Effects of Increased Cerebrospinal Fluid Pressure and Augmented Reflex Sympathetic Activity on the Contractile Force of the Heart"). The studies with cats will include: (1) Observations on the effects of direct stimulation of various areas in the brain stem to determine whether separate "centers" in the brain stem

are concerned with the control of the cardiac contractile force and blood pressure and (2) observations involving measurement of electrical activity in peripheral sympathetic nerves to compare the impulse frequency in cardiac sympathetic postganglionic nerve fibers with the impulse frequency in splanchnic postganglionic fibers before and during reflex sympathetic stimulation.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-92
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,200	$2,270	$7,470	.3	.2	.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	0	0	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-92
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-93
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Pharmacodynamics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Hypersensitivity of the Heart to Epinephrine and Norepinephrine Following Experimental Coronary Artery Occlusion in the Dog
PROJECT TITLE

7. Harriet M. Maling and Neil C. Moran
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: In the course of a study of the effects of antiarrhythmic drugs on the delayed ventricular ectopic activity in dogs following coronary artery ligation, it was noted that intravenous injections of epinephrine produced marked ventricular tachycardia, even after the arrhythmias induced by the ligation had disappeared. The present investigation is a study of the electrocardiographic responses to several selected sympathomimetic amines in unanesthetized dogs before and for several weeks after coronary artery ligation to determine the intensity of the sensitization and its time-course.

Methods Employed: The anterior descending coronary artery was ligated in anesthetized dogs, using aseptic precautions, and following the two-stage occlusion technique of Harris. Most experiments were conducted on unanesthetized dogs. Electrocardiograms were recorded, sometimes simultaneously with femoral arterial pressure. Drugs were tested by intravenous injection before and at varying times after coronary artery occlusion.

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Major Findings: Epinephrine and norepinephrine, in doses which cause little ectopic activity in unanesthetized normal dogs, produced ventricular tachycardia after coronary artery ligation. This hypersensitivity was particularly apparent about the fourth day after ligation, when the arrhythmias caused by the ligation per se had subsided, and gradually disappeared with time so that the responses were again normal 12 days after ligation. Sensitization was slightly greater for norepinephrine than for epinephrine over a wide range of doses. Observations with methoxamine, isoproterenol, methacholine, and atropine indicate that combined myocardial stimulation and vagal slowing are necessary for demonstration of this sensitization.

Significance to HEART Research: The hypersensitivity of the heart after experimental coronary artery occlusion is probably closely related to the "spontaneous" ectopic activity induced in dogs by coronary ligation per se. The duration of the hypersensitivity corresponds closely with the clinical observation that the first two weeks following myocardial infarction in man is the most likely period for the development of paroxysmal ventricular tachycardia. The sensitization to norepinephrine suggests a possible risk of inducing arrhythmias by the use of large doses of norepinephrine in the treatment of shock resulting from myocardial infarction in man.

Proposed Course of Research: Experiments are now in progress on anesthetized normal dogs and on anesthetized dogs 4 days after coronary artery occlusion to clarify the role of the vagus in these sensitized responses. During peripheral vagal stimulation in anesthetized dogs, it is possible to demonstrate sensitization to isoproterenol after coronary artery ligation. This sensitization to isoproterenol is impossible to demonstrate in unanesthetized dogs because of the marked sinus acceleration after the drug.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-93
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,300	$2,603	$8,903	.4	.2	.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-93
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Maling, Harriet M., and Neil C. Moran. Hypersensitivity of the Heart to Epinephrine and Norepinephrine Following Experimental Coronary Artery Occlusion, submitted to Circulation Research.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-94
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Pharmacodynamics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Hypersensitivity of Heart to Small Doses of Norepinephrine Following Large Intravenous Injections of Norepinephrine
PROJECT TITLE

7. Harriet M. Maling
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: These experiments have demonstrated a sensitization of the heart to small doses of norepinephrine for several days following the intravenous administration of large doses of norepinephrine to unanesthetized dogs. The present study is an investigation of the conditions necessary for the production of this sensitization, to determine the intensity and the duration of the sensitization and to correlate the sensitization, if possible, with changes in the myocardial concentration of catechol amines and with histological changes.

Methods Employed: The sedimentation rate and the electrocardiographic responses to small test doses of norepinephrine are determined in unanesthetized dogs on a number of days before and after the intravenous administration of large doses of norepinephrine.

NHI-94
SERIAL NO.

Major Findings: The intravenous injection of a large dose of norepinephrine (6 micromoles/kgm. or approximately 1 mgm./kgm., administered either in 6 doses of 1 micromole/kgm. each, 15 minutes apart, or by continuous infusion over a period of 75 minutes) is followed by a period of sensitization to small test doses of norepinephrine. This sensitization continues for several days. During this period of sensitization, doses of norepinephrine which cause little ectopic activity before the administration of the large dose produce marked ventricular tachycardia.

Significance to Heart Research: The sensitization to norepinephrine produced by large doses of norepinephrine resembles the hypersensitivity of the heart to small doses of norepinephrine after experimental coronary artery occlusion. The drug-induced sensitization supports the hypothesis that the ligation-induced sensitization may possibly be the result of the release of catechol amines from the damaged myocardium with subsequent absorption by the adjacent normal cells. Determinations of myocardial concentrations of catechol amines will test this hypothesis further.

Proposed Course of Research: The investigators hope to collaborate with Dr. Parkhurst Shore in correlating this sensitization with changes, if any, in the myocardial concentration of catechol amines. The myocardial concentration of epinephrine and norepinephrine will be determined in normal dogs, and in dogs one, two, three, and four days after continuous infusion of a large dose of norepinephrine. The electrocardiographic responses to small test doses of norepinephrine will be determined immediately before sacrifice of each dog, as an indicator of the intensity of sensitization, if any, at that time.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-94
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,000	$1,726	$5,726	.2	.2	.4

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	0	0	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-94
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-95
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The Preparation of Compounds with Anti-Digitalis Activity
PROJECT TITLE

7. Elwood O. Titus
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: Some biological evidence suggests that cardiac lactones hydroxylated in the 17 position might act as antagonists to digitalis-like steroids. An effort is being made to prepare these.

Methods Employed: Microbiological hydroxylation of known steroids. Idehtification of products by conventional chemical degradation.

Major Findings: A method for the detection of 17-hydroxylated cardiac aglycones was desired. Cephalothesium roseum, a mold, can hydroxylate cardiac aglycones at carbon 17 and several other positions. Preliminary oxidation of the hydroxyl group at carbon 3 may be a necessary prerequisite for hydroxylation. The 17 hydroxy derivative retained very slight digitalis-like activity in the frog heart.

Significance to HEART Research: Although no compounds are known specifically to antagonize the effects of digitalis on heart muscle, such substances would be of interest in theoretical studies of the mechanism of action of the cardiac steroids. They should be of use in both the diagnosis and treatment of digitalis intoxication.

Proposed Course of Project: Since 17-hydroxylation did not cause any apparent qualitative changes in activity, the project was abandoned.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-95
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,000	$3,523	$10,523	.3	.5	.8

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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(Attachment I)

Calendar Year 1956

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-95
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. CRP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-96
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on Reserpine-Induced Hyperglycemia and Release of Adrenal Catechol Amines
PROJECT TITLE

7. Parkhurst A. Shore
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To determine reserpine-induced effects on blood sugar, epinephrine release and the mechanisms involved.

Methods Employed: The effect of reserpine and other drugs on blood glucose levels and release of catechol amines from the adrenal glands is studied.

Major Findings: It has been shown that the hyperglycemia following reserpine is a result of a centrally induced release of catechol amines from adrenal glands. Thus, the release is blocked by adrenalectomy but not by hypophysectomy. Furthermore, the hyperglycemia

may be blocked by a ganglionic blocking agent, hexamethonium, or by the adrenergic blocking agents ergotamine and dihydroergotamine. Direct analysis of adrenal glands of rabbits has shown that complete depletion of the catechol amine content occurs following large doses of reserpine. This is not a direct effect of reserpine on the adrenals as spinal transection blocks the release. It has been found that of the Rauwolfia alkaloids only the tranquilizing alkaloids effect epinephrine release and hyperglycemia. Chlorpromazine had no effect.

Significance to HEART Research: This study is of significance in the further understanding of the action of reserpine, a drug used for control of hypertension and also of some mental diseases.

Proposed Course of Project: It is planned to investigate possible mechanisms whereby reserpine, which causes a marked parasympathetic predominance, also causes sympathetic hyperactivity as reflected in centrally mediated activation of the adrenal medulla.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-96
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$12,000	$5,990	$17,990	.3	1.3	1.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-96
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Taketomo, Y., Shore, P. A., Tomich, E. G., Kuntzman, R., and Brodie, B. Studies on the Mechanism of Reserpine-Induced Epinephrine Release and Hyperglycemia, Journal of Pharmacology and Experimental Therapeutics, to be published.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-97
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on Central Autonomic Integrations
PROJECT TITLE

7. Donald F. Bogdanski
PRINCIPAL INVESTIGATOR

8. Sidney Spector
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: To study the functions of substances found in the central nervous system as possible neurohumoral agents. Also to determine whether drugs affecting the autonomic nervous system and its effectors do so by a central or peripheral site of action.

Methods Employed: Various objective peripheral autonomic functions were measured in animals before and after spinal section, and administration of ganglionic blocking agents. Stimulating agents were studied under those conditions. Peripheral sites of action were eliminated as sites of action of depressants.

Major Findings: Cocaine was found to cause sympathetic hyperactivity largely by a central action. Chlorpromazine was found to inhibit cocaine and produce sympathetic hypoactivity largely by a central action.

NHI-97
Serial Number

Significance to HEART Research: Provides basic information on drugs affecting the autonomic nervous system.

Proposed Course of Project: The studies described will be continued. Attempts will be made to find drugs which act by releasing certain possible neurohumoral agents in the central nervous system, to determine the functions of such agents and to modify their actions. Actions of additional sympathomimetic agents, such as ephedrine and detroamphetamine will be investigated in relation to their central actions, and their ability to potentiate sympathetic amine peripherally.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-97
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$23,000	$11,557	$34,557	2.0	0	2.0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	0	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-97
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-98
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Physiologic Disposition and Fate of Reserpine
PROJECT TITLE

7. Sidney M. Hess
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: Reserpine is of considerable importance in medicine as a tranquilizing and a hypotensive agent, and in physiology as a tool in elucidating the role of serotonin in the central autonomic nervous system. It is the purpose of this study to determine the fate of administered reserpine.

Methods Employed: Fluorescent methods of analysis have been developed for this problem. Reserpine is a hit and run drug, its action persisting long after it has disappeared.

Major Findings: Reserpine is metabolized differently in various animal species. For instance, rabbits do not hydrolyze reserpine readily, yet

guinea pigs are able to hydrolyze the drug with facility. The mechanism in rabbits is so far unknown.

Among the compounds isolated after administering reserpine to guinea pigs are methyl reserpate, which has been fully identified, and reserpic acid, which has been indicated.

Significance to HEART Research: The elucidation of the action of this hypotensive and tranquilizing drug improves our ability to understand and treat hypertension and mental disease.

Proposed Course of Project: Efforts to learn how reserpine is handled after administration to animals and to humans are continuing. Studies to determine how reserpine enters the brain, how long it or its metabolites persist in the body, and how it is finally eliminated from the body will be investigated.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-98
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$12,500	$6,272	$18,772	1.0	0	1.0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-98
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Hess, Sidney M., Shore, Parkhurst A., and Brodie, Bernard B. Persistence of Reserpine Action After the Disappearance of Drug from Brain: Effect on Serotonin. Journal of Pharmacology and Experimental Therapeutics 118:84, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-99
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Pharmacological Studies on the Interrelationship Between the Cholinergic and Adrenergic Nervous Systems
PROJECT TITLE

7. Neil C. Moran
PRINCIPAL INVESTIGATOR

8. ---
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: To study hitherto unrecognized interrelationships between the adrenergic (sympathetic) and cholinergic (parasympathetic) nervous systems by pharmacological and physiological means.

Methods Employed: Standard physiological techniques for recording blood pressure, blood flow, cardiac contractile force, etc., in animals.

NHI-99
Serial Number

Major Findings: Pilocarpine and other cholinergic drugs inhibit the vasodepressor actions of acetylcholine and isoproterenol (an adrenergic drug), and inhibit the positive isotropic and chronotropic actions of isoproterenol and epinephrine.

Adrenergic blocking drugs (phentolamine, azapetine and dibenzyline) inhibit the hypersalivation induced by pilocarpine and antagonize the inhibitory effect of pilocarpine on the vasodepressor effects of acetylcholine and isoproterenol and on the positive inotropic and chronotropic actions of epinephrine and isoproterenol. This antagonism appears to be competitive in nature.

Significance to HEART Research: The discovery of a more intimate interrelationship between cholinergic and adrenergic systems is important to our knowledge to the autonomic nervous system and of the autonomic control of the cardiovascular system.

Proposed Course of Project: Completed at NHI. To be pursued by senior investigator at Emory University.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-99
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$3,500	$1,488	$4,988	.1	.3	.4

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	0	0	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-99
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-100
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Isolation of Cardiotonic Substances from Mammalian Tissues
PROJECT TITLE

7. Elwood Titus, Stephen Hajdu, Herbert Weiss
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The isolation and characterization of cardiotonic substances occurring in animal tissues.

Methods Employed: Counter-current distribution, column and paper chromatography for isolation. Bioassays using effects on the Bowditch staircase phenomenon in the isolated frog ventricle.

Major Findings: Evidence for the existence of three cardiotonic substances in various mammalian tissues has been obtained in this and other laboratories. The most abundant of these, a factor occurring in the adrenal medulla, has been isolated and characterized as β-palmitoyl

glyceryl phosphoryl choline (palmitoyl lysolecithin). Similar active material from beef heart appears to contain an unsaturated acid, probably linoleic, in place of the palmitic. In the frog heart these substances are about 1/20 - 1/60th as active as the digitalis steroids. The lysolecithins occur very largely as bound forms in which the hydroxyl of the α position of the glycerol is joined by a hemiacetal linkage to a long chain aldehyde. These substances, although inactive in the frog heart, are very rapidly converted to the active form by traces of acid.

Significance to HEART Research: The lysolecithins of mammalian tissue may affect the permeability of cell membranes to cations in a manner similar to that of the digitalis steroids. Either these substances or the as yet unidentified cardiotonic factors may serve as hormones normally involved in control of heart action.

Progress [illegible] cardiotonic principles [illegible] mammalian preparations [illegible] principles will be [illegible].

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-100
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$14,000	$7,047	$21,047	1.2	0	1.2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-100
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

The Isolation of a Cardiac Active Principle from Mammalian Tissue. Elwood Titus, Herbert Weiss and Stephen Hajdu. Science, in press.

The Isolation of a Cardiac Active Principle from Mammalian Tissue. Stephen Hajdu, Herbert Weiss and Elwood Titus. Journal of Pharmacology and Experimental Therapeutics, in press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-101
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Application of Spectrophotofluorometric Assay
PROJECT TITLE

7. Bernard B. Brodie
PRINCIPAL INVESTIGATOR

8. Daniel Duggan, Robert Bowman
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To explore in a general way, the applicability of spectrophotofluorometry to biochemical and pharmacological problems.

Methods Employed: ---

Major Findings: A survey of pure samples of light-absorbing compounds of biochemical or pharmacological importance revealed fluorescence of sufficient intensity as to be utilized for their determination in tissues in the case of the majority of compounds screened. Quantitative procedures for tryptophan, tyrosine and tocopherol have been developed.

Significance to HEART Research: This technique provides the necessary sensitivity required in certain assays employed in cardiovascular studies.

Proposed Course of Project: The exploratory program as outlined above is essentially concluded. Further study will be directed toward the application of spectrophotofluorometry to specific analytical problems.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-101
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$14,400	$7,188	$21,588	1.2	0	1.2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. Daniel Duggan, Fellow, American Instrument Co.

Dr. Robert Bowman, Laboratory of Technical Development

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-101
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

The Spectrophotofluorometric Determination of Tryptophan in Plasma and of Tryptophan and Tyrosine in Protein Hydrolysates. D. E. Duggan and S. Udenfriend. Journal of Biological Chemistry, 223: 313, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

Form No. ORP-1
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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-102
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The Effect of Various Dietary Factors on Microsomal Drug Metabolism
PROJECT TITLE

7. Dr. B.B. Brodie, Dr. Bert N. La Du, Jr.
PRINCIPAL INVESTIGATOR

8. Dr. James R. Gillette
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: Preliminary results have shown that animals which have been starved or have a vitamin C deficiency metabolize drugs and other foreign compounds at a slower rate than normally well fed animals. Since the rate of metabolism of a drug affects its duration of action, it is important to determine how various dietary factors affect the microsomal drug enzyme systems.

Methods Employed: Liver microsomes have been obtained from vitamin C deficient guinea pigs, pair-fed controls and well fed controls. The activities of the various microsomal drug enzyme systems have been compared.

NHI-102
Serial Number

Major Findings: The activity of the ether cleavage enzyme system (p-methoxyacetanilide) of ascorbic acid deficient guinea pigs is lower than in the fed controls. The deficient guinea pigs showed both a decrease in the amount of microsomal protein and a decrease in the specific activity (activity/mg. microsomal protein) of the enzyme system. The pair fed controls also showed a decrease in microsomal protein, but no decrease in specific activity. Therefore, the decrease in the activity of ascorbic acid deficient guinea pigs cannot be explained entirely by a decrease in food intake.

Guinea pigs starved for 48 hours formerly fed a laboratory animal diet (feed A, B and B), results in a decrease in the activity of the microsomal ether cleavage enzyme system and to a lesser extent in the hydroxylation and dealkylation enzyme systems. The reasons for this decrease in activity, induced by this short fast, will be investigated.

Significance to HEART Research: It has been reported that some patients vary widely from the normal as to their sensitivity toward certain drugs. Some of these anomalies may be due to differences in the rates of drug metabolism. This study should help us to understand some of the general factors which affect the activity of the drug enzyme systems.

Proposed Course of Project: The effects of other nutritional deficiencies on the rate of drug metabolism will be studied. Whether or not D-ascorbic acid, as well as L-ascorbic acid, can reverse the effects of ascorbic acid deficiency will be determined. The study of the effect of acute fasting on drug metabolism will be continued.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-102
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,300	$5,144	$15,444	.6	.5	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NBI-1[illegible]
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-103
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Tyrosine Oxidation
PROJECT TITLE

7. Dr. Bert N. La Du, Jr.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: In the oxidation of tyrosine in liver vitamin C is required to hydroxylate one of the intermediary compounds, p-hydroxyphenylpyruvic acid. The role of vitamin C and the mechanism by which the hydroxyl group is introduced into the aromatic ring have not been established.

Methods Employed: The enzyme system catalyzing this hydroxylation reaction has been obtained in a soluble state from dog and rat liver and has been purified by salt and organic solvent fractionation. The reaction has been followed by chemical, manometric and spectrophotometric techniques.

Major Findings: The hydroxylation of p-hydroxyphenylpyruvic acid requires two protein fractions and ascorbic acid. The exact role of each protein

fraction is not known, but one has been identified as catalase. L-ascorbic acid can be replaced by several other compounds having about the same redox potential, such as D-ascorbic acid, hydroquinone and 2,6-dichlorophenol-indophenol dye. These compounds are all required in their reduced form, presumably to reduce a component in one of the enzymes.

Significance to HEART Research: Hydroxylation is a reaction of general importance; the biosynthesis of tyrosine, "dopa," adrenaline, and thyroxine, for example, requires this type of reaction. The hydroxylation of p-hydroxyphenylpyruvic acid to homogentisic acid is a convenient system to use to study biochemical hydroxylation. The fact that vitamin C is required in this reaction is of further interest since a study can also be made of how this vitamin functions in a specific biochemical process.

Proposed Course of Project: Continued studies will require further purification of the enzyme systems involved and localizing the position of ascorbic acid in the reaction.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NEI-103
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$9,000	$4,510	$13,510	.3	.8	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-103
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

La Du, B.N., and Zannoni, V.G. A Requirement for Catalase in Tyrosine Metabolism: The Oxidation of p-Hydroxyphenylpyruvic Acid to Homogentisic Acid, Nature 177:574, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

(Attachment 1)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-104
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Model Enzyme Systems in the Study of Drug Metabolism
PROJECT TITLE

7. Dr. Bert N. La Du, Jr.
PRINCIPAL INVESTIGATOR

8. Dr. James Gillette
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: Many drugs are oxidized by liver microsomes in the presence of TPNH and oxygen. The mechanism of these oxidations is still unknown, but peroxide may be involved. Some of these drugs can be oxidized to the same products by model catalysts and a study of these model systems may help our understanding of the microsomal enzyme systems.

Methods Employed: Drug metabolism is being studied using various model systems and these reactions compared with the liver microsomal systems. The products are measured by specific microchemical methods.

Major Findings: Various alkylamine drugs which are dealkylated by liver microsomes are also dealkylated by hemoglobin or cytochrome c in the presence of H_2O_2.* Normally occurring alkylamines, such as sarcosine or choline are not dealkylated by these systems.

*hematin and $FeCl_3$

Further studies are in progress with the other types of drug metabolism using simple model catalysts.

Significance to HEART Research: Most drugs are extensively metabolized in the body and their pharmacologic effectiveness depends upon how effectively these detoxication mechanisms operate. A study of these model systems may help us learn more about the mechanism of the liver detoxication enzyme systems.

Proposed Course of Project: During the coming year various other catalysts will be tested with drug substrates and the mechanism of these reactions will be determined.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-104
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,600	$3,312	$9,912	.3	.6	.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-104
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-105
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Microsomal Drug Enzymes - Mechanism of Action
PROJECT TITLE

7. Bernard B. Brodie and Bert N. La Du, Jr.
PRINCIPAL INVESTIGATOR

8. James Gillette
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: To establish how various types of drugs are metabolized in the body and whether specific detoxication mechanisms exist.

Methods Employed: Drug metabolism pathways are studied in vivo and in vitro and enzyme systems catalyzing these reactions are studied in detail. Metabolic products are measured by specific microchemical methods.

Major Findings: Many drugs are metabolized by liver microsomes and require TPNH and oxygen. A study of these requirements has shown

that microsomes contain a TPNH oxidase which yields peroxide. The participation of TPNH oxidase in drug metabolism is indicated since compounds which inhibit TPNH oxidase also inhibit drug metabolism. The possibility that the drug enzymes are a series of peroxidases is unlikely since enzymatically generated peroxide cannot replace TPNH.

Significance to HEART Research: Most drugs are extensively metabolized in the body and their pharmacologic effectiveness depends in part on how effectively these detoxication mechanisms operate. Understanding these mechanisms may be helpful in developing new drugs of longer or shorter duration. Since the detoxication mechanisms vary in different animal species, the observed differences in toxicity and response to drugs in different species may now be explained on a biochemical level.

Proposed Course of Project: During the coming year several problems to be investigated are: (1) How many types of drug metabolism are present in liver microsomes, (2) are these special mechanisms for drugs and foreign compounds, and (3) how do they operate (mechanism)?

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-105
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,200	$3,594	$10,794	.6	0	.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-105
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

The Oxidation of Drugs by Liver Microsomes: On the Role of TPNH and Oxygen. J. R. Gillette, B. B. Brodie, and B. N. La Du. Journal of Pharmacology and Experimental Therapeutics, in press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-106
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Pharmacology
SECTION OR SERVICE

5. Goldwater Memorial Hospital,
New York, New York
LOCATION (IF OTHER THAN BETHESDA)

6. Studies with Intravenous Anesthetics
PROJECT TITLE

7. Bernard B. Brodie and J. J. Burns
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: A study of the physiologic disposition and intermediary metabolism of various barbiturates is intended to derive fundamental information concerning the pharmacology of intravenous anesthetics and to provide direction for the development of better intravenous anesthetics. There is a need for a potent intravenous anesthetic which may be used in surgical procedures of long duration. In this respect, an effort is being made to find a nonbarbiturate anesthetic since it has become clear that barbiturates as a class are slowly metabolized and exert a hypnotic and not a truly anesthetic action.

NHI-106
SERIAL NO.

Methods Employed: Chemical assay of drugs and their metabolites in blood and tissues.

Major Findings: Previously we reported that the rapid onset of action of thiopental in anesthesia is due to the speed with which the drug passes into the brain. In fact, the only barrier appears to be the rate of cerebral blood flow. It has now been found that other intravenous anesthetics used in the operating room including Evipal, Surital, Kemithal, Dolitrone and N-Methyl Thiopental also owe their rapid onset of action to rapid penetration into the brain. These anesthetics all have a high degree of fat solubility which apparently accounts for their rapid passage into the brain, and determine their ultra short-acting properties in anesthesia due to their extensive localization in body fat.

Significance to HEART Research: The action of anesthetics on the cardiovascular system in some instances is responsible for their toxicity. Better and safer anesthetics are therefore being sought.

Proposed Course of Project: Further studies are planned to relate plasma levels of thiopental to electric activity of the brain as measured by EEG pattern. Preliminary results show that no correlation exists, presumably due to development of acute tolerance. These findings are of considerable interest because they may afford an experimental procedure to study this phenomenon of importance to anesthetic agents in general.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-106
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,000	$309	$6,309	.4	.2	.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Drs. E. M. Papper and L. Mark, Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, and New York University Research Service, Goldwater Memorial Hospital.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-106
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Clinical Application of Studies on the Physiologic Disposition of Thiopental. L. C. Mark, J. J. Burns, B. B. Brodie, and E. M. Papper. N. Y. State Journal of Medicine, 56: 2819-2822, 1956.

The Passage of Thiopental into the Brain. L. C. Mark, J. J. Burns, C. I. Campomanes, S. H. Ngai, N. Trousof, E. M. Papper and B. B. Brodie. Journal of Pharmacology and Experimental Therapeutics, in press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-107
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Comparative Biochemistry of Drug Metabolism
PROJECT TITLE

7. Dr. Bernard B. Brodie
PRINCIPAL INVESTIGATOR

8. Dr. Leo E. Gaudette
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To investigate the specificity of enzyme systems responsible for the metabolism of a variety of foreign alkylamine compounds and their differentiation from the systems by which normally occurring alkylamines are metabolized.

Methods Employed: Isolation of particulate cell fractions by the method of Schneider and Hogeboom from various animal tissues. The oxidation of various alkylamine compounds was determined by measuring substrate or product by specific chemical methods.

NHI-107
Serial Number

Major Findings: The lack of specificity of dealkylation of foreign compounds observed in mammalian liver microsomes may in part be explained by the presence of more than one enzyme. There are at least two dealkylating enzymes having the same requirements, active on a wide spectrum of alkylamine compounds, only one of which is sensitive to inhibition by SKF 525-A.

A study of the distribution of the microsomal enzyme systems for oxidative dealkylation of drugs in various species of the phylogenetic scale indicates that the dealkylation systems first appear to any appreciable extent in lower forms of terrestrial life, with more efficient oxidation occurring in higher forms. In aquatic species, such as fish, frog and salamander, a mechanism of excretion exists, and the foreign compounds studied were excreted unchanged.

The close association between the development of oxidative systems for the metabolism of foreign compounds and the needs of species for systems of water retention; as well as the fact that the oxidative systems cannot be associated with normally occurring compounds, suggests the evolutionary development of detoxication, non-specific in character, for rendering water-soluble compounds which would otherwise be toxic to the species.

Significance to HEART Research: The accumulating evidence would suggest the presence in the body of oxidative systems evolved for the purpose of species preservation. A better understanding in the use of drugs can be obtained in knowing the character and specificity of a system evolved for its detoxication.

Proposed Course of Project: The distribution of other microsomal enzyme systems, such as side-chain oxidation, hydroxylation and ether cleavage will be sought in various species of the phylogenetic scale, and other mechanisms of detoxication will be investigated in species failing to demonstrate dealkylation and other oxidative processes associated with mammalian liver microsomes. Consideration will be given to the presence of detoxication systems in species which undergo metamorphosis, giving rise to a change from an aquatic to a terrestrial existence, as in the toad, for example.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-107
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$13,300	$6,695	$19,995	1.1	0	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-107
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. CRP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-108
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Pharmacodynamics
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on Length-Tension Curves for Cardiac Muscle *in vivo*
PROJECT TITLE

7. Marion deV. Cotten
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The objective of this project is to determine whether length-tension curves for cardiac ventricular muscle in vivo may possibly serve as a measure of the functional state of cardiac muscle under various conditions.

Methods Employed: The experiments were conducted in anesthetized dogs with intact nervous and circulatory systems. The blood pressure was measured in the usual manner with an electronic pressure transducer. Length-tension curves for both the right and left ventricle were obtained by progressively stretching the segment of muscle directly between the two points of attachment of a strain gauge arch.

Major Findings: Increasing the initial length of ventricular muscle in small increments results in a progressive increase in contractile force until lengths of between 40-60 per cent above the control initial length have been attained. Stretching the muscle segment beyond these limits results in a progressive

decline in the contractile force. These length-tension curves are considered to represent another expression of Starling's Law of the heart. Stretching muscle segments in four or more areas of the ventricular muscle gave a series of length-tension curves with similar contours, but which showed moderate quantitative differences in height. These quantitative variations indicated that the use of length-tension curves as a measure of the function state of cardiac muscle can only be of value when the responsiveness of the muscle is markedly altered. Temporary occlusion of a coronary artery supplying the area of heart muscle under test resulted in the expected development of cyanosis and localized systolic bulging of the affected muscle. Progressive stretching of such ischemic muscle did not result in an increase in contractile force and, therefore, the length-tension curve was essentially flat. Restoration of the blood supply within thirty minutes following occlusion resulted in a return to a "normal" length-tension curve.

Significance to HEART Research: Previously, it has been necessaryto infer the functional state of cardiac muscle from its ability to operate against various stress loads. However, the function of the heart under conditions such as stenosis of an outflow tract may not present a reliable picture of the actual state of the myocardium. It is anticipated that measurement of length-tension curves for ventricular muscle may provide a more direct method for assessing the functional state of cardiac muscle under various abnormal circulatory states.

Proposed Course of Project: Additional experiments will be conducted to determine whether cardiac muscle is altered sufficiently under various abnormal circulatory states to be detected from changes in length-tension curves. These conditions will include coronary artery constriction, hyperthyroidism, acute and chronic anemia and heart failure produced both in the intact dog by pulmonary stenosis and in the heart-lung preparation of the dog.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-103
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$3,800	$1,675	$5,475	.2	.2	.4

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	0	0	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-108
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-109
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Pharmacodynamics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on the Pharmacology of Alkaloids Derived from Ormosia Panamensis
PROJECT TITLE

7. Gertrude P. Quinn and Neil C. Moran
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: Previous studies have shown that oxypanamine, an N-oxide, formerly referred to as NHI-196, is a potent hypotensive agent in animals. The pharmacological actions and mechanism of action have been described by Moran, et al. During the course of study, panamine was found to be a neuromuscular and ganglionic blocking agent and this action was attributed to the presence of the N-oxide in the molecule. During the interval covered in this report, the study concerned with a characterization of oxypanamine as a neuromuscular and ganglionic blocking agent has been completed. Preliminary studies were made on the actions of the parent alkaloid, panamine, N-methyl panamine and the air oxidation product of N-methyl panamine. Their

actions were compared to those of oxypanamine, the air oxidation product of panamine.

Methods Employed: Conventional physiological techniques for recording blood pressure, respiration and neuromuscular and ganglionic transmission were employed. The rabbit head-drop assay was used as a further measure of neuromuscular blockade.

Major Findings: In doses far exceeding the hypotensive dose, oxypanamine has been shown to be a neuromuscular and ganglionic blocking agent in both cats and dogs. The mechanism of action of the neuromuscular blockade was demonstrated to be essentially similar to that of d-tubocurarine; i.e., a competitive inhibition of acetylcholine at the myoneural junction.

The rabbit head-drop assay was used to compare the relative potencies of several derivatives of panamine. No effect was produced with 50 mgm/kgm panamine whereas 1 mgm/kgm of its N-oxide, oxypanamine, produced rabbit head-drop. The head-drop was produced with 22 mgm/kgm N-methyl panamine and 1 mgm/kgm of the air oxidation product of N-methyl panamine.

The cardiovascular actions of the air oxidation product of N-methyl panamine in a dog were similar to those described for oxypanamine and the effective doses were equivalent. Neither panamine nor N-methyl panamine exhibited the cardiovascular actions of their N-oxide derivatives.

There is some evidence to suggest that oxypanamine causes respiratory paralysis by a depression of the respiratory center as well as by neuromuscular blockade.

Significance to HEART Research: Oxypanamine has been shown to be a potent hypotensive agent in animals. The pharmacological properties, the toxicity and mechanism of action have been extensively studied in this and previous research periods. Preliminary studies were made with some derivatives of panamine. These compounds have been found either to be inactive or similar in action to oxypanamine and therefore are probably of no therapeutic value. All the pharmacological actions of oxypanamine may possibly be attributed to the presence of the N-oxide in the molecule. Studies with these drugs have been discontinued.

Proposed Course of Project: The project has been completed and terminated.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 109
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$12,600	$5,207	$17,807	.4	1.2	1.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Laboratory of Chemistry of Natural Products, NHI-77

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-109
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Manuscript in preparation.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-110
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Pharmacology
SECTION OR SERVICE

5. Goldwater Memorial Hospital, N.Y., N.Y.
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on Anti-Rheumatic Drugs
PROJECT TITLE

7. Bernard B. Brodie and John J. Burns
PRINCIPAL INVESTIGATOR

8. Peter G. Dayton
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: Screening of non-steroidal, anti-inflammatory agents in man.

Methods Employed: Micro methods for drug analysis, micro techniques for isolation of metabolites, clinical evaluation of the anti-rheumatic effects of various drugs.

Major Findings: Up to the present 35 analogs of Butazolidin have been studied in respect to their physiological disposition, their anti-rheumatic properties in acute gout and rheumatoid arthritis and their effect on urinary excretion of sodium and uric acid. Results obtained so far give us an idea of what structural features are required in the molecule for the various pharmacological actions of Butazolidin. For instance, introduction of a hydroxyl group in the meta position of one of the benzene rings robs the compound of sodium retention but preserves its anti-rheumatic activity. This is of importance since it

offers the possibility of eliminating one of the more disturbing side effects of Butazolidin. In addition, it has been found that any change in chemical structure which enhances the acidity of the Butazolidin molecule increases uricosuria (urinary excretior of uric acid). This observation aids us not only in screening drugs for the treatment of gout, but it gives us a possible clue to the mechanism of uricosuria. This investigation has, so far, uncovered the most potent uricosuric agent yet described, a sulfoxide analogue of Butazolidin. The compound is so effective that it produces significant uricosuria in gouty subjects in daily doses of as little as 200 mg. Studies are now underway to evaluate it as a potential new drug for the treatment of gout.

Significance to HEART Research: A suitable non-steroidal anti-rheumatic agent would be of value not only in the treatment of rheumatoid arthritis, gout, etc., but also in the treatment of rheumatic fever.

Proposed Course of Project: Work will be continued with our series of Butazolidin derivatives prepared for us by the Geigy Laboratory. Particular attention will be directed to those compounds which have changes in the pyrazolone ring of the parent drug. Studies will be carried out to confirm the relationship of pK to uricosuric effect presented in this report. The evaluation of the sulfoxide metabolite of G-25671 as a uricosuric agent for the treatment of chronic gout will be continued.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-110
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,500	$571	$11,071	.9	0	.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. J. Murray Steele and Dr. Lawrence Berger of the New York University Research Service, Goldwater Memorial Hospital and Dr. Alexander B. Gutman and Dr. T. F. Yü, Mt. Sinai Hospital, New York, N.Y.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-110
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Brodie, B.B., Burns, J.J., Yü, T.F. and Gutman, A.B. Isolation, Identification and Physiological Effects of Phenylbutazone Metabolites. Proc. of the Third European Rheumatism Congress, in press.

Yü, T.F., Paton, B.C., Chenkin, T., Burns, J.J., Brodie, B.B. and Gutman, A.B. Effect of a Phenylbutazone Analog (4-(phenylthioethyl)-1,2-diphenyl 3,5-pyrazolidinedione) on Urate Clearance and Other Discrete Renal Functions in Gouty Subjects. Evaluation as Uricosuric Agent. J. Clin. Invest., 35:374-385, 1956.

Burns, J.J., Yü, T.F., Ritterband, A., Perel, J.M., Gutman, A.B. and Brodie, B.B. A Potent New Uricosuric Agent, the Sulfoxide Metabolite of the Phenylbutazone Analogue, G-25671. J. Pharm. and Exper. Therap., in press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-111
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Pharmacodynamics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Reversal of the Cardiac Effects of Epinephrine by Ouabain During Hypothermia
PROJECT TITLE

7. Marion deV. Cotten and Theodore Cooper
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The objective of this project was to study the effectiveness of cardiac stimulant drugs during hypothermia and to compare these effects with those produced at normal body temperature.

Methods Employed: The experiments were conducted in anesthetized dogs with intact nervous and circulatory systems. Blood pressure was measured in the usual manner with an electronic pressure transducer and cardiac contractile force was measured with a strain gauge arch. Total body cooling was accomplished by packing the animals in ice.

NHI-111
SERIAL NO.

Major Findings: The administratio of epinephrine, norepinephrine and isoproterenol produces substantial inc ements in cardiac contractile force at normal body temperature and at a bo r temperature of 30° C. Similarly, the digitalis glycosides such as ouabai or digoxin also produce substantial increments in cardiac contractile f ce at normal body temperature and at 30° C. The administration of ouaba or digoxin at normal body temperature does not alter, in any way, the car ac or blood pressure responses to the three sympathomimetic amines. Howe r, following the administration of ouabain or digoxin and cooling of t animals to 30° C, the cardiac stimulant effects of epinephrine, n pinephrine and isoproterenol are either completely blocked or, in most inst es, reversed. The pressor responses to epinephrine and norepinephrine ar completely blocked in most instances. The effects of other sympathomimetic mines such as ephedrine and methamphetamine are blocked or reversed at a bo temperature of 30° C following ouabain or digoxin. The body temper ure at which the glycoside is administered does not appear to alter the de lopment of the blockade, being equally effective when administered a normal body temperature with subsequent cooling or when administered ring hypothermia. On the basis of a limited number of experiments, rewa ing the hypothermic animals to normal body temperature appears to re stablish the cardiac stimulant effects of the sympathomimetic amines while s equent recooling again results in blockade or reversal of the cardiac s ulant effects of the amines.

Significance to HEART Research: These indings demonstrate that the cardiac stimulant effects of several sympathom etic amines are either blocked or reversed following administration of o ain and cooling of the animals to approximately 30° C or lower. Using t e observations as tools, it may be possible to provide some information c erning the mechanisms through which the sympathomimetic animes and ca iac glycosides affect cardiac muscle to produce their increases in co ractile force.

Proposed Course of Project: Additional periments will be conducted to extend and confirm the findings outlined bove. Other experiments will be conducted to determine whether adrenergi blocking drugs are more effective in inhibiting the cardiac stimulant acti s of sympathomimetic amines during hypothermia than at normal body te erature. Experiments will also be conducted using the papillary muscle o the cat to determine whether these phenomena can be reproduced in vitr . If the latter experiments prove successful, various means will be employe in attempts to modify or reverse the blocking action of ouabain on the car iac stimulant effects of sympathomimetic amines during hypothermia.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-111
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,100	$1,734	$5,834	.2	.2	.4

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	0	0	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Clinic of Surgery

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-111
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-112
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Absorption of Drugs by the Intestine
PROJECT TITLE

7. Bernard B. Brodie
PRINCIPAL INVESTIGATOR

8. Lewis S. Schanker
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To determine which of the chemical and physical properties of drugs govern their rates of intestinal absorption.

Methods Employed: A saline solution containing the drug is perfused through the rat intestine in situ. The decreased concentration of the drug leaving the intestine provides a measure of absorption and an apparent permeability coefficient. The steady state distribution of a drug is determined by injecting the drug intravenously and then perfusing the intestine with a drug concentration that establishes equilibrium.

Major Findings: A survey of a large number of acidic and basic drugs indicates that there are limiting ionization constants determining absorption from an unbuffered solution in the intestinal lumen. In the

case of acids, the pKa is 2.5; for bases the pKa is 8.5. In no instance has there been evidence of competition between drugs. The rate of absorption is proportional to concentration.

Among those drugs which are rapidly absorbed, there are small, but significant differences in absorption rates. While these differences parallel the lipid: water partitions in some cases, there is lack of agreement in others. Similar findings have been encountered in other biological membranes thought to have an essentially lipoid matrix.

The absorption of these drugs has been examined at several pH's ranging from 4 to 8. Qualitatively the rates of absorption are modified in the direction expected if these drugs were absorbed in the unionized form. Quantitatively the rate of absorption does not change as much as the change in concentration of the unionized form; e.g., the absorption of salicylate changes from 64% at pH 4 to 11% at pH 8.

The dependence of absorption on intestinal lumen pH and the limiting pKa's determining rapid absorption have been clarified by determining the steady state distribution between plasma and intestinal lumen. When the intestinal lumen has a pH of 6.5, the plasma to lumen ratio of salicylic acid is 30:1 and of quinine is 1:30. These observations and others can be interpreted on the basis of the intestinal lumen having a virtual pH of 5.5 and the steady state being determined by both the rapid movement of the unionized moiety and the slow movement of the ionized moiety.

Significance to HEART Research: An understanding of the factors governing drug absorption should be of value in the selection of therapeutic agents for treatment of cardiovascular disease.

Proposed Course of Project: An expansion of the studies on intestine: blood equilibria to include a wider variety of pKa values and intestinal pH values.

To study the relative absorption rates of poorly absorbed drugs by a modification of the present technique.

Analysis of absorption from different regions of the intestine.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-112
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$13,200	$6,624	$19,824	1.1	0	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

C. Adrian M. Hogben, Laboratory of Kidney and Electrolyte Metabolism

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-112
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-113
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Pharmacology
SECTION OR SERVICE

5. Goldwater Memorial Hospital,
LOCATION (IF OTHER THAN BETHESDA)
New York, New York

6. Biosynthesis and Biotransformation of Ascorbic Acid
PROJECT TITLE

7. John J. Burns
PRINCIPAL INVESTIGATOR

8. Nicholas Papadopoulos
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To investigate the pathways of biosynthesis and metabolism of ascorbic acid and the factors involved in its physiologic disposition.

Methods Employed: In vivo administration of radioactive precursors. Administration of drugs which increase ascorbic acid formation.

Major Findings: A possible explanation has been found why man, monkey and guinea pig, unlike all other species, are unable to synthesize L-ascorbic acid (vitamin C), thus requiring vitamin C in their diet to prevent scurvy. In the rat, L-ascorbic acid is synthesized from

D-glucose via D-glucuronolactone and L-gulonolactone. Although the guinea pig can synthesize L-gulonolactone it cannot oxidize this compound further to L-ascorbic acid. The conversion of L-gulonolactone to L-ascorbic acid occurs in microsomes of rat liver but is absent in microsomes of guinea pig liver. These results suggest that the reason the guinea pig, and presumably, man cannot make L-ascorbic acid is due to a missing enzyme system in their liver microsomes.

Significance to HEART Research: Vitamin C (ascorbic acid) is involved in maintaining the integrity of all tissues and organs including the heart and cardiovascular system.

Proposed Course of Project: More detailed studies are planned to investigate the enzyme systems involved in the conversion of D-glucuronolactone and L-gulonolactone to L-ascorbic acid in the rat.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-113
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$21,300	$1,141	$22,441	.8	1.8	2.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. Peter Dayton, Goldwater Memorial Hospital, New York, New York

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-113
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Further Observations on the Biosynthesis of L-Ascorbic Acid from D-Glucose in the Rat. J. J. Burns and E. H. Mosbach. Journal of Biological Chemistry 221: 107-11, 1956.

The Conversion of D-Glucuronolactone and L-Gulonolactone to L-Ascorbic Acid in the Rat. Journal of Biological Chemistry, in press. J. J. Burns and Carole Evans.

The Metabolism of L-Ascorbic Acid. Symposium of Vitamin Metabolism. J. J. Burns. Nutrition Symposium Series 13: 91, 1956.

A Missing Step in Guinea Pigs Required for the Biosynthesis of L-Ascorbic Acid. J. J. Burns, Pincus Peyser and Arnold Moltz. Science, 124: 1148, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-114
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on the Mechanism of Action of Steroid Hormones. Role of Steroids in Cation Transport
PROJECT TITLE

7. Elwood O. Titus, Elliott Schiffmann
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: Certain adrenocortical hormones and related synthetic steroids profoundly affect the passage of cations and water through cell membranes. The cardiac glycosides appear to block the active transport of potassium into a variety of cells. Recent studies suggest that these transport phenomena may involve phospholipids and that the steroids may act by reason of their influence on the carrier function of the lipids. This project is designed to test this hypothesis.

NHI-114
Serial Number

Methods Employed: Paper and column chromatographic isolation of phospholipids and phosphorus containing degradation products thereof.

Measurement of radioactivity of P^{32} containing substances.

Flame photometric estimation of sodium and potassium.

Studies of phospholipid turnover in isolated tissues under various conditions such as electrical stimulation, steroid intoxication, etc.

Major Findings: The project is being initiated. A variety of phospholipids has been isolated from beef heart to serve as model substances.

Significance of HEART Research: Both the mechanism of cation transport and the mechanism of action of the cardiac glycosides are presently obscure. It is possible that a study of the role of phospholipids in membranes may clarify both phenomena.

Proposed Course of Project: If phospholipids are involved in cation transport across membranes, two types of mechanism may be conceived:

(a) A dynamic role in which cations are transported as lipid complexes. Synthesis of carrier on one side of the membrane and degradation on the other would provide a transport mechanism.

(b) A static role in which phospholipid remains inert in the membrane and functions somewhat in the manner of an ion exchanger. Other biochemical functions such as generation of hydrogen ion internally and exchange of H^+ for other cations would provide a transport mechanism. Since condition (a) would require that the passage of cations and effect of steroids thereupon should be reflected in the turnover of specific phospholipids, it is the easier hypothesis to test. The project will be initiated with a study of the effects of steroids, therefore, on phospholipid turnover.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-114
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$13,300	$6,695	$19,995	.8	.5	1.3

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-114
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-115
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on the Blood-Brain Barrier
PROJECT TITLE

7. Dr. Steven E. Mayer
PRINCIPAL INVESTIGATOR

8. ---
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To determine some of the factors involved in the selective lack of permeability of the central nervous system to substances in the circulation. Consideration of such variables as protein binding, lipid solubility, etc., was indicated in order to permit a quantitative appraisal of the relationship between chemical structure and brain permeability.

Methods Employed: In vivo animal experiments and determinations of physico-chemical constants.

NHI-115
SERIAL No.

Major Findings: The blood-brain barrier can be studied from two aspects: its action on impeding the rate of entrance of substances into the brain, and its influence on the final steady state concentration reached in the central nervous system. Any evaluation of brain permeability must involve a study of several different compartments between which interchange occurs at different rates. One should not consider that the blood-brain barrier is merely a membrane which is less permeable than those found in the capillary walls of other tissues.

Significance to HEART Research: Many drugs used in the treatment of cardiovascular diseases act on the central nervous system but little is known of the requirements for a compound to pass through the blood-brain barrier.

Proposed Course of Project: The project is being terminated.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-115
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,500	$3,242	$9,742	.3	.5	.8

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-115
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

The Permeability of the Central Nervous System to Some Pharmacologic Agents. S. E. Mayer and R. P. Maickel. Journal of Pharmacology and Experimental Therapeutics, to be published.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-116
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Role of Norepinephrine in the Central Nervous System
PROJECT TITLE

7. Dr. P.A. Shore
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: Norepinephrine has been implicated as a possible neurohumoral agent in the brain. The concept has been developed that serotonin and norepinephrine may be chemical transmitters of mutually antagonistic centers in the central autonomic nervous system, and that reserpine acts by an alteration of serotonin in one center while chlorpromazine may act by inhibition of norepinephrine in the other. The action of many centrally acting drugs could conceivably be explained in terms of an interaction with norepinephrine in the brain. The development of a physico-chemical method for norepinephrine in brain has made possible studies, on a biochemical level, of possible interactions of drugs with brain norepinephrine.

NHI-116
Serial Number

Methods Employed: Various drugs are administered to animals and the effects on norepinephrine in the brain are determined.

Major Findings: This is a new project made possible by the development of assay procedure for norepinephrine. It has already been found however, that administration of reserpine depletes rabbit brains of norepinephrine, confirming previous observations of other investigators.

Significance to HEART Research: This study is of significance and it will aid in understanding the role of norepinephrine, a substance believed to be implicated in many body functions including control of blood pressure.

Proposed Course of Project: The effects of various drugs on brain catechol amines will be investigated. A correlation will be made of the pharmacologic effects of reserpine and the alteration of norepinephrine levels in brain.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-116
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,800	$5,426	$16,226	.2	1.3	1.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	2	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-116
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-117
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The Metabolism of Toluene and Some Alkylbenzenes by Mammalian Liver Preparations.
PROJECT TITLE

7. James Gillette
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: It is known that animals can oxidize toluene to benzoic acid. However, little is known about this biotransformation on an enzyme level. Since many foreign compounds are metabolized by enzyme systems localized in the microsomal fraction of liver, it is of interest to determine whether toluene is metabolized by a microsomal enzyme system.

NMI-117
Serial Number

Methods Employed: Standard biochemical and chemical techniques will be employed in this study.

Major Findings: The 9,000 x g supernatant fraction of rabbit liver homogenate contains an enzyme system which catalyzes the oxidation of toluene to benzoic acid. Since nicotinamide, which inhibits the destruction of DPN and TPN, is required for this biotransformation, it is probable that either one or both of these coenzymes are necessary.

Significance to HEART Research: A number of alkylbenzene derivatives are used as drugs in medicinal practice. This study should help us to understand how these pharmacological agents are metabolized on an enzyme level.

Proposed Course of Project: The pathway by which toluene is oxidized to benzoic acid will be studied. The intercellular localization and the requirements for the enzymes involved in this biotransformation will be determined. Other alkylbenzenes will be used as possible substrates for this enzyme system.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-117
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$3,700	$1,832	$5,532	.3	0	.3

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	0	0	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-117
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-118
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Mechanism of Action of Reserpine - Studies of the Biochemical Effects of Reserpine Influencing Serotonin
PROJECT TITLE

7. Parkhurst A. Shore
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To study the biochemical mechanisms whereby reserpine causes a prolonged pharmacological effect and effect on serotonin levels in the body.

Methods Employed: Reserpine is administered to animals and the effects on serotonin in the body are studied.

Major Findings: Previous reports have described the prolonged pharmacologic effects and depletion of serotonin in the brain, which persist after administered reserpine is no longer detectable

in the brain. Also described were experiments demonstrating that reserpine causes a marked deficiency in the ability of blood platelets and brain to take up added serotonin. This action may be the primary effect of the drug.

It has been thought by other investigators that perhaps reserpine causes its prolonged pharmacological effects and depletion of serotonin by means of a metabolic product of the drug which might be undetectable by the usual analysis. This has been shown to be unlikely as brain serotonin was observed to decline to the same extent whether 1 or 5 mg/kg of reserpine was administered to rabbits. The same intensity and duration of pharmacologic effects and the same time for the restoration of serotonin levels were seen following the two different doses. It would be expected that the larger dose of reserpine would have resulted in the formation of more of a metabolic product than the smaller dose and therefore should have caused a more prolonged response.

The structural specificity required for release of serotonin has been further emphasized. It has been found that none of the following drugs cause the release of serotonin. Central stimulants (leptazol, picrotoxin), other tranquilizing agents (chlorpromazine, meprobamate, benactyzine), or the serotonin analogue and anti-hypertensive agent, Benzyl Anti-Serotonin.

Experiments on the effect of reserpine on serotonin of various species have shown that serotonin is almost completely released following administration of reserpine to rats and hamsters. In chickens, however, it has been found that only about 65-70 per cent of apparent serotonin can be released following even very large doses of reserpine. It is hoped that by using the chicken, "free" serotonin following reserpine may be distinguished from "bound" serotonin.

Significance to HEART Research: This study is of significance in two aspects: (1) an understanding of the action of reserpine, a drug used in the control of hypertension and mental disorders, (2) understanding the normal function of serotonin, a substance which is implicated in many body functions including control of blood pressure.

Proposed Course of Project: Studies on the mechanism whereby reserpine exerts its pharmacologic effects and effects on serotonin will be continued.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-118
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,600	$2,819	$8,419	.3	.3	.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-118
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Shore, P. A., Pletscher, A., Tomich, E. G., Carlsson, A., Kuntzman, R., and Brodie, B. B. Ann. N. Y. Acad. Sci., in press.

Brodie, B. B., and Shore, P. A., Ann. N. Y. Acad. Sci., in press.

Shore, P. A., Pletscher, A., Tomich, E. G., Kuntzman, R., and Brodie, B. B., J. Pharmacol. Expt. Therap. 117: 232, 1956.

Brodie, B. B., Shore, P. A., and Pletscher, A., Science 123, 992, 1956.

Brodie, B. B., Tomich, E. G., Kuntzman, R., and Shore, P. A. J. Pharmacol. Expt. Therap., in press.

Shore, P. A. and Brodie, B. B. Proc. Soc. Exp. Biol. and Med., submitted for publication.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Travel award for Dr. Parkhurst A. Shore to attend the Twentieth International Physiological Congress, July 29 - August 4, 1956, Brussels, Belgium.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-119
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The Enzymatic Oxidation of Benzyl Alcohol and Other Aromatic Alcohols
PROJECT TITLE

7. James R. Gillette
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: It is well known that benzyl alcohol and other aromatic alcohols are oxidized in vivo to their respective acids. However, very little is known about the metabolism of these compounds on an enzyme level. The purpose of this investigation is to study the enzymes involved in these biotransformations. Such a study may help us to understand the metabolism of a number of drugs.

NHI-119
Serial Number

Methods Employed: Standard biochemical and chemical methods will be employed.

Major Findings: Rabbit liver homogenate contains an enzyme system localized in the 9,000 x g supernatant fraction, which oxidizes benzyl alcohol to benzoic acid. This system is stimulated by the addition of either DPN or to a lesser extent TPN. Furthermore, the DPN supplemented system is stimulated even more by the addition of methylene blue. These data may indicate that a dehydrogenase may participate in the oxidation of benzyl alcohol.

Significance to HEART Research: A number of drugs have aromatic alcoholic groups as a part of their molecular structure. Since the oxidation of these groups may affect the activity of the drugs, it is important to study this type of reaction.

Proposed Course of Project: The possible pathways in the biotransformation of benzyl alcohol will be studied and the enzymes involved will be determined. The metabolism of some other alcohols will be investigated.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-119
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$8,000	$3,347	$11,347	.5	.3	.8

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-119
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-120
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The Pharmacological Actions of Oxypanamine, NHI-196, an Alkaloid Derived from Ormosia panamensis
PROJECT TITLE

7. Neil C. Moran
PRINCIPAL INVESTIGATOR

8. Gertrude P. Quinn
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: With the discovery of oxypanamine (NHI-196) as an oxidation product of panamine, a new alkaloid from Ormosia panamensis, a study of the pharmacological actions of oxypanamine was undertaken.

Methods Employed: Standard physiologic and pharmacologic techniques were employed for measuring blood pressure, blood flow, cardiac function, etc.

NHI-120
Serial Number

Major Findings: Oxypanamine produces in dogs a complex pattern of actions including a fall in blood pressure, hemoconcentration, broncho constriction, rise in pulmonary artery pressure, stimulation of the small intestine, cutaneous erythema and urticaria and in high doses neuromuscular and ganglionic blockade. It does not release histamine, does not block the autonomic nervous system and is active in spinal dogs. No direct vasodilation occurs when oxypanamine is injected into the femoral artery. The fall in blood pressure, broncho constriction, rise in pulmonary artery pressure and hemoconcentration are partially or completely inhibited by antihistamine drugs. It is concluded that oxypanamine acts through a histamine mechanism. The compound is virtually inactive in rabbits, rhesus monkeys and man.

Significance to HEART Research: Primary significance is in the basic study of mechanisms of eliciting a fall in blood pressure and in furthering knowledge of biological significance of histamine.

Proposed Course of Project: Completed.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-120
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$8,600	$3,573	$12,173	.5	.4	.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-120
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Neil C. Moran, Gertrude P. Quinn and William M. Butler, Jr. Pharmacological Actions of Oxypanamine, an Alkaloid Derived from the Seeds of Ormosia panamensis. Manuscript in preparation for J. Pharm. and Exper. Therap.

Neil C. Moran, Gertrude P. Quinn and William M. Butler, Jr. An Evaluation of the Histamine-like Actions of Oxypanamine. Manuscript in preparation for J. Pharm. and Exper. Therap.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-121
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on the Biosynthesis of Cardiotonic Steroids
PROJECT TITLE

7. Elwood O. Titus and Elliott Schiffmann
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The presence of a cardiotonic steroid in the South American toad represents one of the few examples of the existence of digitalis-like materials in animals. The biosynthesis of this material might illustrate a general scheme of cardiotonic steroid formation. For these reasons it was of interest to investigate the biological production of the cardiotonic lactones.

NHI-121
Serial Number

Methods Employed: Synthesis of radioactively labeled precursors for administration to animals and *in vitro* preparations.

Preparation of enzyme systems capable of *in vitro* synthesis of cardiac lactones.

Chromatographic isolation and determination of radioactivity of cardiac lactones.

Major Findings: Cholesterol is a precursor of cardiac lactones in toads. Because of certain unique structural features of these lactones their synthesis represents a type of metabolic pathway not hitherto demonstrated in animals.

Significance to HEART Research: The mechanism for biogenesis of cardiac lactones in toads may exemplify a general metabolic pathway used for synthesis of these substances.

As yet unidentified cardiotonic substances in mammalian tissue may resemble the toad lactones chemically.

Proposed Course of Project: The experiment with tritium to determine initial transformations of cholesterol is being carried on. It appears from recent results with cholesterol metabolism that some poly-hydroxy sterols are intermediates. Work is contemplated using some of these compounds, depending on the results of the tritium experiment. It is also contemplated to investigate possible relations between steroids and lipids in transport processes.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-121
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$8,600	$4,299	$12,899	.7	0	.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-121
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Siperstein, M.D., Murray, A.W. and Titus, E.O. The Biosynthesis of Cardiotonic Sterols from Cholesterol in the Toad, Bufo marinus. Archives Biochemistry and Biophysics (1956), in press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-122
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Development of a Physico-Chemical Assay Procedure for Norepinephrine and Epinephrine in the Brain
PROJECT TITLE

7. Parkhurst A. Shore
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: In order to examine the proposed role for norepinephrine in the brain (see report entitled "Role of Norepinephrine in the Central Nervous System"), a simple physico-chemical method for the estimation of this substance in tissues is needed.

Methods Employed: Optimal conditions for extraction of catechol amines, oxidation to a fluorescent material and determination of this fluorescence are studied.

NHI-122
SERIAL NO.

Major Findings: A technique has been developed to extract norepinephrine and epinephrine from brain tissue. This procedure is far superior to past methods for extraction as it involves extraction of these amines into an organic solvent rather than simply a precipitation of proteins.

Based on this extraction, an assay procedure has been developed by modification of the usual process of oxidation of these catechol amines to form fluorescent products.

The method appears to be specific for the catechol amines. Ultraviolet activation and fluorescent spectra of the oxidation products of the substances extracted from brain are identical with the spectra of the oxidation product of norepinephrine.

It appears that the catechol amine in rabbit is mostly norepinephrine, as the pH requirements for oxidation of the substance from brain most closely resemble norepinephrine rather than epinephrine.

Preliminary experiments indicate that the administration of reserpine to rabbits causes a depletion of norepinephrine in rabbit brains. This represents a further proof of identity of the brain substance as it has been reported that reserpine causes the depletion in brain of a substance shown by bioassay to be norepinephrine.

It appears that as little as 0.5 microgm of catechol amine is needed for the physico-chemical assay which should be able to differentiate between epinephrine and norepinephrine.

Significance to HEART Research: Norepinephrine and epinephrine are the mediators of sympathetic tone in the body, and therefore are important in the control of blood pressure. Furthermore, norepinephrine has been implicated in the central nervous system as a chemical transmitter in the central sympathetic component of the autonomic nervous system.

Proposed Course of Project: Development of the method will be continued. It is planned to further determine the specificity of the method for catechol amines in brain and other tissues by paper chromatography of counter-current distribution. It is also planned to estimate the content of catechol amines in various parts of the brain and in various tissues.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-122
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$8,200	$4,087	$12,287	.2	.9	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-122
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-123
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Drug Enzyme Systems
PROJECT TITLE

7. James Fouts
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: A large number of drugs are oxidized along a variety of pathways by liver microsomes in the presence of TPNH. This work stresses reductive enzymes which metabolize azo and nitro compounds. These reactions occur in soluble as well as microsomal fraction of cell and are TPNH dependent. They represent a new type of flavoprotein in mammals, with so little specificity for substrate or for flavin that they may be perhaps regarded as "primitive" prototypes in the evolution of enzyme systems.

NHI-123
SERIAL NO.

Methods Employed: Drug metabolism is being studied using various liver fractions. The products are measured colorimetrically and spectrophotometrically.

Significance to HEART Research: A knowledge of the metabolism of drugs is important in the development of new therapeutic compounds and in understanding of drug action; study of drug enzymes can lead to the discovery of fundamental mechanisms involved in the normal body economy.

Proposed Course of Project: Studies on other types of reductive processes used by body to detoxify foreign compounds will be continued. The nature of the relationship of the prosthetic group to the protein enzyme will be studied.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-123
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$13,700	$6,836	$20,536	.6	1.0	1.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-123
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

On the Enzymatic Reduction of Prontosil and Other Azo Compounds by Mammalian Liver Systems. J. R. Fouts, J. J. Kamm, and B. B. Brodie. Submitted for publication.

On the Enzymatic Reduction of Aromatic Nitro Compounds. J. R. Fouts and B. B. Brodie. Journal of Pharmacology and Experimental Therapeutics, in press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-124
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The Fate of Substances Introduced into the Cerebrospinal Fluid
PROJECT TITLE

7. Steven E. Mayer
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To measure the rate of disappearance of organic compounds from the cerebrospinal fluid and their entrance into the solid matter of the central nervous system after administration into the cisterna magna.

NHI-124
Serial Number

Methods Employed: In vivo animal experiments and standard radioisotope techniques.

Major Findings: Substances which enter the central nervous system rapidly from the circulation, leave the cerebrospinal fluid at approximately the same rates, while those which enter slowly also leave slowly. All the substances enter the brain in small amounts (about 1% of the injected dose) with the exception of N-acetyl-4-aminoantipyrine which averages about 3% of the injected dose per gram of brain. A test of the possibility of active transport of compounds from brain to circulation was negative with one of these compounds. The results have suggested a different compartmentalization of the brain after intravenous and intracisternal administration.

Significance to HEART Research: Almost nothing is known regarding the distribution of substances injected into the ventricles or subarachnoid space of the brain, although many pharmacologic agents are active when administered in this fashion.

Proposed Course of Project: Project has been terminated.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-124
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$8,500	$4,228	$12,728	.5	.4	.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-124
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-125
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Chemical Pharmacology
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on the Role of Serotonin in the Body - The Mechanism of Its Storage and Release
PROJECT TITLE

7. Parkhurst A. Shore
PRINCIPAL INVESTIGATOR

8. Barbara B. Hughes
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: Previous studies have suggested that serotonin is a neurohumoral agent in the central autonomic nervous system, and that reserpine exerts its action primarily by an interaction with sites in the brain which normally bind serotonin in an inactive form.

Of a fundamental nature is the question of the mechanisms whereby a proposed neurohormone is stored and released. The release of stored serotonin has been demonstrated *in vitro* by the addition of reserpine to a suspension of rabbit blood platelets, and it has been demonstrated that reserpine administration blocks the uptake of serotonin added to blood platelets *in vitro* and brain *in vivo*.

NHI-125
SERIAL NO.

Methods Employed: The process by which serotonin is released by reserpine and other agents is studied in vivo and in vitro. Also studied is the process by which added serotonin is taken up by various tissues.

Major Findings: The presence of "specific" reserpine-sensitive binding sites for serotonin has been demonstrated. Thus, the administration of reserpine blocks uptake of serotonin, that results from administration of the precursor of serotonin, 5-hydroxytryptophan, in brain, but does not block the uptake in liver, an organ which does not normally contain serotonin.

Experiments designed to study the intracellular distribution of serotonin indicate that the amine is not bound to any definite particle of the cell.

It has been found that, contrary to published reports, the parenteral administration of serotonin in mice causes a rise in brain serotonin, indicating that the blood-brain barrier is slightly permeable to serotonin.

Significance to HEART Research: This study is of significance as it will aid in understanding the fundamental processes by which serotonin, a substance implicated in many body functions including control of blood pressure, is bound and released.

Proposed Course of Project: Efforts will be made to reduce the serotonin content of brain by means other than Rauwolfia administration.

It is hoped that a technique will be developed to differentiate between "free" and "bound" serotonin.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-125
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,000	$3,523	$10,523	.3	.6	.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-125
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

B. B. Brodie, E. G. Tomich, R. Kuntzman, and P. A. Shore, Journal of Pharmacology and Experimental Therapeutics, in press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-126
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Lab. of Clinical Biochemistry
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on Phenylpyruvic Oligophrenia
PROJECT TITLE

7. Dr. Chozo Mitoma
PRINCIPAL INVESTIGATOR

8. Mr. Herbert S. Posner
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The association of dementia with a block in conversion of phenylalanine to tyrosine in patients with phenylpyruvic oligophrenia suggests a chemical etiology for the mental defect. These studies are designed to establish the exact nature of this chemical defect.

Methods Employed: Chemical analysis of blood, urine, and tissues in phenylketonuric patients. Enzymatic studies with liver from these patients.

Major Findings: In previous studies on animal tissues it has been shown that two protein fractions (enzymes) are needed to catalyze the conversion of phenylalanine to tyrosine; I - is found exclusively in the liver, II - is found in all organ tissues. Since hydroxylation of phenylalanine takes place only in the liver, enzyme I may be regarded as specifically involved in the conversion, whereas enzyme II must be an auxiliary enzyme involved in many other functions of the body. Using liver autopsy samples from phenylketonuric patients it has been

shown that enzyme II is present in normal amount. Since phenylketonuria liver does not carry out the hydroxylation it must be assumed then that the block is in a specific liver enzyme. Thus, the mental defect may be secondary to liver disfunction.

The o-hydroxyphenylacetic acid excreted such large amounts in patients with phenylketonuria (200-300 mg. as compared to 1-3 mg. in normal) has been shown to be derived from phenylalanine. The suspected intermediate in the process, o-tyrosine, has been shown to have marked central excitatory effects similar to d-amphetamine. These actions are apparently mediated by o-tyramine which appeared in the tissues following administration of the amino acid. This is further evidence of the production of a centrally "toxic" substance by the liver in phenylketonuric patients.

Significance to Heart Research: Aromatic amines are important humoral substances and profoundly influence the cardio-vascular system (adrenalin, noradrenalin, serotonin). o-Tyramine may be a normally occurring amine whose production is elevated in phenylpyruvic oligophrenia making such patients valuable for this study.

Proposed Course of Project: Patients with phenylketonuria will be admitted to the Clinical Center to continue studies on the enzymatic block in liver hydroxylating enzyme. Tissues from these patients will also be used to look for o-tyramine and o-tyrosine. The proposed pathway leading from phenylalanine through o-tyrosine, o-tyramine and o-hydroxyphenylacetic acid will be investigated *in vivo* and *in vitro*.

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October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 126
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$11,400	$5,708	$17,108	.3	.5	.8

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. Albert Sjoerdsma

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-126
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Diminished Phenylketonuria in Phenylpyruvic Oligophrenia after Administration of L-Glutamine, L-Glutamate or L-Asparagine, A. Meister, S. Udenfriend, and S. Bessman, J. Clin. Invest. 35, 619 (1956).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-127
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Lab. of Clinical Biochemistry
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on Serotonin
PROJECT TITLE

7. Herbert Weissbach and Sidney Udenfriend
PRINCIPAL INVESTIGATOR

8. --
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: To investigate the biogenesis, disposition and metabolism of serotonin and to determine the functions of serotonin and its implications in certain disease states.

Methods Employed: Preparation and purification of enzymes and evaluation of drugs and analogues as inhibitors of their activity. Determination of effects of drugs and various reactions on serotonin metabolism, in vivo, by measurement of serotonin disappearance or increase in blood and tissues.

Major Findings: It has now been shown that not only is serotonin present in the brain but that it can be formed and destroyed in the central nervous system. Furthermore, serotonin and the enzyme which forms it, 5-hydroxytryptophan (5HTP) decarboxylase, are concentrated in the brain stem areas suggesting that these areas are involved in its actions. When 5HTP is administered to animals

the serotonin content of brain is markedly increased, the greatest increase being found in the brain stem areas. The marked pharmacologic effects following 5HTP administration to animals, which are no doubt due to its conversion to serotonin, resemble the effects produced by administering the hallucinagenic indole lysergic acid diethylamide. Resolution of D,L-5HTP has been achieved and it has been shown that only the L antipode possesses pharmacologic activity and that only this form can be decarboxylated enzymatically to serotonin.

In man 5HTP has proved to have hypotensive activity and to produce marked gastro-intestinal motility when administered in doses of 25-75 mg. Because of these toxic effects no attempt has been made to evaluate the central effects of this compound in man.

Direct demonstration of pyridoxal phosphate as a cofactor of 5HTP decarboxylase has been achieved. Furthermore, marked serotonin depletion has been shown in brain, blood and tissues of pyridoxine deficient chickens. Isoniazid which has been widely used to produce acute pyridoxine deficiency does not inhibit the decarboxylation of 5HTP to any great extent.

Administration of the monoamine oxidase inhibitor, iproniazid has been shown to produce a rapid increase in brain serotonin (threefold within five hours). However, this drug does not appreciably effect peripheral depots of serotonin. Iproniazid also increases the amounts of serotonin formed in brain following administration of 5HTP but has little effect on that formed in the carcass. Administration of iproniazid in vivo was found to abolish the activity of monoamine oxidase in homogenates prepared after sacrifice of the animals. The monoamine oxidase activity of slices was found to be unaffected. Since iproniazid does potentiate the central actions of serotonin it must do so by inhibiting serotonin destruction in a very specific portion of the brain.

It has been shown that blood platelets absorb serotonin both in vitro and in vivo. This probably accounts for the high concentration of serotonin in platelets. This property of platelets is not limited to serotonin but extends to adrenaline, histamine, bufotenine, etc. Platelets may thus provide a mechanism for inactivating amines when they enter the circulation.

Significance to Heart Research: Serotonin is known to be a vasoconstrictor substance. Furthermore, it seems to be involved in the functioning of those areas of the brain which regulate blood pressure, temperature, etc. Its significance to heart research is, therefore, obvious.

Proposed Course of Project: Attempts will be made to purify the enzymes tryptophan hydroxylase, 5HTP decarboxylase and monoamine oxidase and to study their mechanisms of action. Inhibitors of these enzymes will also be investigated in attempts to develop pharmacologic agents. Compounds which can inhibit peripheral actions of serotonin will be checked on malignant carcinoid patients.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 127
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$26,000	$13,037	$39,037	.8	.9	1.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. Albert Sjoerdsma NHI - 133

Dr. Bernard Witkop NIAMD

Dr. Fred Leonard Visiting Scientist, Geigy Pharmaceutical Co.

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-127
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Studies on Tryptophan and Serotonin in Patients with Malignant Carcinoid, S. Udenfriend, H. Weissbach and A. Sjoerdsma, Science 123, 669 (1956).

2. A Clinical, Physiological and Biochemical Study of Patients with Malignant Carcinoid. A. Sjoerdsma, S. Udenfriend and H. Weissbach, American J. Med. , 20, 520 (1956).

3. Identification and Assay of Serotonin in Brain, D. Bogdanski, A. Pletscher, B. Brodie and S. Udenfriend, J. Pharm. Exper. Therap. 117, 82 (1956).

4. Increase in Tissue Serotonin Following Administration of Its Precursor 5-Hydroxytryptophan, S. Udenfriend, H. Weissbach and D. Bogdanski, J. Biol. Chem. (in press).

5. Biochemical and Pharmacological Studies with D- and L-5-Hydroxytryptophan, K. Freter, H. Weissbach, S. Udenfriend and B. Witkop, Proc. Soc. Exper. Biol. and Med. (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Dr. Sidney Udenfriend - Awarded Senior Research Fellowship, NIH
March 1957 - September 1957

6. Biochemical Studies on Serotonin and Their Physiological Implications, S. Udenfriend, H. Weissbach and D. Bogdanski, Symposium on Neuroendocrinology, chap. 7 (in press).

7. The Distribution of Serotonin, 5-Hydroxytryptophan Decarboxylase and Monoamine Oxidase in Brain, D. Bogdanski, H. Weissbach and S. Udenfriend, J. Neurochemistry (in press).

8. The relationship of Platelet Serotonin To Disturbances of Clotting and Hemostasis, M. Weiner and S. Udenfriend, Blood (in press).

9. Biochemistry and Metabolism of Serotonin as it Relates to the Nervous System, S. Udenfriend, D. Bogdanski and H. Weissbach, Proc. Second International Neurochem. Symp. (in press).

10. Biochemical, Physiological and Pharmacological Aspects of Serotonin, S. Udenfriend, P. A. Shore, D. Bogdanski, H. Weissbach and B. Brodie, Recent Progress in Hormone Research (in press).

11. Biochemical Findings Relating to Serotonin Action, S. Udenfriend, H. Weissbach and D. Bogdanski, Annals N. Y. Acad. Sci. (in press).

12. Further Observations on Patients with Malignant Carcinoid, A. Sjoerdsma, H. Weissbach, L. Terry and S. Udenfriend, Amer. J. Med. (in press).

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October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-128
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Lab. of Clinical Biochemistry
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Hydroxylation and Biogenesis of Aromatic Compounds
PROJECT TITLE

7. Dr. Chozo Mitoma
PRINCIPAL INVESTIGATOR

8. Mr. Herbert S. Posner
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The formation and hydroxylation of aromatic and cyclic compounds are important biochemical processes. Such reactions will be investigated with respect to histidine, tyrosine, 5-hydroxytryptophan and hydroxyacetanilid.

Methods Employed: Standard enzymatic procedures.

Major Findings: Although the microsomal hydroxylating system of rats, rabbits and guinea pigs converts aniline exclusively to p-aminophenol, o-aminophenol is excreted in the urine appearing in very large amounts in cat and dog. It is impossible to demonstrate that in dog and cat liver both the o- and p-hydroxylating system are present in the microsomes.

It has been shown that the major product of the action of liver microsomes on naphthalene is the corresponding dihydrodiol. This substance is readily dehydrated to yield naphthol and may be the intermediate in the hydroxylation of naphthalene. Studies are under way to determine whether dihydrodiol intermediates occur in all aromatic hydroxylations and it has already been demonstrated that such a compound appears during the hydroxylation of quinoline to 3-hydroxyquinoline.

Significance to Heart Research: Aromatization of hydroxylation are important processes on the biosynthesis of the humoral agents which act on the cardio-vascular system and in the detoxication of drugs.

Proposed Course of Project: Studies will be continued on the o- and p-hydroxylating enzymes of microsomes. Mechanism of aromatic hydroxylation will be investigated particularly with due respect to dihydrodiol intermediates. Dihydrodiol analogues of acetanilide and other compounds will be synthesized and tested as intermediates in the hydroxylating system.

Studies on the mitochondrial system which converts cyclohexanecarboxylic acid to benzoic acid will be continued and comparison will be made between this system and the fatty acid oxidase system.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 128
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$11,500	$5,778	$17,278	.3	.5	.8

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. Bernard Witkop NIAMD

Form No. ORP-1
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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-128
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Studies on Partially Purified Phenylalanine Hydroxylase, C. Mitoma, Arch. of Biochem. and Biophys. 60, 476 (1956).

2. Enzymatic Hydroxylation of Aromatic Compounds, C. Mitoma, H. Posner, H. C. Reitz and S. Udenfriend, Arch. of Biochem. and Biophys. 61, 431 (1956).

3. Aromatic Hydroxylating Enzymes, S. Udenfriend, C. Mitoma and H. Posner, Amer. Chem. Soc. Symposium, Sept. 1956, (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-129
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Lab. of Clinical Biochemistry
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The Role of Serotonin in Anaphylaxis
PROJECT TITLE

7. Herbert Weissbach
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To determine to what extent serotonin release is a factor in anaphylaxis and related conditions and to determine whether some allergic manifestations can be alleviated by inhibitors of serotonin.

Methods Employed: Standard procedures are used to sensitize animals to various antigens. The antigen is then administered and the changes in serotonin concentration in blood and various tissues is measured; comparison is made with histamine.

Major Findings: It has been shown that both serotonin and histamine are released from platelets of sensitized rabbit blood *in vitro* upon addition of the specific antigen. When antigen is administered to sensitized rabbits serotonin and histamine are released and are found free in the plasma.

Serotonin has been found to be present in the lung of many animal species. It was found that guinea pig lung contains histamine but little, if any, serotonin whereas mouse lung contains serotonin but little histamine. Since antihistaminics completely protect guinea pigs from anaphylactic shock but have little effect on mice, serotonin may be a factor in the pulmonary aspects of anaphylaxis.

Significance to Heart Research: It is recognized that in allergic manifestations there are released agents having pronounced effects on the cardiovascular system. Histamine release has been demonstrated and has led to development of antihistaminics drugs to alleviate some of these effects. Release of serotonin may be another factor in allergy and may lead to development of newer therapeutic agents.

Proposed Course of Projects: These studies will be extended to other animal species and to patients. Release of serotonin from specific organs such as lung and skin will be investigated. Agents which modify the anaphylactic reaction will be checked for their effect on serotonin and agents which modify the status of serotonin in tissues will be checked for their effect on anaphylaxis.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 129
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$14,000	$7,047	$21,047	.6	.2	.8

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. T. Philip Waalkes — NHI - 143

Dr. John Bozicevich — National Institute of Allergy and Infectious Diseases

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-129
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. The In Vivo Release of Histamine from Rabbit Blood by Reserpine, T. P. Waalkes and H. Weissbach, Proc. Soc. Exper. Biol. and Med. (in press).

2. The Presence of Serotonin in Lung and Its Implication in the Anaphylactic Reaction, H. Weissbach, T. P. Waalkes and S. Udenfriend, Science (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-130
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Lab. of Clinical Biochemistry
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Hydroxyproline and Hydroxylysine Metabolism and Their Implications in Collagen Formation
PROJECT TITLE

7. Dr. Chozo Mitoma
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To determine how hydroxyproline and hydroxylysine form and how these two amino acids are incorporated into collagen.

Methods Employed: Chemical analysis of blood, urine and tissues for hydroxyproline and hydroxylysine using patients and experimental animals; tissue culture enzymatic procedures.

Major Findings: Implantation of polyvinyl sponges in animal skin has been found to result in the rapid and reproducible formation of collagen. Fibroblasts formed in the sponge have been shown to convert proline to hydroxyproline and incorporate both amino acids into collagen. The most interesting finding is

that conversion of proline to hydroxyproline takes place within 3-4 hours, making it possible to carry out relatively simple enzyme studies. Using fibroblasts from sponges it has already been shown that the conversion of proline to hydroxyproline requires oxygen and it proceeds at certain optimal requirements of pH and temperature.

Methods for the determination of hydroxyproline in urine, blood and tissues have been developed.

A large number of proline and hydroxyproline analogues have been synthesized.

Significance to Heart Research: Connective tissue plays an important role in maintaining integrity and normal functions of the heart and tissues. Collagen is the major protein in these connective tissues.

Proposed Course of Project: Studies on the conversion of proline to hydroxyproline will be continued to determine mechanisms and intermediates. The effects of various analogues of the amino acid on the formation of hydroxyproline and collagen will be investigated to determine whether they may serve as *in vivo* inhibitors of connective tissue formation.

The effects of hormones, drugs and anti-metabolites on the formation of hydroxyproline and collagen on intact animals and patients will be investigated. The possible conversion of proline to hydroxyproline in plant tissue culture will also be studied.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 130
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$25,500	$12,755	$38,255	.3	1.8	2.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. Albert Sjoerdsma - National Heart Institute

Dr. Bernard Witkop -NIAMD

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-130
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-131
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Lab. of Clinical Biochemistry
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on Adrenaline, Noradrenaline and Related Catechol Compounds
PROJECT TITLE

7. Dr. Sidney Udenfriend
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To determine the intermediates involved in the formation of adrenaline and noradrenaline and study the tissue catalysts involved in these conversions. To apply this information in furthering our knowledge of the physiological function of these humoral agents and to investigate their implication in certain disease states.

Methods Employed: Standard enzyme procedures using extracts from adrenal glands, sympathetic nerve tissue and pheochromocytoma tumors. Perfusion of intact adrenals. Administration of C^{14} labeled compounds to experimental animals and man.

Major Findings: It has been shown that the isolated perfused calf adrenal can carry out all the chemical conversions leading from tyrosine to adrenaline. The methylation of noradrenaline to yield adrenaline is not reversible. Methionine

was found to be an excellent methyl donor, formate and formaldehyde having some activity. Choline was totally inactive in this respect.

C^{14} labeled dihydroxyphenylalanine and hydroxytyramine when administered to patients with pheochromocytoma were converted to noradrenaline. From such studies the turnover rate of noradrenaline in two pheochromocytoma patients was estimated to have a half life of about 8 hours. Enzymes involved in adrenaline formation and metabolism have been demonstrated in pheochromocytoma tumor itself. One patient with pheochromocytoma was shown to have significantly lowered fasting tyrosine blood levels although tryptophan values were normal suggesting a serious impairment of tyrosine metabolism in general.

Methods for assaying noradrenaline in urine of normals and pheochromocytoma patients were perfected.

Significance to Heart Research: Noradrenaline and adrenaline are important regulatory substances of cardio-vascular function.

Proposed Course of Project: Studies on the perfused calf adrenal will be completed. Purification and study of enzymes involved in adrenaline formation. Further studies on pheochromocytoma patients to determine the magnitude of noradrenaline formation and its possible interference with other tyrosine pathways of metabolism. Interrelationship of adrenaline formation with pigment formations requiring similar intermediates such as dihydroxyphenylalanine will be investigated in animals and in patients with albinism and melanoma.

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October 1956
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 131
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$23,000	$11,557	$34,557	.5	1.2	1.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. Albert Sjoerdsma - National Heart Institute

Dr. George Rosenfelt - Naval Medical Research Center, Bethesda, Md.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-131
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Precursors of Adrenal, Epinephrine and Norepinephrine in vivo, S. Udenfriend and J. Wyngaarden, Biochem. and Biophys. Acta 20, 48 (1956).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-132
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Lab. of Clinical Biochemistry
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on Indoleacetic Acid
PROJECT TITLE

7. Herbert Weissbach
PRINCIPAL INVESTIGATOR

8. ---
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To determine how indoleacetic acid is formed and what its significance may be in animal tissues in health and disease.

Methods Employed: Enzyme studies on the conversion of precursors to indoleacetic acid; the use of C^{14} labeled tryptophan in intact animals and in patients; measurement of indoleacetic acid in urine and tissues after tryptophan administration in normals and in patients with various disorders.

Major Findings: The normal excretion of indoleacetic acid in man averages about 6 mg/day. Only about 20 per cent of the normally excreted indoleacetic acid is conjugated. One patient with cerebellar ataxia had a significantly elevated excretion (15 mg/day). However, this was not very marked and is nowhere near the 100-200 mg. reported by Jepson et al.

An unidentified water soluble indole compound has been found in large quantities in a number of urines. This may not be related to indoleacetic acid but will be investigated further. The extent of conversion of tryptophan to indoleacetic acid in homogenates has been found to vary considerably from tissue to tissue and from species to species.

Significance to Heart Research: This project is part of the basic research program of the National Heart Institute. Although it does not relate directly to heart disease the knowledge gained relative to cellular metabolism, in general, will further our understanding of cardiovascular function.

Proposed Course of Project: Patients with cerebellar ataxia, diabetes and other disorders in which indoleacetic acid is implicated will be studied to determine the extent of conversion from tryptophan and its significance, if any, in the pathology of the disorder.

Enzymatic pathways leading to indoleacetic acid will be investigated. Comparisons will be made with comparable systems in plants.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 132
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$11,600	$5,849	$17,449	.3	.5	.8

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. Albert Sjoerdsma - NHI 137

Dr. James D. Solomon - St. Elizabeth's Hospital, Washington, D.C.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-132
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-133
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Experimental Therapeutics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on Vasoactive Substances
PROJECT TITLE

7. Dr. Albert Sjoerdsma
PRINCIPAL INVESTIGATOR

8. Drs. J. D. Davidson, B. J. Haverback, and L. L. Terry
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: Relate naturally occurring vasoactive substances to cardiovascular disease and response to drugs.

Methods Employed: Largely as described previously or published elsewhere in the literature. Numerous problems have arisen in chemical assay of catechol amines in blood and urine.

Major Findings: (1) Malignant Carcinoid Syndrome - Several patients were admitted for study during the past year and numerous analyses were done on specimens sent from elsewhere. Elevated blood serotonin and urine 5-OH indoleacetic acid (5-HIAA) are consistent findings and the total number of

cases studied by us has now reached 30. It is of interest that at least 2 of the patients appeared to have their primary tumor in the lung. Findings of low fasting plasma tryptophan and urinary N'methylnicotinamide in some patients substantiate our previous suggestions of a disorder in tryptophan metabolism in this condition. A tracer study, in one patient, with the serotonin precursor, 5-hydroxytryptophan, enabled calculation of the tumor pool of serotonin (2800 mgm), its turnover rate (½ life of 5½ days), and the tumor mass (1-3 kgm). No measurable difference was found in the serotonin content of mixed venous and arterial blood which, if present, might account for predominant right-heart involvement. However, measurements of plasma serotonin may be unreliable due to problems of separating it from the formed elements of blood, particularly platelets, in which the bulk of circulating serotonin is carried. The absence of serotonin from cerebrospinal fluid probably indicates that this substance does not penetrate readily into the central nervous system. Therapy with so-called serotonin antagonists, with the possible exception of chlorpromazine, has been disappointing. Reserpine therapy causes rapid depletion of platelet serotonin, but in a dosage as high as 10 mgm/day has not affected the serotonin content of the tumors. Chlorpromazine therapy has been shown to interfere with direct assay of 5-OH-indoles in urine, but as shown by our usual extraction procedure for 5-HIAA, serotonin production is actually unaffected.

(2) Studies with Serotonin Precursor, 5-OH-tryptophan (5HTP) - Since serotonin is rapidly metabolized and does not readily penetrate the CNS, its precursor was administered acutely to man and chronically to rats. In man, in a dosage range of 25 to 125 mgm of the D-L compound, increased amounts of serotonin were found in the urine for several hours. It was anticipated that central effects might be observed but gastrointestinal stimulation and 3 instances of vascular collapse have prevented our achieving a dose-level at which this might occur. Twice daily injection of 5HTP in a dosage of 200 mgm/kgm to rats was shown to result in sustained elevations of tissue serotonin. Chronic administration (4 months) failed to produce any cardiac or other tissue pathology of consequence. Considering the potency of serotonin, and the pathology in carcinoid patients, this was a surprising result.

(3) Pheochromocytoma - Using C^{14} label, both dihydroxyphenylalanine (DOPA) and dihydroxyphenylethylamine (DOPamine) have been shown to be precursors of nor-adrenaline in man. The calculated rate of nor-adrenaline turnover in two patients was about 8 hours, this being much more rapid than for adrenal catechol amines in experimental animals. In order to obtain patients for study, numerous assays have been done on blood and urine, and a few on pheochromocytoma tissue. The precursor relationship of DOPA and DOPamine to nor-adrenaline has also been shown in pheochromocytoma tumor tissue in vitro.

(4) Miscellaneous - Since the vasoactive substances of concern to us are derived from amino acids (tryptophan and tyrosine) we have become interested in studying various amino acids which might be important in cardiovascular disease. (a) A specific and sensitive method for assay of indoleacetic acid (tryptophan metabolite) in tissue and urine has been developed and a condition found (hereditary ataxia) which is characterized by excessive excretion of I.A.A. (b) We have collaborated at the pre-clinical level with our colleagues in biochemistry in development of methods for studying the metabolism of hydroxyproline, and amino acid found only in collagenous

protein. (c) Members of our group have embarked on studies in hypersensitivity and intestinal function as a result of the studies and observations on patients with malignant carcinoid (since these patients develop asthma, "allergic-like" skin eruptions and hypermotility of the gut). These studies are described in other reports.

Significance to Program of the Institute: The importance of studying conditions characterized by over-production of naturally occurring substances and associated cardiovascular disease is obvious. We feel that studies of amino acid metabolism in man will afford additional clues to the pathogenesis of C-V disease.

Proposed Course of Project: (1) Study pulmonary A-V serotonin difference in the plasma of carcinoid patients whose platelet serotonin has been reduced to zero by administration of reserpine. Some of the patients admitted to NHI will be transferred to NCI for use of anti-neoplastic drugs. We await the development by our associates in biochemistry of an agent which will inhibit serotonin formation in vivo. (2) Additional studies of catechol amine metabolism in pheochromocytoma patients are planned, particularly with the idea of finding metabolites in urine which might be easily measured and afford a simpler means of diagnosis. We hope to extend our studies of nor-adrenaline turnover to patients with normal and high blood pressure in order to learn more about chemical events at sympathetic nerve endings. (3) Other patients to be admitted for study will be those with various abnormalities in amino acid metabolism (e.g., phenylketonuria, albinism, hereditary ataxia, urticuria pigmentosa, hypersensitivity states, connective tissue disorders, etc.).

Form No. ORP-1
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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-133
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$30,000	$93,364	$123,364	1.2	2.7	3.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	3	4	1,000

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

a) Dr. Chozo Mitoma - NHI-127

b) Dr. W. K. Engel, NINDB

c) Dr. T. W. Mattingly, Walter Reed Army Hospital, Washington, D.C.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-133
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Sjoerdsma, A., Terry, L.L. and Udenfriend, S.: Malignant Carcinoid, A New Metabolic Disorder. Monograph. U.S.Dept. H.E.W., NHI, Bethesda, Md. October 1955, Revised July 1956.

2. Sjoerdsma, A., Weissbach, H., Udenfriend, S.: A Clinical, Physiologic and Biochemical Study of Patients with Malignant Carcinoid (argentaffinoma). Am. J. Med. 20: 520, 1956.

3. Udenfriend, S., Weissbach, H. and Sjoerdsma, A.: Studies of Tryptophan and Serotonin in Patients with Malignant Carcinoid. Science 123: 669, 1956.

4. Sjoerdsma, A., Kornetsky, C.B. and Evarts, E.: Lysergic Acid Diethylamide in Patients with Excess Serotonin. Arch. Neurol. & Psychiat. 75: 488, 1956.

5. Mattingly, T.W. and Sjoerdsma, A.: The Cardiovascular Manifestations of Functioning Carcinoid Tumors. Mod. Concept. Cardiovasc. Dis. 25: 337, 1956.

6. Sjoerdsma, A., Terry, L.L. and Udenfriend, S.: The Malignant Carcinoid Syndrome. Modern Medicine. 24: 127, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

During the past year, our scientific exhibit was shown at medical meetings in Boston, Chicago, New York, Washington, Havana and Seattle. The following honors were conferred:

a) Certificate of Merit, Section of Experimental Medicine and Therapeutics American Medical Association, Chicago, June, 1956

b) First Prize, American College of Gastroenterology, New York City, October, 1956

16. PUBLICATIONS (CONTINUED)

7. Haverback, B.J., Sjoerdsma, A. and Terry, L.L.: Urinary Excretion of the Serotonin Metabolite, 5-hydroxyindoleacetic acid, in Various Clinical Conditions. N. Eng. J. Med. 255: 270, 1956.

8. Sjoerdsma, A., Weissbach, H., Terry, L.L. and Udenfriend, S.: Further Observations on Patients with Malignant Carcinoid. Am. J. Med. In Press.

9. Davidson, J.D. Sjoerdsma, A., Loomis, L. and Udenfriend, S.: Studies with the Serotonin Precursor, 5-hydroxytryptophan, in Man and Experimental Animals. In preparation.

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-134
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Endocrinology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Study of the Movement of Large Molecules Through Aortic and Other Connective Tissues
PROJECT TITLE

7. Dr. Leroy E. Duncan, Jr.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: A better understanding of the factors which affect the movement of large molecules from the blood stream into these tissues.

Methods Employed: The substance to be studied is injected into a series of animals. At desired times the animals are killed and the concentration of the test substance in the serum and in the tissues determined.

Major Findings: The movement into and out of aorta, skin, tendon, sclera and cornea of albumin tagged with radio-iodine has been studied in the rabbit. A mathematical model which satisfactorily expresses the experimental findings has been developed.

Significance to Heart Research: Information on factors which affect the rate of movement of various sized molecules into the aortic intima may be pertinent to the movement of lipoproteins into the aortic intima in atherosclerosis.

Proposed Course of Project: Contemplated work includes (A) the study of the movement of larger molecules in experimental animals, (B) the study of the variables affecting the movement of large molecules in connective tissues, (C) the *in vitro* measurement of the movement of large molecules through aortic intima, and (D) an attempt to devise methods for the study of the movement of large molecules in living man.

Form No. ORP-1
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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-134
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$26,000	$10,972	$36,972	1.0	2.5	3.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	3	4	None

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-134
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-135
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Experimental Therapeutics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Vasomotor Responses Related to the Gastrointestinal Tract
PROJECT TITLE

7. Bernard J. Haverback, M.D.
PRINCIPAL INVESTIGATOR

8. Henry Wagner, M.D. and Albert Sjoerdsma, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The objectives of this project are to (1) investigate the vasomotor mechanisms involved in the "dumping syndrome" and (2) evaluate the status of the parasympathetic nervous system in patients with orthostatic hypotension.

Methods Employed: (1) Catechol amines are measured in the blood and urine of patients before and during the dumping syndrome. (2) The status of the parasympathetic nerves to the gastrointestinal tract is evaluated by determining (a) the gastric secretory response following insulin-induced hypoglycemia, and (b) the sigmoid colonic motility response following insulin-induced hypoglycemia.

Patient Material:	Admissions	No.	Average Stay (Days)
	Adult [illegible]	7	8

Major Findings: (1) Preliminary studies indicate that circulating catechol amines may be increased during the dumping syndrome. (2) Some patients with orthostatic hypotension have a defect in the parasympathetic autonomic nervous system as well as in the sympathetic autonomic nervous system.

Significance to Heart Research: (1) A study of the mechanisms of the release of catechol amines is pertinent to many phases of cardiovascular investigation. (2) The status of the parasympathetic nervous system may be evaluated by employing tests which affect gastrointestinal function. In patients with orthostatic hypotension, an evaluation of the status of the parasympathetic nervous system may be of help in determining the site of the lesion.

Proposed Course of Project: Further studies are planned to extend the number of observations.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-135
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$17,400	$53,755	$71,155	1.2	.7	1.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	56

13. BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION	
REVIEW & APPROVAL		PROFESSIONAL & TECHNICAL ASSISTANCE	
BIOLOGIC STANDARDS			

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Laboratory of Kidney and Electrolyte Metabolism, NHI

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-135
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-136
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Experimental Therapeutics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The Action and Metabolism of Drugs
PROJECT TITLE

7. Dr. John D. Davidson
PRINCIPAL INVESTIGATOR

8. Drs. A. Sjoerdsma, B. J. Haverback, T. P. Waalkes, L. L. Terry
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To screen new agents for desirable pharmacologic effects in man and learn more about the action of drugs through studies of their metabolism.

Methods Employed: Intravenous and oral administration of drugs with measurements of the drug in urine and blood and measurements of other appropriate parameters, i.e., blood pressure, pulse, and respiratory rate, pupil size, EKG etc.

Patient Material: Patients with persistent hypertension and other patients without hypertension and with normal renal and hepatic function.

Major Findings:

(A) Drug Action

(1) Anti-hypertensive drugs

(a) Ormosia panamensis - Ormosia is an alkaloid extracted from the seeds of a tree indigenous to Panama and a few other Central American countries. It was found to exert marked hypotensive effects in dogs. Evaluation of this drug in man revealed no effect in doses which were 25% greater than the amount necessary to cause respiratory paralysis in dogs and five times greater than an amount which invariably resulted in a blood pressure fall in dogs.

(b) Drug Potentiation Studies - Clinicians all agree that at least additive benefit occurs in the treatment of arterial hypertension by the concomitant administration of two or more anti-hypertensive drugs. The pharamologic nature of this enhanced effect has been studied by infusing less than minimal threshold doses of hexamethonium after priming with similar less than threshold doses of reserpine. Investigations to date suggest that this enhanced effect is in the nature of true potentiation rather than mere additive effect.

(c) Effects of reserpine - Reserpine was found to increase the volume and free acidity of gastric secretion while chlorpromazine reduced the volume but did not affect the free acidity.

(d) Methoxyphenylpiperazine - This substance was found to produce hypotension only in conjunction with the appearance of undesirable side reactions. The mechanism of action of the compound is probably related to an inhibition of the sino-auricular node and a decrease in cardiac output. In view of these findings this project has been abandoned.

(2) Anti-arrhythmic drugs

(a) Evaluation of MC-4112 (2-diethylaminoethylisonicotinamide) completed and paper has been published.

(b) Evaluation of RO 2-7302/4 [17-(2-piperidylmethyl)-3β, 17β-androstanediol lactate hemihydrate] is in progress. This compound appears useful in ventricular arrhythmias but of little use in supra-ventricular arrhythmias.

(3) Miscellaneous Drugs

(a) Tolazoline (Priscoline) etc., was found to evoke severe cardiac pain in a patient with a past history of angina pectoris. This phenomenon was not readily explicable in the absence of any measurable changes in cardiodynamics such as an increased pulse rate, lowered diastolic pressure, etc. An increase in myocardial contractile force of 25% was produced in a dog by the injection of therapeutic amounts of

Tolazoline. It is postulated that this sudden obligate increase in workload is sufficient to evoke myocardial ischemia in a patient with coronary atherosclerosis.

(b) Chlorpromazine Sulfoxide - This compound, the major metabolite of chlorpromazine was found to exert some of the properties of chlorpromazine in lower animals such as sedation. Postural hypotension was not observed, however, in sedative doses, contrary to what is found with chlorpromazine. For these reasons a study of this compound's metabolism and its pharmacologic effect in man was undertaken. Administration of chlorpromazine sulfoxide by a double blind technique to 12 different hypertensive and normotensive patients revealed definite sedation with virtually no postural hypotensive effect. Administration of this compound to 3 disturbed, agitated schizophrenic patients demonstrated that this compound is sufficiently active to calm psychotic patients. Increased tractability, less rigidity in catatonic states, and cessation of catatonic chatter were among the responses noted in 3 psychotic patients.

(c) Aranthol, (2-methylanine-6-hydroxy-6-methylheptane). In animals this sympathominetic amine has the property of increasing myocardial contractile force without significant pressor or central excitatory effects. In man, up to 3.0 gm/day in divided dosage produced nervousness and palpitations and failed to benefit the signs and symptoms of congestive heart failure.

(B) Drug Metabolism

(1) Papaverine: A specific and sensitive method for the estimation of papaverine in biologic material has been developed. The physiological disposition of the drug was studied in man and animals. In man, papaverine was rapidly and completely absorbed from the gastrointestinal tract and only a trace of the drug was excreted unchanged in the urine. After the intravenous administration of 3 mgm/kgm, the biological half-life in plasma was found to range from 1 to 2 hours in 3 human subjects. A relatively constant plasma level was maintained by oral administration of 200 mgm of papaverine every 6 hours for 6 days. Tissue distribution studies in dogs showed a considerable localization of the drug in fat depots and liver with uniform distribution in other tissues including brain. At therapeutic plasma levels the drug was found to be bound to plasma proteins about 90 percent. In vitro studies indicate that papaverine is cleaved by a microsomal enzyme system in liver to yield formaldehyde and presumably a phenolic metabolite. Counter-current distribution studies have shown three phenolic metabolites in urine.

(2) Chlorpromazine Sulfoxide: A specific and sensitive fluorometric method was developed for estimation of this compound in plasma and urine. Studies in man indicate it to be completely absorbed from the gastrointestinal tract, largely metabolized in the body with a biologic half-life of about 2 hours, and to accumulate slightly when given in oral dosage of 200 mgm every 6 hours.

Significance of these Studies to Heart Institute: In the past decade the only widely applicable, practical, and promising approach to the therapy of hypertension and cardiac arrhythmias has been with drugs.

Proposed Course of Project: We plan to continue and extend these types of studies to other promising compounds, particularly those developed at NIH.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-136
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$31,700	$99,022	$130,722	1.9	1.8	3.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	2	4	3,000

13. BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION	
REVIEW & APPROVAL		PROFESSIONAL & TECHNICAL ASSISTANCE	
BIOLOGIC STANDARDS			

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

a) Dr. Sidney Udenfriend - Laboratory of Clinical Biochemistry, NHI

b) Dr. Julius Axelrod - NIMH

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-136
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Davidson, J.D.: Induction of Cardiac Pain with Orally Given Tolazoline (Priscoline) Hydrochloride. J. Am. Med. Assoc. 162: 108, 1956.

2. Sjoerdsma, A., Maling, H., Pratt, H.W., Axelrod, J., Kayden, H. J., and Terry, L. L.: Evaluation of the Antiarrhythmic Action of Ambonestyl (2-Diethylaminoethylisonicotinamide, MC-4112). New Eng. J. of Med., 255: 213, 1956

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-137
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Experimental Therapeutics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The Effect of Indole Compounds on the Gastrointestinal Tract
PROJECT TITLE

7. Bernard J. Haverback, M.D.
PRINCIPAL INVESTIGATOR

8. Albert Sjoerdsma, M.D., C. Adrian Hoglen, M.D., Donald Boydanski, Ph.D. Luther L. Terry, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The objectives of this project are (1) to determine the effect of naturally occurring and synthetic indole substances on gastric secretion and intestinal motility, (2) to investigate the possibility that indole compound affect gastrointestinal functions by a common mechanism and (3) to evaluate serotonin antagonists.

Methods Employed: Indole substances have been administered to dogs with gastric fistulae and Heidenhain pouches and to man to determine their effects on gastric secretion and intestinal motility. Intestinal motility was

measured by means of open-tip tubes connected to pressure transducers. In the human, continuous gastric aspiration was accomplished by intubating the stomach under fluoroscopic guidance and constant suction was applied by a mechanical pump.

Patient Material:	Admissions	No.	Average Stay (Days)
	Adult Males	6	10
	Adult Females	6	10

Major Findings: Serotonin and its precursor, 5-hydroxytryptophan, inhibit gastric acid secretion. These substances inhibit gastric secretion stimulated by insulin induced hypoglycemia. The stimulus to gastric secretion by histamine and reserpine are not inhibited by 5-hydroxytryptophan. Reserpine and lysergic-acid-diethylamide both of which contain the indole nucleus stimulate gastric acid secretion. It has also been shown in man that when reserpine is administered in a dose of 1 mg. daily, platelet serotonin becomes virtually depleted at the end of a week. Following depletion of platelet serotonin, reserpine does not stimulate gastric acid secretion.

Serotonin and 5-hydroxytryptophan are potent stimuli to gastrointestinal motility. Lysergic-acid-diethylamide, which has been reported to be a serotonin antagonist *in vitro*, potentiates the stimulus of serotonin to intestinal motility. Bromlysergic-acid-diethylamide inhibits the stimulus of serotonin to intestinal motility.

The administration of 5-hydroxytryptophan produces gastric mucosal erosions in the rat. This finding takes on added significance as the incidence of peptic ulceration in autopsied cases of the malignant carcinoid syndrome is high. The benzyl analogue of serotonin which has been reported to be a serotonin antagonist did not prevent erosion formation but pretreatment with atropine was effective in preventing gastric mucosal erosion.

Significance to Heart Research: As serotonin has been implicated in hypertension and also in the production of valvular heart disease in the malignant carcinoid syndrome, the evaluation and clinical trial of serotonin antagonists is of interest.

Proposed Course of Project: Further studies are in progress to evaluate (1) different indole compounds on gastrointestinal function and (2) serotonin antagonists.

Form No. ORP-1
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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-137
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$34,500	$107,510	$142,010	2.7	.8	3.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	3	1	4	120

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

NHI-132

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NII-137
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Haverback, B.J., Dutcher, T.F., Shore, P.A., Tomich, E.G., Terry L.L. Brodie, B.B.: Serotonin Changes in Platelets and Brain Induced by Small Daily Doses of Reserpine. New Eng. J. of Med. In Press.

2. Haverback, B.J., Hogben, C.A., Moran, N.C. and Terry, L.L.: Effect of Serotonin (5-hydroxytryptamine) and Related Compounds on Gastric Secretion and Intestinal Motility in the Dog. Gastroenterology. In Press.

3. Haverback, B.J., Sjoerdsma, A., and Terry, L.L.: Urinary Excretion of the Serotonin Metabolite 5-hydroxyindolacetic Acid, in Various Clinical Conditions. New Eng. J. of Med. 255: 270, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-138
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Hemodynamics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Cardiac Output Determinations and Calculation of Aortic and Mitral Valve Size During Surgery and Left Heart Catheterization
PROJECT TITLE

7. Herbert L. Tanenbaum, M.D.
PRINCIPAL INVESTIGATOR

8. A. G. Morrow, M.D., Eugene Braunwald, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To measure cardiac output during left heart catheterization, calculate aortic valve and mitral valve size from pressure and flow data and to do similar determinations during mitral and aortic valve surgery.

Methods Employed: Cardiac output obtained by dye dilution curves injecting Evan's Blue dye into the left ventricle. Pressure measured in the conventional way and valve size calculated from the above information by use of Gorlin's hydraulic formulae.

Patient Material: 11 patients during left heart catheterization
3 patients at surgery
Average stay - 14 days

Major Findings: Pressure gradients vary directly with changes in the square of the flow hence the importance of measuring both simultaneously. Valve area gives a relative estimation of degree of valvular stenosis and benefit following surgery.

Significance to Heart Research: Better definition of dynamics of mitral and aortic valve disease.

Proposed Course of Project: Collect more data. Relate valve areas to symptoms and other objective findings pre- and post-operatively. Establish bronchoscopic approach to left heart catheterization as valid means of defining more closely mitral and aortic valve disease.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-138
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$17,500	$7,253	$24,753	1.3	.2	1.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	196

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-138
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-139
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Endocrinology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Studies of the Relationship of Steroid Structure to Function
PROJECT TITLE

7. Frederic C. Bartter, M.D.
PRINCIPAL INVESTIGATOR

8. Grant W. Liddle, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The object of this project is to attempt by comparison of steroids with analogous compounds bearing a single structural alteration to determine the fundamental relationship of steroid structure to physiologic action.

Methods Employed: Metabolic balance studies were conducted in normal volunteer subjects and in patients with Addison's disease. Studies of renal function were performed at intervals throughout the studies. Assays for the acute effects of the steroids on renal sodium and potassium excretion were carried out in dogs.

Patient Material	Admissions	No.	Average Stay (Days)
	Adult Females	5	100
	Adult Males	4	60

Major Findings: It was found that introduction of a methyl group on the second carbon atom of steroids increased sodium retaining and potassium losing activity of the steroids which also had a hydroxyl group in the 11-beta position. The same structural alterations decreased the biologic activity of steroids possessing a ketone group or no oxygen function on the 11-carbon. It was found that steroids bearing a methyl group on the 2-carbon atom were much more slowly degraded in the body than their non-methylated analogs.

Significance to Heart Research: These studies are designed to elucidate the mechanism whereby steroids exert their characteristic actions. This should contribute understanding both of the basic processes involved in inflammatory diseases (e.g., rheumatic fever) and of those involved in pathologic salt retention. It is hoped that they may also give rise to steroids effective either directly or through competition with endogenous mechanisms.

Proposed Course of Project: Newer steroids will be tested as they are made available, largely through pharmaceutical houses. The close cooperation of the pharmaceutical houses in synthesizing steroids designed to elucidate mechanisms has been an indispensable part of this program. Syntheses have not been attempted in this department in view of this cooperation.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-139
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,500	$24,048	$31,548	.3	.7	1.0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	160

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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(Attachment I)

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-139
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Liddle, G.W., Richard, J.E. and Tomkins, G.M.: Studies of Structure-Function Relationships of Steroids: The 2-Methyl Corticosteroids. Metabolism. V: 384, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-140
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Endocrinology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Chemical and Physiological Studies of Aldosterone Metabolism
PROJECT TITLE

7. Frederic C. Bartter, M.D.
PRINCIPAL INVESTIGATOR

8. Philip Chen, Ph.D., Harold P. Schedl, M.D., Grant W. Liddle, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The objectives of this study are to elucidate the mechanisms whereby sodium and water homeostasis is normally maintained and to investigate the pathologic physiology of salt and water retention in edema formation. Because of its central role in sodium metabolism, aldosterone has commanded the large part of our attention.

Methods Employed: (A) In metabolic balance studies, normal subjects have been studied under various experimental conditions during which sodium and potassium balance were altered, and aldosterone excretion studied. (B) Renal clearances were performed in subjects with Addison's disease to determine the acute effects of aldosterone on renal function. (C) Chemical studies on the isolation and measurement of aldosterone in urine and in serum were instituted.

Patient Material:	Admissions	No.	Average Stay (Days)
	Adult Males	4	90
	Adult Females	12	90

Major Findings: (A) Studies on role of ACTH in the control of aldosterone secretion were completed. These are described in the first paper under "Publications" and will not be referred to further. The effect on aldosterone secretion of changes in dietary potassium was investigated further. Studies wherein marked alterations in potassium balance were produced by potassium loading and by potassium depletion were performed on the metabolic ward. Determinations of inulin space were carried out in potassium depleted and potassium loaded subjects.* The previous observation that potassium loading increased aldosterone excretion was confirmed. The effect of this procedure on extracellular fluid volume is still under investigation. When extracellular fluid volume was expanded at the same time that potassium loading was done, aldosterone excretion fell. The effect of changes in extracellular fluid volume was investigated further. Changes in the intravascular volume were produced by the withdrawal and reinfusion of blood and by the infusion of albumin in the normal and hypoproteinemic subjects. It was found that the initial effect of all measures which decrease intravascular fluid volume was to increase aldosterone secretion and that of all the measures which increased intravascular volume was to decrease aldosterone secretion. (B) Renal clearances were performed on 4 Addisonian subjects before and during the administration of aldosterone intravenously. Aldosterone administration was consistently followed by retention of sodium and by increased excretion of potassium and of hydrogen ions. (C) The method of Neher and Wettstein for the physical-chemical measurement of aldosterone was set up and determinations parallel with those of our bioassay method were instituted. A number of chromatographic reactions were investigated in the attempt to produce better quantitative methods for the estimation for aldosterone.

Significance to Heart Research: It has been shown repeatedly that the salt retention in edematous states including cardiac failure is accompanied by high levels of urinary aldosterone. It is clearly of importance in determining the physiologic significance of edema and the fundamental mechanism by which it is produced to understand the normal mechanisms whereby aldosterone secretion is controlled.

Proposed Course of Project: The physiologic studies in man will be extended to the dog where such a procedure is feasible. The chemical studies will be pursued as aggressively as permitted by distribution of manpower.

* These studies form part of another project performed in conjunction with Dr. Ernest Cotlove.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-140
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$26,800	$83,461	$110,261	2.0	.8	2.8

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	1	3	1,000

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. Ernest Cotlove - Laboratory of Kidney & Electrolyte Metabolism, NHI

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-140
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Bartter, Frederic C.: The Role of Aldosterone in Normal Homeostasis and in Certain Disease States. Metabolism, V: 369, 1956

2. Liddle, Grant W., Duncan, Leroy E., Jr. and Bartter, Frederic C.: Dual Mechanism Regulating Adrenocortical Function in Man. Amer. J. of Medicine, XXI: 380, 1956.

3. Duncan Leroy E. Jr., Liddle, Grant W., and Bartter, Frederic C.: The Effect of Changes in Body Sodium on Extracellular Fluid Volume and Aldosterone and Sodium Excretion by Normal and Edematous Men. J. of Clinical Investigation, 35: 1299, 1956.

4. Bartter, Frederic C., Liddle, Grant W., Duncan, Leroy E. Jr., Barber Joan K. and Delea, Catherine: The Regulation of Aldosterone Secretion in Man: The Role of Fluid Volume. J. of Clinical Investigation, 35: 1306, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-141
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Endocrinology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Action of Parathyroid Hormone
PROJECT TITLE

7. Frederic C. Bartter, M.D.
PRINCIPAL INVESTIGATOR

8. Pacita Pronove, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The objectives of this project are to study the physiology of the parathyroid gland and to improve the measures available for establishing the diagnosis of hyperparathyroidism.

Methods Employed: Four types of tests were carried out in a number of normal subjects and in four patients suspected of hyperparathyroidism. These were (1) Tm of phosphorus, (2) response of the urine phosphorus to intravenous calcium, (3) response of the serum and urine calcium to amphogel ingestion and (4) response of urine calcium to ammonium chloride administration.

Patient Material:	Admissions	No.	Average Stay (Days)
	Adult Males	5	40
	Adult Females	5	40

Major Findings: The tests indicated the probable presence of hyperparathyroidism in one subject and removal of a parathyroid tumor was carried out. The normal variation of the response to the tests described was delineated. It appeared from these studies that the response to serum calcium and phosphorus to a low phosphorus intake or to amphogel, and the Tm of phosphorus convey the most reliable information with regard to the presence or absence of parathyroid ademona.

Significance to Heart Research: These studies are designed to throw light on the fundamental mechanisms of phosphorus and calcium metabolism in biology. The information so attained may be expected to throw light on the role of abnormal phosphorus and calcium metabolism in disease states.

Proposed Course of Project: These studies will be pursued both in the normal and in the patients suspected of hyperparathyroidism and when at all possible in patients known to have hyperparathyroidism.

Patient Material:	Admissions	No.	Average Stay (Days)
	Adult Males	5	40
	Adult Females	5	40

Major Findings: The tests indicated the probable presence of hyperparathyroidism in one subject and removal of a parathyroid tumor was carried out. The normal variation of the response to the tests described was delineated. It appeared from these studies that the response to serum calcium and phosphorus to a low phosphorus intake or to amphogel, and the Tm of phosphorus convey the most reliable information with regard to the presence or absence of parathyroid ademona.

Significance to Heart Research: These studies are designed to throw light on the fundamental mechanisms of phosphorus and calcium metabolism in biology. The information so attained may be expected to throw light on the role of abnormal phosphorus and calcium metabolism in disease states.

Proposed Course of Project: These studies will be pursued both in the normal and in the patients suspected of hyperparathyroidism and when at all possible in patients known to have hyperparathyroidism.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-141
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$17,400	$53,755	$71,155	1.2	.7	1.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	400

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-141
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Bartter, Frederic C.: Metabolic Bone Disease in Diseases of Metabolism, George Smart, Editor.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI - 142
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Endocrinology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Cellular Transport Systems
PROJECT TITLE

7. A. Despopoulos
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To describe the reactions by which tissues can accumulate the specific substances required for synthesis of biologically required materials and eliminate the unessential products of cellular metabolism.

Methods Employed: The general objectives described are approached specifically by the examination of renal function in patients, in intact animals and in tissue experiments. The data derived from in vitro experiments are correlated with studies in patients and in intact animals.

Major Findings:
1. Seventeen derivatives of uric acid and fourteen derivatives of barbituric acid were examined for their ability to depress the accumulation of p-aminohippuric acid by slices of rabbit kidney cortex. The inhibitory potency of the urates depended upon the presence of a carbonyl radical at position 2 or 8 of the molecule. N-methylation of the molecule increased the inhibition. Barbituric acid, barbital and

phenobarbital possessed essentially equivalent potency but were less active than uric acid. N-methylation of the barbiturates increased the inhibition, but N-ethylation produced no effect. The data may be interpreted as demonstrating a non-ionic interaction between urates or barbiturates and a component of the tubular excretory system for organic anions. The inhibition produced by uric acid appear to be non-competive and apparently is produced without influencing the respiratory function of the tissue.

2. 5-hydroxyindolacetic acid, the end product of tryptophane metabolism is eliminated by an active tubular excretory process in patients with malignant carcinoid and is concentrated actively by slices of rabbit kidney cortex. These findings indicate that the renal excretion of this compound is similar to that of p-aminohippurate.

Proposed course of project: The findings above represent the first demonstration of the active renal tubular excretion of an indole acid. Additional indoles will be examined in order to describe the structural requirements for renal transport and to attempt a correlation with other molecular types which are known to be excreted by tubular activity. In addition, inhibitors of the transport system will be studied in order to establish, if possible, their locus of action in the renal cellular structure.

Significance to Heart Research: An understanding of renal excretory mechanisms increases the probability of designing drugs which will hasten the excretion of undersirable metabolites or which will retard the excretion of essential metabolites or of beneficial drugs. As applied to the indoles, this information should increase the understanding of the metabolism and physiological action of this important class of compounds. An extension of this work to other tissues may ultimately permit a clarification of the mode of action of pharmacological agents and of the mechanisms responsible for the maintenance of tissue integrity.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-142
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$17,000	$8,527	$25,527	1.0	1.0	2.0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	None

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI - 142
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI - 143
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Experimental Therapeutics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Anaphylaxis and Hypersensitivity
PROJECT TITLE

7. T. Phillip Waalkes, Ph.D., M.D.
PRINCIPAL INVESTIGATOR

8. Herbert Weissbach, Ph.D.; Sidney Udenfriend, Ph.D.
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: Anaphylaxis in animals has been studied during the past year to determine what possible physiologically active substances, may be released within the animal from a bound, inert form to a free active form during this process. The emphasis during this time has been on the possible release of serotonin in anaphylaxis in the rabbit and to study this release along with the simultaneous liberation of histamine. Further long range objectives are to gain a better understanding of anaphylaxis and by so doing gain knowledge into the process of hypersensitivity and allergic phenomenon. By so doing, it is hoped to be able to study and to understand better those disease of hypersensitivity which affect the cardiovascular system, e.g., rheumatic fever.

Methods Employed: During this year, anaphylaxis has been studied both by *in vitro* and *in vivo* techniques in the rabbit. For the *in vitro* work, rabbit blood from a sensitized animal was used and the specific antigen mixed with it. Serotonin and histamine were measured in the plasma after anaphylaxis both *in vitro* or *in vivo*.

Major Findings: The above studies have shown that serotonin is released during anaphylaxis in a similar manner to histamine both as to time and to amount.

Significance: The above findings indicate that another vaso active substance (serotonin) is released during anaphylactic shock in addition to histamine. Serotonin may also be liberated during less severe or during chronic allergic phenomena and may be a factor in hypersensitivity diseases. An understanding of the processes involved in anaphylaxis may give clues as to those processes involved in diseases of hypersensitivity in which the cardiovascular system is a fundamental part.

Proposed Course of Project: The study of anaphylaxis will be extended to other animal species. Whether serotonin is a major factor in the acute manifestations of anaphylaxis of animals other than rabbits should be determined. In addition, the release of other substances during anaphylaxis (e.g. adrenalin) should be investigated. By *in vitro* techniques, these studies in anaphylaxis will be extended to human blood.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-143
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$39,000	$19,520	$58,520	2.0	1.0	3.0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	3	1	4	None

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

a) John Bozicevich-NIAID

b) H. H. Weissbach-NHI 129

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI - 143
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI - 144
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Clinical Electrocardiography
PROJECT TITLE

7. Robert P. Grant, M.D.
PRINCIPAL INVESTIGATOR

8. Herbert L. Tanenbaum, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

We have for some years been studying the usefulness of vector methods in clinical ECG interpretation. During the past year we completed a study of ventricular conduction defects, arrhythmias, and a clinical autopsy correlation study (see publications). The past six months has been devoted to preparing a new edition of the book "Spatial Vector ECG" which McGraw-Hill will publish this winter. Projected work for the next year includes a study of the pre-excitation syndrome and further study of hemodynamic factors in the genesis of T wave abnormalities.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-144
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,600	$32,536	$43,136	.7	.4	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	60

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

a) Dr. George Kelser, George Washington University Medical School

b) Dr. George Manning, Royal Canadian Air Force

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI - 144
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Grant, R. P., LEFT AXIS DEVIATION, Vol. XIV, No. 2, August, 1956, Circulation

2. Grant, R. P., H. T. Dodge, MECHANISMS OF QRS COMPLEX PROLONGATION IN MAN, June Issue, Volume XX, number 6, pages 834-852, The American Journal of Medicine, Inc., (Left Ventricular Conduction Disturbances)

3. Dodge, H. T., R. P. Grant, MECHANISMS OF QRS COMPLEX PROLONGATION IN MAN, Oct. Issue, Volume XXI, number 4, pages 534-550, The American Journal of Medicine, Inc., (Right Ventricular Conduction Disturbances)

4. Grant, R. P., THE MECHANISM OF A-V ARRHYTHMIAS, March Issue, Volume XX, number 3, pages 334-344, The American Journal of Medicine, Inc.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI - 145
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Hemodynamic and Metabolic Factors of Heart Disease
PROJECT TITLE

7. Robert P. Grant, M.D.
PRINCIPAL INVESTIGATOR

8. H. Tanenbaum, A. G. Morrow, F. Bartter
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

The volumetric and pressure changes in the various chambers of the heart are studied by catheter and angiocardiographic technique. We have completed a study of the pressure-volume changes in mitral valve disease and presented this material at the recent American Heart Association Meetings in Cincinnati. We are now concentrating on the cases of mitral insufficiency and giant left atrium, studying blood volume compartmentalizing, renal-electrolyte, and tissue nitrogen metabolic alterations in these subjects.

We are also studying the pulmonary vascular resistance in patients with heart disease, examining the extent and mechanisms of adaptation to increased pressure produced by the G-suit.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-145
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$19,800	$62,242	$82,042	.7	.4	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	2,000

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Collaborative with the Surgery Branch and the Section on Endocrinology of the General Medicine and Experimental Therapeutics Branch

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI - 145
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI - 146
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The Evaluation of Cardiac Reserve in Human Subjects as Reflected by Alterations in Lung Elasticity and Resistance to Gas Flow
PROJECT TITLE

7. Donald L. Fry, M.D.
PRINCIPAL INVESTIGATOR

8. Robert Hyatt, M.D., Charles McCall, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Project: To evaluate the cardiac reserve in human beings as reflected by the alterations in lung elasticity and resistance to gas flow.

Objectives: Previous studies have shown that the elastic properties of the lung and the resistance to gas flow are markedly altered in cardiac decompensation. The purpose of this study is to determine at what level of "cardiac reserve" these changes become apparent. It is hoped that these alterations of pulmonary function may reflect embarrassment of cardiac reserve not detectable by conventional means.

Methods Employed: The intraesophageal pressure recording balloon method was used to measure the elastic properties of the lung. Other procedures as outlined by D. L. Fry et al. The Mechanics of Pulmonary Ventilation in Normal and in Patients with Emphysema. Amer. J. Med. XVI:80, 1954.

Major Findings: Working in conjunction with the National Instrument Laboratories an electromechanical system was devised to maintain constant gas volume in a patient spirometer system. A thermal conductivity cell senses the concentration of a tracer gas, helium. Any change in concentration is thereby converted to an electrical impulse through a servo-mechanism which admits oxygen to the spirometer. In this way the metabolic needs of the subject are constantly met in spite of wide variations in oxygen consumption.

A new type of respiratory flow meter has been developed for this project. This meter with two conventional types has been evaluated as to accuracy and stability.

Respiratory flow patterns under various conditions have been obtained with this meter and subjected to harmonic analyses. Although the diagnostic significance of the harmonic content of these patterns is as yet unclear, much valuable knowledge has been obtained for theoretical computations in the field of ventilating mechanics and in the field of respiratory instrument design.

Significance to Heart Research: The possible development of a method for early detection of reduced cardiac reserve.

Proposed Course of Project: Considerable difficulty has been met in perfecting the constant gas volume system. The injecting mechanism tends to "hunt". Present efforts are toward perfection of this device for patient use.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-146
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$37,000	$114,583	$151,583	2.0	2.5	4.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	3	5	None

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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(Attachment I)

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI - 146
SERIAL NUMBER

16. **LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:**

Fry, D. L., Mallos, A. J., and Casper, A.G.T., A Catheter tip method for measurement of the instantaneous aortic blood velocity, Circulation Research 627:5, 1956

Fry, D. L., Noble, F. W., and Mallos, A. J., An electrical device for the instantaneous and continuous computation of the aortic blood velocity, Circulation Research in press, Vol 6, 1957

17. **LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:**

None

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI - 147
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Evaluation of the Recording Characteristics of Modern Physiological Pressure Measuring Systems
PROJECT TITLE

7. Donald L. Fry, M.D.
PRINCIPAL INVESTIGATOR

8. Frank W. Noble, M.E.E.
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Project: The evaluation of the recording characteristics of commercially available physiological pressure recording systems.

Objectives: A comprehensive evaluation of the stability, static accuracy and dynamic accuracy of the many combinations of catheters and physiological pressure gages that are commonly used. To make available to the investigator a fund of reference data from whic he may choose a pressure recording system for his specific study which will reduce recording artefacts to a minimum.

Methods Employed: High fidelity pressure pulse tracings cannot be recorded via conventional catheter-manometer systems, although they are adequate for measuring mean pressures. When high frequency response if required, a gage attached directly to a needle or a catheter tip manometer should be used. Gages and catheter systems varied widely in the qualities for which they were evaluated. Care must be exercised to select the proper system for the particular study.

Significance to Heart Research: Data have been compiled and presented to the investigator who is interested in accurate measurement of pressure events. Although pressure manometer systems are in common use in connection with cardiac catheterization and other laboratory procedures, these limitations are little understood. A knowledge of the characteristics of his measuring instruments, should enable the investigator to obtain more faithful pressure contours and more confidently interpret his experimental data.

Proposed Course of Project: Finished.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-147
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$11,400	$5,708	$17,108	.5	1.0	1.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	None

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI - 147
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Fry, D. L., Noble, F. W. and Mallos A. J., An Evaluation of Modern Hydraulic Pressure Measuring Systems, Circulation Research in press Vol. 5, 1957

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-148
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Investigations
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The Evaluation of the Mechanical and Hydrodynamic Characteristics of the Cardiovascular System in Animals
PROJECT TITLE

7. Donald L. Fry, M.D.
PRINCIPAL INVESTIGATOR

8. Frank W. Noble, M.E.E.
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Project: It was the original aim of this study to evaluate the power output of the heart only. The techniques devised to do this however opened up a new approach to the entire field of cardiovascular mechanics and hemodynamics. It is proposed now to expand the original study of heart power outpu. to include the measurement of:

1) the viscous and elastic properties of the vascular bed and aorta in vivo,
2) the measurement of the transmission time of the pulse wave between the various points of the vascular beds
3) the dynamic dimensions of the aorta in vivo
4) the mean pressure throughout the vascular bed
5) the phase and group velocity of the pressure pulse wave
6) the ejection curve of the heart
7) the flow curve in the distal aorta

Objectives: On the basis of theoretical considerations, the above measurements should lead to: 1) the power output of the heart

2) the power losses in the aorta and peripheral vascular bed 3) elucidation of the "standing waves" mechanism 4) elucidation of the role of elasticity and viscosity in the normal function of the vascular system 5) prediction of the ejection curve from the peripheral pressure pulse.

Methods employed: Blood velocity is measured by means of a new type flow-meter developed for this study and which is inserted directly in the aortic arch. Aortic pressure is measured by means of a short flexible trocar inserted in the aorta. Instantaneous aortic diameter is measured by electronic calipers developed for this project. A Survey Gage is utilized to measure pressures in the arteries at various points in the vascular system. By mathematical consideration of the above measurements, we hope to attain the objectives stated.

Major Findings: 1) Two new types of blood velocity measuring techniques have been developed and reported (see below), a) a nylon orifice meter which can be introduced low in the aorta and passed to a point just above the valves, b) a catheter tip blood velocity measuring technique consisting of a double lumen catheter attached to a differential pressure measuring device. The catheter technique will be applicable to human beings. 2) An electrical computer has been developed to instantaneously and continuously compute the aortic blood velocity from the "raw data" furnished by the above noted catheter and differential pressure gage system. 3) It has been established that the mean pressure varies only slightly between the aortic valves and the femoral arteries although marked changes in contour occur.

Significance to Heart Research: The development of an accurate method for measuring instantaneous cardiac output would make possible the evaluation of pharmacologic agents and surgical procedures in the treatment of heart and vascular disease. A broader knowledge of the mechanical and hydrodynamic principles of the cardiovascular system might lead to a greater insight into the etiology and treatment of cardiovascular disorders.

Proposed course of project: Current research is directed along avenues leading to simultaneous measurement of all parameters outlined above.

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October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-148
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$12,800	$5,393	$18,193	.9	.5	1.4

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	None

13. BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION	
REVIEW & APPROVAL		PROFESSIONAL & TECHNICAL ASSISTANCE	
BIOLOGIC STANDARDS			

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Laboratory of Technical Development, NHI-209

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI - 148
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

A catheter tip method of measurement of the instantaneous aortic blood velocity, Circulation Research, September, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI - 149
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Clinic of General Medicine and Experimental Therapeutics
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Dynamics of Aortic Stenosis
PROJECT TITLE

7. Dr. Harold T. Dodge - Dr. Herbert L. Tanenbaum
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Project: Development of methods to further evaluate the dynamics of aortic stenosis

Objective: A better definition of the pathologic physiology in the patient with aortic stenosis

Methods Employed: In conjunction with the surgical group who have developed methods for measuring left intraventricular and aortic pressures, we have been doing cardiac outputs by means of the dye methods, at first using a multiple sampling device with analysis of individual timed dye containing blood samples.

Patient Material:

		No.	Average Stay Days
Admissions:	Adult males	3	21

Major Findings: After a period of trial and error concerning site of dye injection, method of sampling and analysis of curves, etc., we are finally in a position to start collecting data.

Significance to Heart Research: These studies will make it possible to calculate not only the pressure gradient across the aortic valve, but also left ventricular work, effective left ventricular work, aortic valve orifice size. The data can also then be compared to post operative data

Proposed Course of Project: Work is now in progress to record outputs by means of a cuvette and densitometer with direct recording of the dye curves. Also further studies on methods to inject and measure dye directly into the left atrium at the time of bronchoscopy and left atrial puncture.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-149
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$16,400	$50,926	$67,326	1.3	.3	1.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	0	?	63

13. BUDGET ACTIVITY:

RESEARCH	A	ADMINISTRATION	
REVIEW & APPROVAL		PROFESSIONAL & TECHNICAL ASSISTANCE	
BIOLOGIC STANDARDS			

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Surgery Branch, NHI

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NH1 - 1149
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-150
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Gerontology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5. Baltimore City Hospitals,
Baltimore 24, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Metabolism & Endocrinology a. Thyroid function
b. Vitamin B_{12}
PROJECT TITLE

7. George W. Gaffney
PRINCIPAL INVESTIGATOR

8. Thyroid function studies:
Gregerman, Bahn,
Shock, Kitzes, Hollander
Vitamin B_{12} studies:
Shock,
Show (Johns Hopkins)
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To gain information on alteration with age in "normal" human adult males of:

a. Thyroid function
1. In "working state"
2. In response to thyroid stimulating hormone (TSH)
b. Adequacy of body stores of vitamin B_{12} as measured by:
1. Serum levels
2. Absorption of orally-administered vitamin B_{12}

NHI-150
SERIAL NUMBER

Methods Employed: a. Thyroid gland uptake and disappearance from the plasma of iodide^{131}, protein-bound iodine in the serum, BMR (open circuit), body water determinations by antipyrine and thiocyanate methods.
b. 1. Microbiological estimation of B_{12} in serum. 2. Appearance of radioactivity in urine after oral administration of radioactive vitamin B_{12} followed by a large intramuscular "flushing" dose of unlabelled B_{12}.

Patient Material: Patients of the Gerontology Branch and Infirmary Division of the Baltimore City Hospitals.

Major Findings: a. Thyroid function: 1. In "resting state". Preliminary evaluation of studies not yet completed indicated decrease in the uptake of radioactive iodide^{131} by the thyroid gland with advancing age in "healthy" adult males. 2. Response to TSH: Studies were designed to evaluate, in men of various ages, maximal response to administration of thyroid stimulating hormone (TSH). In two middle-aged (ages 45,51) and three elderly (ages 80,86,92) males there was no significant age difference in response, with respect to increment in BMR, PBI, and rate of uptake of I^{131} by the thyroid gland.

b. Vitamin B_{12}: 1. Serum B_{12} levels: In this study of 511 "healthy" human subjects of ages 20 to 94, there was significant decrease in serum B_{12} level with advancing age. Referred to an estimated B_{12} level at age 50 of about 230 micromicrograms per ml. of serum, the B_{12} level decreased about 20 micromicrograms per ml. for each decade of age. If diet played any significant role in this decrease, the evidence suggested, it was due to selection from an adequate diet by the subjects themselves.

2. Absorption: Urinary excretion of orally-administered radioactive vitamin B_{12}, following parenteral administration of a large "flushing" dose of unlabelled B_{12}, was not significantly different in elderly male subjects as compared to young adult males.

Significance of the Program to the Institute: The program serves the needs of the Gerontology Branch as a portion of the Institute devoted largely to the study of aging as a biological phenomenon.

Proposed Course of the Project: The above-noted studies will be completed during the next six months.

Further studies of thyroid function in the "resting state" will utilize measurements of the protein-bound iodine and I^{131}-thyroxine disappearance rate in order to estimate the rate of thyroid hormone synthesis and degradation in men of various ages.

Beyond this point it is anticipated that there will be increasing need for animal studies for confirmation, under controlled laboratory conditions, of the results obtained in man, and also for further study to determine the mechanisms involved in the observed changes with age. Initially such

studies will include evaluation, in rats of various ages, of thyroid I^{131} uptake, the rates of synthesis and degradation of thyroid hormone using the thyroxine-disappearance method, of the maximal response of the thyroid gland to TSH administration, and of the BMR and PBI in the rat.

Following or concurrent with the above studies, there should be tissue studies in the rat to search for physiological alterations which account for the observed alterations of function, if any, with advancing age.

The studies described above would require from three to ten years to complete, depending on personnel and other budgetary support and, to some extent, on good fortune in choice of approaches to elucidate the key metabolic defects, if existent.

It is anticipated that further studies with vitamin B_{12} will include measurement of plasma levels at appropriate intervals following the administration of much smaller oral doses of radioactive B_{12} than heretofore utilized. These studies will include measurement of B_{12} appearing in stools. Attempt will also be made to measure radioactivity appearing in the urine in the absence of a "flushing" dose of unlabelled B_{12}, but it is not expected that the latter will be practical except to set upper limits on the amount of B_{12} lost from the plasma into the urine.

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October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-150
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$49,800	$2,663	$52,463	2.6	3.3	5.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	3	4	7	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Baltimore City Hospitals

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-150
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Shock, N. W.: Physiological aspects of mental disorders in later life. Chap. IV in: Oscar J. Kaplan (Editor), Mental disorders in later life. Stanford Univ. Press, Stanford, 1956, 2nd Edition, pp. 47-97.

Shock, N. W.: Some physiological aspects of aging in man. Bull. N.Y. Acad. Med., 32: (4), 268-283, April 1956.

Shock, N. W.: The effects of some of the steroid hormones on the metabolic balances in aged males. In: E. T. Engle and G. Pincus, (Editors), Hormones and the aging process. Academic Press, Inc., New York, 1956, pp. 283-298.

Shock, N. W.: Some physiological aspects of aging in man. Amer. Practitioner, 7: (9), 1423-1428, Sept. 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

N. W. Shock was appointed to the Program Committee of the Fourth International Gerontological Congress to be held in Mirano and Venice, Italy in July 1957.

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-151
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Gerontology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5. Baltimore City Hospitals, Baltimore 24, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Age Changes in the Chemical Composition of Various Tissues of the Rat
PROJECT TITLE

7. Marvin J. Yiengst
PRINCIPAL INVESTIGATOR

8. C. H. Barrows, N. W. Shock
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: The objectives of this project are to investigate age changes in chemical composition of tissues. The principal aim of the project is the development of a suitable means for the estimation of cell mass.

NHI-151
SERIAL NUMBER

Methods Employed: Standard methods of chemical analysis are used for the determination of tissue components such as sodium, chloride, potassium, phosphorus, nitrogen, fat and water in liver and muscle of rats of different ages. A smaller number of components are determined in brain, kidney and heart because of the size limitation of these tissues.

Major Findings: A comparison of the chemical composition of muscle was made between young rats aged 12-15 months and older animals aged 24-27 months. Examination of this tissue in male rats showed an agewise increase in extracellular electrolytes, a decrease in cellular components and no change in total water. Intracellular water was calculated by difference between total water and chloride space. The three cellular components and intracellular water all showed a decrease of 6% which was statistically significant at the 0.1% level. There was no change with age in the ratios of the cellular components. A similar but less significant trend was found in muscle of old female rats. These findings indicate 1) a loss in cell mass of skeletal muscle during aging and 2) suggest that this may be an actual loss of cell numbers because of the constancy of cell composition.

There were no significant changes, due to age, in any of the liver components examined. Work, now in progress, is directed toward obtaining information on the chemical composition of brain and kidney.

Significance to Heart Research: This project is directed toward an evaluation of the aging process by providing information on the degree of change of the intracellular phase of tissues. Such cellular phase changes are one of several important contributing factors to reduced tissue metabolism in old age, the other being circulatory impairment. Thus the role of the cardiovascular system in aging may be better evaluated by estimations of cell mass.

Proposed Course of Project: Studies on the chemical composition of tissues will be extended to include heart as old animals become available. Work currently in progress on tissues will be completed.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-151
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$18,200	$975	$19,175	.7	1.8	2.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Baltimore City Hospitals

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-151
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-152
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Gerontology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. ____
SECTION OR SERVICE

5. Baltimore City Hospitals, Baltimore 24, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Age Changes in Renal Physiology
PROJECT TITLE

7. N. W. Shock and C. H. Barrows
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The objectives of this project are to describe and elucidate the mechanisms of age changes in renal function.

Methods Employed: For studies on the human, standard clearance methods for estimating GFR, renal plasma flow and T_m are used.

Studies on tissue slices and homogenates prepared from rats of different ages are analyzed by standard methods for specific enzyme activities.

NHI-152
SERIAL NUMBER

Major Findings: With rising plasma levels of vitamin B_{12} produced by continuous intravenous infusion in male adults, the amount of B_{12} appearing in the urine was significantly less than the amount filtered at the glomerulus. Although the data connot offer proof of tubular reabsorption of B_{12}, it is apparent that under the conditions of these experiments, there was retention of B_{12} in the body.

In old female rats there was a decrease (21%) in the cytochrome C oxidase activity of kidney tissue (wet weight basis) that was greater than the age reductions in DNA, RNA on protein N of the tissue. In male, rats, no significant changes occurred in this enzyme system.

Tests of oxidative phosphorylation in old (24-27 month) and young (8-10 month) rat kidney tissue showed a decrement in the old tissue when enzyme activity was based on wet weight. The decrease in the rate of esterification of inorganic phosphate was greater than the reduction in oxygen uptake. Thus a reduction in P to P ratio was found in the old kidney tissue.

Thus evidence of age changes in cellular metabolism is beginning to accumulate.

Significance to Heart Research: The incidence of renal disease increases with age. Consequently it is important to identify changes in renal function that may occur with age prior to the development of clinically identifiable renal disease. Knowledge about age changes in renal mechanisms is necessary for the development of rational methods for the prevention and treatment of kidney disease.

Proposed Course of Project: Serial determinations on age changes in kidney function in the same subjects will be continued.

The experiments on rats will be extended to other enzyme systems. In addition, studies on the concentrating ability of kidney slices with respect to PAH will be initiated.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-152
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$9,700	$523	$10,223	.5	.6	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Baltimore City Hospitals

Johns Hopkins University School of Hygiene and Public Health

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-152
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Stoloff, I., D. M. Watkin and N. W. Shock: Age and the ratio $T_m PAH/T_m$ diodrast. J. Geront., 11: (4), 388-390, Oct. 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-153
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Gerontology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5. Baltimore City Hospitals, Baltimore 24, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Age Changes in Cellular and Tissue Biochemistry
PROJECT TITLE

7. Charles H. Barrows
PRINCIPAL INVESTIGATOR

8. Shock, Yiengst, Falzone and Gregerman
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The objective of this project is to examine various tissues of rats for age changes in the amount of protoplasm and to determine the metabolic characteristics of the existing protoplasm.

NHI-153
SERIAL NUMBER

Methods Employed: These experiments have been carried out on slices, and homogenates prepared from various tissues of 12-14 month old and 24-27 month old rats, bred in our laboratory animal quarters. Established methods have been employed for the determination of specific enzyme systems and of various tissue components such as DNA, RNA and protein N.

Major Findings: Previous studies indicated that a decreased succinoxidase of kidney and heart but not liver may represent an initiating change which occurs during aging. Although the enzyme system succinoxidase is an intregrated system composed of two enzymes viz succinic dehydrogenase and cytochrome C oxidase, no agewise decrements in the concentration of succinic dehydrogenase based on the protoplasmic mass of the tissue (concentrations of DNA, RNA and protein N) were observed. Experiments now in progress indicate that the proposed agewise decrease in the concentration of cytochrome C oxidase does exist. Since this enzyme is important in the formation of the high energy phosphate bonds of ATP, the oxidiative phosphylation of various tissue of young and old rats is also presently being examined. These data indicate that the rate of oxidiative phosphylation may be reduced in certain tissues of senescent rats when the activity is based on the wet weight of the tissue samples. Thus these results imply that the energy production within the tissue of old rats is decreased.

Since all enzymes thus far isolated from tissues are proteins, the estimation of changes of these activities provides a means of measuring tissue protein synthesis. Therefore the concentration of plasma cholinesterase, an enzyme whose concentration is known to be readily changed by conditions which effect tissue protein synthesis, was determined in men and female rats. A comparison of the concentration of this enzyme in 12 and 24 month old female rats demonstrated a marked decrease in the older animals ($P < .001$). Although no significant difference in the concentration of this enzyme in the liver was observed, inspection of the individual values within the older group showed approximately 40% of the old animals with liver cholinesterase values of only 50-75% of all other animals. The corresponding plasma cholinesterase was extremely low. Data thus far obtained on the concentration of plasma cholinesterase of 129 men between the ages of 20-89 years demonstrate a decrease in subjects over 70 years but little if any effect before this age. These data may indicate an impaired tissue protein synthesis by the liver of old female rats and men.

The mean DNA per nucleus of washed nuclear preparations isolated from liver failed to demonstrate any agewise differences. It has been shown that at least two different populations of nuclei can be isolated from liver homogenates. Separation of the nuclei has been successfully carried out using the density gradient technique. The two fractions thus isolated were found to be 95% homogeneous. The mean DNA per nucleus of the fraction containing the larger nuclei was twice that of the fraction containing the smaller nuclei.

NHI-153
SERIAL NUMBER

Significance to Heart Research: These studies attempt to examine the aging process at a tissue and cellular level. Since the loss of cells of various tissues is a primary factor in the reduction in reserve capacity of various organ systems that occurs with age, it is important to determine what functional changes occur that prevent individual cells from maintaining their existence. It is also important to know whether these changes are a fundamental characteristic of the cell or whether it is secondary to circulatory impairments in aging animals.

Proposed Course of Project: Additional enzyme systems will be surveyed for age changes, including estimates of oxidiative phosphorylation in isolated mitochondria. Age differences in the quantitative aspect of tissue protein synthesis of rats will be examined using the depletion-repletion method as well as adaptive enzyme systems. In addition qualitative differences in the tissue protein synthesis of rats of different ages will be investigated by examining the hydrolytic products of homogenates treated with specific proteolytic enzymes. Since the feeding of diets containing whole desiccated liver to young female rats results in a marked increase in plasma cholinesterase, it is of interest to ascertain whether this procedure is capable of increasing the concentration of this enzyme in senescent animals.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-153
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$31,300	$1,688	$32,988	1.0	3.2	4.2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	2	4	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Baltimore City Hospitals

Johns Hopkins University School of Hygiene and Public Health

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-153
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Shock, N. W.: Aging as a biological problem. Fed. Proc., Baltimore, 15: (3), 938-941, Sept. 1956.

Barrows, C. H., Jr.: Cellular metabolism and aging. Fed. Proc., Baltimore, 15: (3), 954-959, Sept. 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-154
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Gerontology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5. Baltimore City Hospitals,
Baltimore 24, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Cardiovascular Hemodynamics. III. The peripheral circulation in man.
PROJECT TITLE

7. Milton Landowne
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To study the circulation in the extremities of living human subjects, with respect to changes with age, disorders in function, and to increase our understanding of factors governing the blood flow to these tissues.

7110-191
SERIAL NUMBER

Methods Employed: Skin temperature is used as an index of circulation to the skin, and venous occlusion plethysmography as a measure of blood flow to an extremity. Studies are carried out on rate of skin cooling under controlled thermal environment, and on the resting and 'vasodilated' flow to the foot. Rectal temperature is recorded as an index of "core" temperature.

Clinical Material: Subjects are from our research ward, other hospital wards, and members of the staff.

Major Findings: Age differences in equilibrated temperature of the extremities exposed to a cool (22.5°C) environment are not explained by consistent differences in cooling rate or "core" temperature.

The response of skin temperature to the reflex vasodilatation induced by heating the trunk has been used as an aid to evaluation in clinical and asymptomatic disorders of the peripheral circulation.

Significance to Heart Research: Describes the peripheral vascular responses of 'normal' adult and older men, providing standards.

Shows how commonly limitation in peripheral vascular function may be encountered among adult males without clinically demonstrable disease.

Represents an aid to the diagnosis of peripheral vascular disease. Provides a critical evaluation of the use and limitations of secondary indices of circulatory function.

Proposed Course of Project: Venous occlusion plethysmography will be used to estimate peripheral circulation under various conditions of 'maximal' vasodilatation. 'Minimal' peripheral resistance and the changes induced in resistance are to be studied in relation to alterations of arterial pressure.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-154
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$14,500	$785	$15,285	.4	1.6	2.0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Baltimore City Hospitals

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NBI-154
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-155
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Gerontology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5. Baltimore City Hospitals, Baltimore 24, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Cardiovascular Hemodynamics. II. Cardiac performance in man.
PROJECT TITLE

7. Milton Landowne
PRINCIPAL INVESTIGATOR

8. J. A. Falzone and T. Rieff
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To study the performance and functional limitations of the living human heart as affected by age and disorders of the circulation.

Methods Employed: Cardiac output is measured by dye dilution technique at rest and during graded exercise at two levels of exercise. Femoral arterial pressure is measured by intra-arterial needle and capacitance manometer. Arterial blood gases are determined manometrically. Ventilation, O_2 uptake and CO_2 production are determined to provide measures of ventilation and respiratory gas exchange. Calculations of cardiac output, work

'power' and peripheral resistance are considered in relation to rest, exercise, ventilation, O_2 uptake and work performed.

Clinical Material: Subjects are obtained from our 60 bed ward, the other wards of Baltimore City Hospitals and the Hospital Infir ary.

Major Findings: For moderate exercise the increase in cardiac output is related to the increase in oxygen uptake. In middle aged and old males the increase averages about 500 ml./100 ml. O_2, a ratio within the lower limits reported as normal by other workers. Ratios below 500 reflect less adequate circulatory performance, implying diversion or altered redistribution of circulation to other organs. In 4 subjects ratios were less than 300. After more strenuous exercise the ratios tend to be lower. There has been no evidence of an agewise trend in these ratios in the relatively limited number of studies completed. The subjects were all of sedentary habits, about half had clinically suspected or diagnosed disorders of cardiovascular, pulmonary or central nervous systems, but the clinical diagnosis did not appear to characterize the circulatory response to exercise. Increases in cardiac left ventricular pressure work and power under exercise have been related to the resting performance and the increase in oxygen uptake. Increase in the kinetic energy component of work has been estimated. Peripheral circulatory resistance tends to rise slightly and stroke volume falls in the subjects with the lowest ratios of increase in output to increase in O_2 uptake. Peripheral resistance falls and stroke volume is maintained in subjects who support a more adequate perfusion of body tissues.

Significance to Heart Research: Represents a contribution to the understanding of cardiac and total circulatory function, how these are affected by age and exercise. Helps to explain the logistical pattern of circulatory supply, by finding out how the circulation to organs is altered by diversion as well as augmentation, in response to a change in requirements for perfusion.

Suggests that decreasing circulatory performance of age and disease may be expressed in an altered distribution of circulation at rest, and revealed under conditions of demand, by diversion to areas of relatively lower risistance.

Proposed Course of Project: Continuation of careful study of subjects, with and without clinically diagnosable disorders of the cardiorespiratory and neuromuscular systems; at rest and at two levels of exercise.

The response of 2 body sites to an applied sinusoidal force of essentially constant amplitude and over a selected frequency range will be compared for subjects of different age and ballistocardiographic patterns.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-155
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$21,500	$1,165	$22,665	1.5	.6	2.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	1	3	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Baltimore City Hospitals

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-155
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Landowne, M.: Methods and limitations in the study of human organ system function. Ciba Foundation Colloquim on Methodology of the study of aging. July 1956. To appear.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-156
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Gerontology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. ____
SECTION OR SERVICE

5. Baltimore City Hospitals, Baltimore 24, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Cardiovascular Hemodynamics. I. Arterial performance in man.
PROJECT TITLE

7. Milton Landowne
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: To investigate the functioning of the arterial circulation in living human subjects in the following manner:

a. To develop and to test critically methods of studying the dynamic behavior of large and medium sized arteries in situ.

b. Using these, and existing methods, to describe individual, and agewise differences in arterial function in ostensibly normal subjects of mature age.

c. To characterize evidences of pathophysiological performance in arteriosclerosis, hypertension and other circulatory disorders.

Methods Employed: The way in which arteries function to transmit pressure and flow of blood to the small vessels is determined by viscous and elastic properties of the arterial wall. We are using 3 methods of investigating these properties and arterial performance. a. Small transient or sustained waves of pressure are created in arteries by a method developed in this laboratory. c. The decline of blood pressure during diastole (between heart beats) is compared to the theoretical behavior of models of increasing complexity.

Pertinent intra-arterial pressures are detected at various positions within the arterial tree by intra-arterial needles and special catheters attached to capacitance type sensing devices, and recorded, with sensitive and accurate equipment.

The speed of pressure propagation, and its distortions, damping, resonance and reflection are then computed at varying pressures, and for waves of different frequencies. These data provide indices of elastic and viscous behavior.

Graphic and mathematical analysis of pressure curves in diastole provide information about the validity and practicality of simplifying assumptions regarding the behavior of the arterial system.

Patient Material: Subjects from our 60 bed male ward, the Baltimore ity Hospitals Infirmary and other wards of Baltimore City Hospitals.

Major Findings: The age changes in the brachio-radial arteries have been systematically examined, and show descriptive and statistical significance. Findings are consistent with the hypothesis that entropy change, normally occurring during physiological stretch of the wall of medium sized human arteries, diminishes with age. The age differences are found even in arteries which are clinically considered non-sclerotic. Because the high incidence of clinical sclerosis with increasing age, morphologically identifiable arteriosclerosis cannot be excluded as the cause of the observed changes.

We have sought for an approximation of cardiac output and central arterial elasticity which might be valid. Several established and some new formulations which have been examined critically are based on the fall of pressure during diastole. The information obtained has been reproducible, and provided estimates of cardiac output usually accurate to less than $\pm$ 10% in the individual normal subject at rest. During exercise or under changing cardiovascular conditions, however, reproducibility and appropriateness of the information is not satisfactory.

The circulatory analogues upon which our formulas are based are thus inadequate to deal with more than limited conditions. The practical value and the limitations of the underlying cardiodynamic theory have been revealed.

The validity of deducing central arterial behavior from peripheral arterial records has been examined. From harmonic analysis of central arterial records we have obtained information about the behavior of aortic pressure waves.

Significance to Heart Research: Represents advance in concepts and a knowledge of the physiology of the circulation in human subjects. Illustrates the role of more nearly basic scientific inquiry in human circulatory physiology. Establishes use and limitations of formulae which have been proposed for use in individuals to estimate cardiovascular performance.

Proposed Course of Project: Continuation of recording and analyses of pressure curves under various experimental conditions and at several sites in the arterial tree. Continued study of the influence of reflected components.

Form No. ORP-1
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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-156
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$13,600	$737	$14,337	.5	1.2	1.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Baltimore City Hospitals

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-156
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Landowne, M.: Pulse wave velocity as an index of arterial elastic characteristics. Proceedings of the Conference on Elasticity held at Dartmouth College 1955, National Science Foundation. Published by the American Physiological Society to appear February 1957.

Landowne, M., and R. W. Stacy: A list of terms used to describe the mechanical properties of tissues. Proceedings of the Conference on Elasticity held at Dartmouth College 1955. To appear February 1957.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-157
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Gerontology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5. Baltimore City Hospitals,
Baltimore 24, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Pulmonary Physiology as Related to Age
PROJECT TITLE

7. A. H. Norris
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To describe age changes in pulmonary function. These studies involve measurements of the volumes of lung compartments, the functional capacity of the pulmonary system, including the mechanical aspects of bellows function and the responsiveness of the pulmonary system to experimental stimulation and displacement.

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SERIAL NUMBER

Methods Employed: In addition to the standard methods of measuring lung volumes, a helium washout technique has been developed to give estimates of functional volumes as well. An attempt will be made to relate functional measurements to anatomical measurements made directly on the chest and roentgenographic measurements, including motion of the diaphragm. In addition, the laboratory measurements of pulmonary function are being compared with responses to exercise and with clinical estimates of pulmonary and work performance limitations of older subjects.

Major Findings: The ventilatory and metabolic changes during and after 15 minutes of helium breathing have been compared in 135 subjects from 20 to 89 years of age. Oxygen uptake, CO_2 elimination, ventilation volume and tidal volume were increased during helium breathing. Oxygen uptake and CO_2 elimination (on the average) recovered to resting levels following helium breathing, while ventilation and tidal volumes remained at helium breathing levels for ten minutes or so. Younger subjects tended to over recover resting CO_2 elimination levels following helium breathing, while older subjects did not recover their resting levels. In addition, younger subjects recovered ventilation volume while older subjects increased ventilation volume in the ten minutes following helium breathing.

Significance to the Program of the Institute: Prevention of increased incidence of chronic pulmonary disease in elderly people requires knowledge about age changes in pulmonary function. Previous investigations from this laboratory have shown that older subjects increase their pulmonary ventilation volumes much more than do younger subjects when a standard exercise is performed, even when the oxygen requirements for the work are the same. Hence, studies of pulmonary ventilation, functional, and dead space volumes of the lungs, and the rates of transfer of gases across the alveolar membrane are of fundamental interest.

Proposed Course of Project: Studies of age changes in the elastic properties of the intact lung will be attempted. Since aging is accompanied by a loss of tissue elasticity, measurements on the lung may afford a useful index of physiologic age. In addition, estimates of the work involved in respiration will be made. Studies on permeability of alveolar membranes are also under consideration.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-157
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$21,000	$1,117	$22,117	.7	2.1	2.8

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Baltimore City Hospitals

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-157
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Norris, A. H., N. W. Shock, M. Landowne and J. A. Falzone, Jr.: Pulmonary function studies: Age differences in lung compartments and bellows function. J. Geront., 11: (4), 379-387, Oct. 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-158
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Gerontology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5. Baltimore City Hospitals, Baltimore 24, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Age Differences in Body Size Composition
PROJECT TITLE

7. A. H. Norris
PRINCIPAL INVESTIGATOR

8. N. Shock and Yiengst
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: This project is designed to describe age differences in body size and composition, to compare various size and composition measures made concurrently in individual subjects, and to examine the relationship of these age differences and comparisons to physiological responses.

NHI-158
SERIAL NUMBER

Methods Employed: Height and weight data will be obtained by the usual anthropometric methods. The volume of the body will be measured by its displacement of helium in a closed chamber. Body fat will be estimated from skinfold thickness and roentgenographic techniques. Basal metabolic rate data will be obtained from standard closed circuit methods. Body water and fluid distribution will be determined from distribution curves of injected antipyrine and sodium thiocyanate. Bone density may be estimated from the roentgenographic films.

Major Findings: Preliminary analysis of height and weight data have been completed for 840 patients, staff and employees of the Baltimore City Hospitals who have participated in experimental procedures conducted in the Gerontology Section. In this sample, there was a statistically significant reduction of both height and weight with increasing age. Linear regression estimates yield values for average changes of -.18 cm./yr. in height and -.16 Kg./yr. in weight.

Significance to the Program of the Institute: One of the requirements for interpreting age changes in physiological functions in the total animal is an adequate index of the amount of tissue present in the aged as compared to the young animal. Neither body weight nor surface area offer adequate indices. These studies aim to investigate other indices that may be more useful. Standards of body composition would also be helpful in the differential treatment according to age of obesity and associated cardiovascular diseases. A comparison of various methods of determining body fat might justify the use of simplified estimates which are, at present, considered unreliable.

Proposed Course of Project: An integrated measurement program which includes all available indices of body size and composition will be initiated. Some techniques may be provided through cooperation of investigators outside the Public Health Service, while others are standardized procedures used in this laboratory. Data will be made available for comparison with other physiological data which may be collected on subjects of these studies. Moreover, subjects whose size (or composition) varies widely from mean values will be selected for study, and experimental and therapeutic displacements of body composition may be attempted.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-158
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$20,400	$1,094	$21,494	.9	1.6	2.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	0

13. BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION	
REVIEW & APPROVAL		PROFESSIONAL & TECHNICAL ASSISTANCE	
BIOLOGIC STANDARDS			

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Baltimore City Hospitals

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-158
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-159
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Gerontology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5. Baltimore City Hospitals, Baltimore 24, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Age Changes in Human Performance
PROJECT TITLE

7. A. H. Norris and J. A. Falzone
PRINCIPAL INVESTIGATOR

8. LeVora, Shock, Landowne and Reiff
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: This project is designed to study the effects of aging on (a) the physiologic responses to exercise, (b) the rate of recovery of physiologic equilibrium after exercise, (c) muscular efficiency and (d) work output and fatigue. In addition, the factors responsible for limitations in performance observed in older people will be evaluated.

NHI-159
SERIAL NUMBER

Methods Employed: Measured amounts of physical work will be obtained in subjects of varying ages by means of a calibrated arm ergometer and quantitative mechanical analysis of limb movement. A treadmill will be used to induce higher levels of work. Measurements of oxygen uptake, CO_2 elimination, pulmonary ventilation volume, heart rate, blood pressure, and cardiac output (by the dye method) will be taken before, during and after standardized amounts of exercise. Each experiment involves analysis of 3-8 samples of expired air for standardization of automatic gas analyses. Other studies will include measurements of speed of nerve conduction, reflex delay time, and muscle action potentials. These phenomena will be recorded on a six channel oscillograph or dual beam oscilloscope as the experiment demands.

Major Findings: A screening procedure designed to select subjects who can perform a "maximal" exercise and to classify those subjects who cannot perform this exercise has been initiated. The procedure includes measurements of muscle strength, maximum work rate, responses to a "maximal" exercise, and clinical evaluations of the pulmonary, cardiovascular, and neuromuscular systems. 115 subjects between 20 and 90 years of age have been screened. Of these, 65 have completed satisfactorily "maximal" exercise curves with simultaneous estimates of metabolic responses, blood pressure and heart rate. These subjects showed a decrease in the strength of the muscles used in cranking exercise with increasing age, a decrease in the maximum cranking work output with increasing age, and decreased maximum work output at higher cranking rates. Responses of maximum ventilation volume, CO_2 elimination, and oxygen uptake to the "maximal" exercise were reduced with increasing age as was the exercise used to induce the responses. In fact, the total oxygen required to do the work was proportional to the total work done, so that the average net mechanical efficiencies were the same for all age groups.

Seventeen of these subjects (50 to 89 years of age) have had simultaneous measurements during exercise of cardiac output and the metabolic, cardiovascular, and ventilatory responses mentioned above. Two levels of exercise were used: a "steady state" level (135 Kg.M./min. for 4 minutes) and a "maximal" level as above. Although age differences did not appear, the ratio of oxygen uptake to blood flow increased with each increase in level of exercise. Consequently, arterial blood oxygen levels were maintained above resting levels during both bouts of exercise.

Experiments designed to analyze the mechanics of limb movement and determine the mechanical efficiency of well defined groups of muscles have been completed in a preliminary sample of 20 subjects (20 to 88 years of age). Subjects were tested in a semi-recumbent position with their upper arms supported so that back and forth movements (wagging) of the forearm were made in a horizontal plane. Mechanical analysis of

movements, performedat maximum voluntary speed for one minute, indicated that the displacement of the arms did not change with age while the maximum accelerations and velocities were decreased with increasing age. Thus, the period of swing was increased with age. Although the data suggest a decrease in net mechanical efficiency with increasing age, the ratio of average duration of biceps and triceps action potentials measured during arm movement to the period of swing was similar for old and young subjects.

Significance to the Program of the Institute: The effect of age on human performance is of importance to both industry and medicine. With the increased number of elderly workers in our population, industry is concerned with the question of retirement and has expressed a need for objective methods to determine individual retirement. In medicine, the question of the degree of activity that can be permitted elderly patients with varying degrees of cardiovascular disease is of practical importance. This program represents an attempt to provide baseline data, but also looks to the development of reliable tests that can be applied to large numbers of subjects. In addition, specific knowledge about the effect of agirg on performance will increase our understanding of aging in the human.

Proposed Course of the Project: The screening procedures and measurements of responses to "maximal" exercise will be continued. These measurements, plus cardiac output determinations, will be made in selected subjects. The limb movement studies will be continued. An additional condition of loading the arms with external weights during wagging may increase differences in speed and coordination between old and young subjects. Studies of the movements of other limbs are being considered.

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October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-159
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$39,300	$2,116	$41,416	1.7	3.1	4.8

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	3	5	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Baltimore City Hospitals

Human Performance Study (H-2004) through Dr. Robert Ramsey of the Medical College of Virginia.

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-159
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Shock, N. W.: Skill and employment. In: J. E. Anderson (Editor). Psychological Aspects of Aging. Amer. Psychol. Assoc., Inc., Washington, 1956, pp. 249-523.

Falzone, J. A., Jr. and N. W. Shock: Physiological limitations and age. Publ. Hlth. Rep., Wash., 71: (12), Dec. 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI 160
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Cation Transfer Across the Red Cell Membrane
PROJECT TITLE

7. Edward T. Dunham
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The principal immediate objective of this project is the characterization and, if possible, isolation of a presumed rate limiting enzymatic reaction coupled to active sodium extrusion and active potassium uptake in the human red cell.

Methods Employed: Red cells from freshly drawn human blood are suspended in simulated plasma or modified media and maintained in suspension at constant temperature in a Barcroft-Warburg apparatus. By means of established and modified tracer procedures, unidirectional movements (fluxes) of ions across the cell membrane are followed and analyzed. Ion exchange chromatography for the separation and quantitation of adenine derivatives has been employed extensively during the past year.

Major Findings: A good correlation between the decay of ATP and of active cation transport in the starved human red cell has been demonstrated. Strophanthidin, an inhibitor of active cation transport, has been found to retard the breakdown of ATP in this system. This is consistent with the hypothesis that an enzymatic hydrolysis of ATP is the rate limiting step of active cation transport. Effects of cardiac glycosides on the kinetics of cation transport have been extended by the following observations: a) maximal strophanthidin inhibition of Na outflux and K influx is effected within 2 minutes, and b) abolition of the linked components of Na outflux and K influx is effected by this drug (10^{-5} M).

Significance to HEART Research: The human erythrocyte provides one of the least complex and most easily manipulated systems for an intensive study of active cation transport across cell membranes. An understanding of the mechanism of active cation transport will further our appreciation of the cellular regulation of electrolyte metabolism.

A fuller understanding of the action of cardiac glycosides on cation transport in the erythrocyte would almost certainly implement present knowledge of their effects on cation transport in heart muscle, and this in turn might shed light upon the cardiotonic effects of these drugs.

Proposed Course of Project: An assay of a number of agents and conditions known to inhibit active transport for their effect on both transport and ATP breakdown in the substrate deprived system will be attempted. If results justify this correlative study will be extended to include an isolated erythrocyte stroma ATPase (apyrase) system. The effect of strophanthidin on the rate of P^{32} incorporation into erythrocyte ATP will be investigated.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-160
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$20,600	$10,359	$30,959	.8	1.6	2.4

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-160
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

In preparation:

I. Passive Cation Transfer by the Human Red Cell

II. Active Cation Transfer by the Human Red Cell

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-161
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Ionic Exchange in Secreting Cells
PROJECT TITLE

7. Dr. Ernest Cotlove and Dr. C. Adrian M. Hogben
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Project: Study of ionic exchange in secreting cells.

Objectives: The object of this project is to study ionic exchange in secreting cells particularly any differences in exchange rates at the opposite nutrient and secretory surfaces, and the effects of experimental variables.

Methods Employed: The isolated frog gastric mucosa is mounted between lucite chambers and bathed by modified Ringer's solution on the nutrient and secretory surfaces. The electrical potential and current between the solutions is measured and any desired potential can be imposed. Radioactive or stable ions are introduced into or analyzed in samples from the bathing solution. The mucosa is analyzed by standard methods for tissue analysis. The extracellular spaces are determined with C-14 inulin.

Major Findings: The experiments previously described were repeated using more accurate techniques, in particular the determination of the extracellular space on the nutrient side of each mucosa with C-14 inulin, along with use of radiochloride-36. Accurate methods were devised for radioassay of C-14 and Cl-36 in combination by means of differential absorption. The chemical analysis of chloride in the stomach mucosa was shown to be accurate by attaining constant specific activity with varied conditions of chemical treatment. The individual cell fluxes were calculated and the results confirmed the conclusion drawn from preliminary experiments of the marked asymmetry of chloride exchange at the opposite surface of the gastric epithelial cells. The secretory flux is at least five times higher, - a minimum figure uncorrected for the not quite complete saturation of the extracellular space by radioinulin in five hours. This ratio was the same in experiments conducted at 0 millivolts in the short-circuited membrane (where the net flux of chloride is to the secretory side) and at 60 millivolts positive on the nutrient side (where the net flux of chloride is to the nutrient side).

Significance to HEART Research: Information on the basic processes by which cells maintain their composition and perform their activities is essential to an understanding of the function of the organs, such as heart contraction, gastric secretion or renal excretion. The present study contributes information on the mechanism and possible localization of chloride secretion, and to interpretation of overall exchange rates studied in intact animals and humans.

Proposed Course of Project: The effect of metabolic inhibitors on the asymmetric exchange rate of chloride will be studied.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-161
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,800	$5,426	$16,226	.5	.8	1.3

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-161
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-162
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. C^{14}-Labelled Inulin as a Tracer for Inulin
PROJECT TITLE

7. Dr. Ernest Cotlove
PRINCIPAL INVESTIGATOR

8. ---
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Project: Evaluation of Inulin C^{14} carboxylate as a tracer for inulin and application to measurement of renal function and extracellular fluid.

Objectives: The object of this project is to develop a tracer for inulin which will 1) simplify the analytical procedure for the measurement of inulin clearance, 2) permit the analysis of inulin at very low concentration in body fluid and tissue by elimination of blanks which interfere with the colorimetric methods, and 3) enable study of kinetics of distribution and excretion.

Methods Employed: The physiologic procedure which have been employed are standard procedures for the evaluation of renal function. Varying degrees of equilibration of inulin in the body are obtained with constant infusion and the post-infusion rate of excretion is determined.

Major Findings: The method of radioassay of C-14 inulin has been further improved. Conditions have been found to permit assay of C-14 in the urine at a concentration as low as 0.01 microcurie per liter. Radioinulin has been infused in normal volunteers and the rates of excretion have been measured over the subsequent six-day period. The data have been analyzed to show that inulin penetrates into two major extracellular areas at markedly different rates. The half-time of equilibration in the fast compartment is 1.4 hours or less, and in the slow compartment is about 40 hours. It is possible to estimate the equilibrium values from the partial equilibrium attainable within the experimental limitation in humans (15% of completion in the slow compartment after a nine-hour infusion). In the normal, the inulin space as usually measured underestimates the extracellular space by about 35%. The actual volume of the slow compartment appears to be about 30% of the total extracellular volume.

Significance to HEART Research: The availability of C-14 inulin for the measurement of glomerular filtration together with the simple and accurate method of radioassay which has been developed should greatly simplify and possibly increase the accuracy of this procedure for evaluation of kidney function. Measurement of extracellular volume and of the rates of exchange of various portions of extracellular fluid should provide basic information in understanding the physiologic control of extracellular volume and the abnormal collections of fluid in edematous states (as in heart failure, nephrosis, cirrhosis of liver).

Proposed Course of Project: Further studies will be done using C-14 inulin in normal human subjects and in patients on the comparative clearances of radioactive and non-radioactive inulin; on the volumes and rates of exchange of extracellular fluid; and on the correlation of extracellular volume and the amount of secretion of the salt-conserving hormone aldosterone. Further studies of C-14 inulin distribution in individual tissues of animals will also be done.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-162
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$9,600	$4,792	$14,392	.3	.9	1.2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION	
REVIEW & APPROVAL		PROFESSIONAL & TECHNICAL ASSISTANCE	
BIOLOGIC STANDARDS			

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-162
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-163
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Water Transfer Across the Gastrointestinal Epithelium
PROJECT TITLE

7. Dr. C. Adrian M. Hogben
PRINCIPAL INVESTIGATOR

8. Dr. Irving L. Cooperstein
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

No

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: Even though the formation of hypertonic urine is still an enigma, no satisfactory evidence has been developed for the active transport of water. There is suggestive evidence that water might be actively transported across the gastrointestinal epithelium during active transport of solutes. The phenomenon will be critically studied using the isolated colon of the frog.

Methods Employed: Isolation of the surviving intestine as a flat sheet between well stirred solutions will allow quantitive study of water and solute movement as a function of concentration and electrical potential.

Major Findings: The ability of the isolated colonic epithelium to transfer water and solute has been demonstrated using tied sacs incubated in bicarbonate saline. There is an associated depletion of chloride from the mucosal surface and accumulation at the serosal surface. The technique of isolated sacs has been evaluated and improved. Equipment has been developed permitting definitive study of the dependence of water movement upon solute transport.

Significance to HEART Research: This experimental technique will clarify the regulation of water movement during secretion.

Proposed Course of Project: The nature of solute transport by the colon will be clarified by simultaneous measurement of the membrane potential and current. The net flow of water will be studied as a function of osmotic and electrical gradients.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-163
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$17,800	$8,950	$26,750	1.2	.9	2.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-163
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-164
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Salt Transfer across the Small Intestinal Epithelium
PROJECT TITLE

7. Dr. C. Adrian M. Hogben
PRINCIPAL INVESTIGATOR

8. Dr. David Chalfin
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

No

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The small intestine is one of the most important sites of exchange between the organism and its environment. Across its surface there may be either absorption or secretion of ions and water. Little is known about the factors governing the ionic movement. By utilizing an *in vitro* preparation of the frog intestine which permits measurement and regulation of the transmembrane potential it should be possible to define some of the physical chemical factors governing electrolyte transfer.

Methods Employed: By mounting the intestinal epithelium as a flat sheet between two solutions of saline which are vigorously stirred, it will be possible to relate the unidirectional movements of ions, measured with radioisotopes, to the electrochemical gradients of the bulk solutions.

Major Findings: The *in vitro* intestinal epithelium apparently survives many hours of isolation. In most instances its electrical resistance does not deteriorate and it transports glucose. When bathed with Ringer's solution on both sides it does not develop an appreciable potential though a few millivolts (serosa positive) is consistently observed. The electrical potential created by passing current is not proportional to current. No significant pH changes have been observed when jejunal segments are exposed to 100% O_2.

The ionic exchange of Na^+ and Cl^- has been measured simultaneously. While the flux of Na^+ is almost constant along the small intestine, Cl^- flux is higher in the duodenum and lower in the ileum.

The ability of isolated intestine to transport salt and water was demonstrated using tied sacs. A 0.5 gm sac is able to transfer 0.5 ml of H_2O and 50 microequivalents of chloride in four hours.

Significance to HEART Research: This investigation will permit investigation of apparently associated transport of both sodium and chloride. It will lead to a better understanding of regulation of salt and water across the intestinal wall.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-164
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$16,000	$8,033	$24,033	1.2	.7	1.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-164
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-165
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Anion Transport Across the Gastric Mucosa
PROJECT TITLE

7. Dr. C. Adrian M. Hogben
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To elucidate the cynamics of anion transport and to determine the nature of the anion transport system.

Methods Employed: The methods used in general have followed the principles set forth by Ussing, i.e., the measurement of unidirectional ion fluxes across isolated membranes in relation to the electrical potential with regulation of the electrical potential at desired levels.

Major Findings: The mechanism responsible for the selective transport of weak acids and bases across the spontaneously secreting isolated frog gastric mucosa has been clarified by studying the diffusion of bases and transfer of radiolactate. The bases aniline and quinine diffuse more rapidly from serosal to mucosal surface than they do in the opposite direction. In the presence of thiocyanate and a reversal of the normal pH gradient, the rates of the unidirectional diffusion of quinine are reversed. The flux ratio of radiolactate is somewhat

reduced by the presence of an appreciable concentration of bicarbonate buffer. When hydrogen ion secretion is significantly depressed by a large concentration of thiocyanate and when the pH gradient across the mucosa is reversed by a concentration gradient of bicarbonate, the net movement of lactate is reversed such that it then moves more rapidly from serosa to mucosa.

The SCN ion in low concentration, 0.5 mM, was found to inhibit hydrogen ion secretion by 25% compared to a 90% inhibition obtained at a concentration of 25 mM.

Significance to HEART Research: The frog gastric mucosa presents a more or less isolated anion transport system which can serve as a guide and model for anion transport systems elsewhere in the body.

Proposed Course of Project: Observations on the carbonic acid bicarbonate system in relation to chloride transport will be extended. Study of the flux of nitrate and its relationship to the movement of chloride will be carried out. The electrical potential profile of the gastric tubule will be determined to indicate the locus of that portion of the active transport of chloride which is responsible for the membrane potential and whether hydrogen and chloride are transported by the same cell.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-165
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,600	$3,312	$9,912	.2	.7	.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION	
REVIEW & APPROVAL		PROFESSIONAL & TECHNICAL ASSISTANCE	
BIOLOGIC STANDARDS			

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NIH-165
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-166
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The Metabolism of Urea in Man
PROJECT TITLE

7. Mackenzie Walser
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: (1) To determine the rate at which urea is destroyed in normal man and whether its destruction can be eliminated by antibiotics.

(2) To determine the significance of the apparent renal delay time for urea.

Methods Employed: C^{14} labeled urea is administered intravenously by single injection or continuous infusion, and its concentration determined in blood and urine at intervals.

Major Findings: Normal subjects destroy about 1/3 of the urea produced. This destruction has been eliminated by intestinal bacteriostasis in one subject, but not in 4 others. Urinary urea specific activity is consistently higher than blood urea specific activity.

Significance to HEART Research: These findings are pertinent to the study of nitrogen metabolism, the problem of hepatic coma, the determination of total body water with urea, the interpretation of urea clearance data, and the mechanism of urea excretion.

Proposed Course of Project: Further studies of a similar nature are planned.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-166
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,400	$16,975	$22,375	.3	.4	.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	25

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-166
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"Reliability of Estimated Rates of Production in Simple Turnover Experiments" by M. Halperin and M. Walser, Arch. Biochem. Biophys., in press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-167
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Factors Involved in the Production of Ammonia by the Kidney, and the Relation of Production to Ammonia Excretion in the Dog.
PROJECT TITLE

7. Jack Orloff
PRINCIPAL INVESTIGATOR

8. Douglas Davidson, Floyd Rector
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Project: To investigate effects of alterations in acid-base balance and urine pH on renal artery and vein ammonia and enzyme concentration on the excretion of ammonia and other organic substance.

Objectives: To elucidate some of the mechanisms whereby ammonia excretion is modified by urine pH and acid-base balance.

Methods Employed: Simultaneous femoral artery, renal vein and urinary ammonia and glutamine concentrations will be measured during infusions of various substances. Renal blood flow and glomerular filtration rate will also be measured.

Major Findings. Methods for the measurement of all three enzyme systems and the technique for renal vein catheterization have been perfected. To date no reliable method for the determination of blood ammonia has been perfected.

Measurements have shown that ammonia excretion at any given urine pH is higher in dogs during acidosis and lower during alkalosis than during periods of normal acid-base balance. However, there were no significant differences in the activities of the three enzyme systems assayed to account for the differences in ammonia excretion.

Significance to HEART Research: The studies are of importance insofar as they may elucidate the factors involved in electrolyte transport by the kidney. Specifically they bear on the overall problem of the renal defect in edema, the mechanism of action of diuretics and their potentiation.

Proposed Course of Project: The diffusion technique of Seligson has proven to be an unsatisfactory measure of blood ammonia in our hands. Attempts are being made to develop a technique of measuring blood ammonia more directly, possibly by extraction with organic solvents. These studies are progressing and will be extended.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-167
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$8,500	$4,228	$12,728	.2	1.1	1.3

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-167
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

The Mechanism of the Excretion of Ammonia in the Dog. Jack Orloff and Robert W. Berliner. J. Clin. Invest. 35:223-235, 1956.

The Role of the Kidney in the Regulation of Acid-Base Balance. Jack Orloff. Yale Journal of Biology and Medicine (in press).

Carbonic Anhydrase Inhibitors. Robert W. Berliner and Jack Orloff. Pharm. Reviews 8:137-174, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NIH-168
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Effect of Reducing Glomerular Filtration Rate on Renal Function
PROJECT TITLE

7. Robert W. Berliner , D. G. Davidson
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Project: Effect of reducing glomerular filtration rate on:

a) capacity to produce a solute urine
b) the clearance of Creatinine and Inulin
c) the action of Acetazolamide (Diamox) and Salyrgan
d) the effects of lowering of the glomerular filtration rate on maximal urine concentration.

Objectives: a) To determine the effect of reducing glomerular filtration on the concentration of the urine produced during water diuresis. The information secured will provide evidence concerning the mechanism by which the urine is diluted and the mechanism of action of pitressin. b) If lowering the filtration rate decreases the clearance of creatinine with respect to the clearance of inulin, and if this discrepancy occurs because of the back diffusion of creatinine at the site where

pitressin acts, theoretically the discrepancy might be greater during maximal pitressin activity than in the absence of pitressin. c) To determine the effect of reducing the glomerular filtration rate on the action of acetazolamide and Salrgan. It is desired to obtain information regarding the action of the drugs when the filtered load of sodium is reduced.

Methods Employed: Multiple studies have been done in 18 dogs. The method for unilateral renal artery constriction, and separate urine collections from each kidney have been reported in detail in a previous report. a) The glomerular filtration rate was acutely lowered during water diuresis at low rates of solute excretion. Mannitol infusions, if used, were stopped when the clamp was set. Following suitable control periods with maximal water diuresis, the renal artery clamp was inflated. b) The clearance of inulin and creatinine were compared at reduced levels of glomerular filtration rates. Suitable control periods were secured during a water diuresis, then the glomerular filtration rate was reduced, and periods were obtained during continued water diuresis. Pitressin was then added to the infusion and periods were obtained during maximal ADH activity.
d) The effect of lowering glomerular filtration rate during Mannitol and NaCl diuresis was studied. The glomerular filtration rate was lowered when solute excretion was minimal. Pitressin - 50 mU/kilo/hr. was infused throughout. Animals were dehydrated for 24-36 hours prior to these studies.

Major Findings: a) When the glomerular filtration rate was reduced during water diuresis at low rates of solute excretion, the urine concentration rose to levels of 450 to 480 milleosm. These hypertonic urines were secured with 30 to 35% reductions in the glomerular filtration rates. A marked fall in the rate of sodium excretion was found. These results are interpreted to indicate:
1) that the urine is diluted by the reabsorbtion of sodium "salts",
2) that during osmostic diuresis induced by Mannitol infusion more sodium "salts" are presented to the distal tubule with a consequent greater volume of dilute urine presented to the concentrating site,
3) that the mechanism which yields a hypertonic urine is not necessarily under the control of A.D.H.
4) that the effect of A.D.H. is on the permeability of the distal tubule to the diffusion of water and that A.D.H. assures the isotonicity of the urine delivered to the concentrating site.
b) The ratio of the clearance of creatinine with respect to the clearance of inulin was found to be significantly less than unity when the filtration rate was reduced. The fall in the clearance of creatinine could best be correlated with the degree of reduction of the filtration rate. There was no significant fall in the clearance of creatinine unless the filtration rate (as measured by inulin) was reduced by at least 60% of the control kidney. No correlation was found with pitressin activity.

c) During mercurial or acetazolamide diuresis; the rate of sodium excretion if reduced with lowering of the glomerular filtration rate. In one experiment equality of potassium excretion was maintained despite a 40% reduction in the glomerular filtration rate. This finding was taken as evidence that the reduction in glomerular filtration rate produced by clamping the renal artery was produced by a decreased perfusion pressure per nephron and not a "shutting off" of nephron units. With acetazolamide diuresis the urine pH was higher on the side of reduced glomerular filtration rate. Despite 30-40% reduction in the glomerular filtration rate, an appreciable rate of Na excretion was maintained.

d) With elevated levels of solute excretion achieved by infusions of Mannitol or hypertonic NaCl, acute reductions of the glomerular filtration rate effect a rise in urine concentration. At minimal levels of solute excretion, increases in urine concentration occur with minimal reductions of the glomerular filtration rate. With marked reductions in the glomerular filtration rate, when the solute excretion rate is low, a fall in urine concentration occurs. However reduction of the solute excretion rate by reducing the glomerular filtration rate does not always effect the degree of rise of urine concentration expected by spontaneous falls in solute excretion. As with previously reported experiments the unclamped kidney serves as a reference control. The problems of dead space and delay time at the very low urine flows necessary to achieve maximal urine concentrations have made the measurements of the glomerular filtration rate a difficult problem. When the urine concentration did not change or fall with reduction in the glomerular filtration rate, the excretion of Na^+ was quite low.

Significance to HEART Research: These studies help to clarify the role of glomerular filtration rate in the excretion of salt and water.

Proposed Course of Project: Experiment will be designed to secure more information with regard to: 1) spontaneous changes in "Maximal" urine concentration, 2) failure of the urine concentration to rise with reduction of the glomerular filtration rate at low levels of solute excretion. 3) further experiments will be done to show equal potassium excretion when the filtration rate is reduced during Salrgan diuresis.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-168
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$9,800	$4,933	$14,733	.6	1.5	2.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-168
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-169
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Isolation of a Cardiotonic Substance From Mammalian Tissues
PROJECT TITLE

7. Stephen Hajdu
PRINCIPAL INVESTIGATOR

8. Dr. Elwood O. Titus and Dr. Herbert Weiss
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: Previous studies on the frog heart suggested the presence of a digitalis-like substance in blood serum. The purpose of this research is to isolate this substance, to characterize it chemically and to determine its role in the control of the contraction of the heart.

Methods Employed: An assay for digitalis-like activity has been developed using the staircase phenomenon of the frog heart. Methods of isolation have involved extraction with organic solvents, chromatography and counter current distribution.

Major Findings: Previous reports have disclosed that beef heart and, to a lesser extent, liver and blood contained a substance which strongly resembled strophanthin, both in its effects on the staircase phenomenon in the frog heart and in the extraordinary firmness with which it is bound to the heart. Although up to about 20% of the substance may occur free in these tissues, most of it is found in the form of an inactive precursor from which it may be released by treatment with 0.001 to 0.01 N acid at

room temperature. By far the most abundant source, however, is adrenal medulla, in which equal amounts of free substance and inactive precursor exist, and it was from the latter tissue that sufficient material for chemical characterization was obtained.

The material was isolated by acetone deproteinization of tissue, fractionation of the acetone extracts by partition between solvents, and chromatography. Counter current distribution of the chromatographic eluates gave material which could be crystallized. Results of recent experiments are summarized as follows:

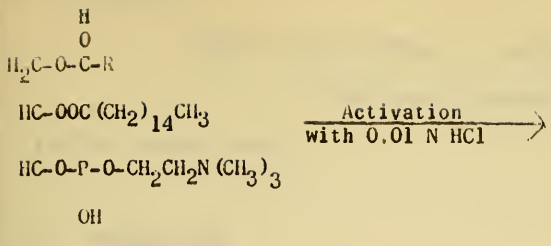
a). The active principle has been characterized as -palmitoyl lysolecithin. On a molar basis it is approximately 1/60 as active as strophanthin, 1/30 as active as digitoxin and 1/3 as active as digitoxigenin in the frog heart including the property of being very firmly bound to the heart membrane.

b). Cardiotonic activity of this type appears to be a general property of -lysolecithins, since synthetic -myristyl and -oleyl as well as a mixed lysolecithin prepared from vegetable lipids were all active.

c). A toxic agent which caused very rapid contracture in a manner reminiscent of saponins like digitonin but which was without effect on the staircase phenomenon, occurred in many of the tissue preparations. This has been identified as -lysolecithin. It appears to be an artefact arising by intra molecular rearrangement of the lysolecithin during chromatography and crystallization.

d). The phospholipase A of Crotalus adamanteus venom has been found to hydrolyse the ester bonds of -lysolecithins rapidly and completely, but is without effect on the -isomers. This enzyme promises to become a useful tool in investigations of these phospholipids.

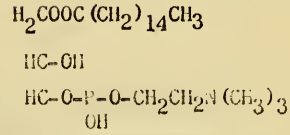
Although efforts to isolate the inactive precursor in pure form have not yet succeeded, the presence of fatty aldehyde in impure preparations and the extreme ease with which the precursor is activated by very dilute acids, suggest that it is probably a hemiacetal of the structure which has recently been proposed by Klenk for certain beef heart phospholipids. The name "aldolecithin" has been suggested as a means of differentiating such structures from the acetal structures which have hitherto been assumed to account for the aldehyde containing phospholipids. The following structures would account for the phenomena discussed in this report.



"Aldolecithin"
Inactive precursor

-lysolecithin

Parital rearrangement during isolation



-lysolecithin
"Contracture activity"

The biological importance of the active substance has been further indicated by two observations: (1) It exerts its characteristic cardiotonic effect on the heart of the tropical toad, an organ which is completely insensitive to all known cardiac glycosides. (2) This substance exhibits the characteristic properties of a cardiac glycoside when tested on isolated carotid strips.

The active substance has been obtained in crude form as a fraction occurring in close association with unidentified choline-containing lipids.

Significance to HEART Research: The identification and study of a substance which may play a fundamental role in regulating heart muscle contraction is obviously of the greatest importance to our understanding of the function of the heart.

Proposed Course of Project: Efforts are being made to isolate or to synthesize pure aldolecithin, to study its physiological effects in intact animals and to investigate the distribution of enzymes concerned in its biogenesis and conversion to -lysolecithin.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-169
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,500	$3,242	$9,742	.3	.4	.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-169
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Isolation of Cardiac-active Principle from Mammalian Tissue.

Stephen Hajdu, Herbert Weiss, and Elwood Titus. In press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-170
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on the Mechanism of Action of Diuretics
PROJECT TITLE

7. T. J. Kennedy, Jr.
PRINCIPAL INVESTIGATOR

8. R. W. Berliner
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

a) Objectives: The objectives of this project is to evaluate compounds which reduce the net transport of sodium and chloride across the renal tubule from two points of view. The first point of interest has to do with the mechanism if discernable whereby sodium transport is reduced, in the hope that fundamental knowledge about the modus operandi of the tubular transport process may be advanced. The second is to evaluate the clinical usefulness of these drugs in the management of patients with edema, especially when caused by cardiac failure, and also when due to primary renal or hepatic disease.

b) Methods employed: Studies in animals utilize standard clearance techniques. If indicated, the effect of the drug on certain metabolic features of renal slices or homogneates of kidney tissue may be used. Patient studies require electrolyte balance studies on normal and edematous patients wherein dietary intake of electrolyte is varied and where the efficacy of this drug is studied in comparison to mercurial diuretics under relatively standard and comparable conditions. When drugs look to be promising, more elaborate clearance studies are undertaken.

c) Patient material: Patient material includes normal controls as well as edematous patients recruited from local physicians and hospitals.

d) This year, a new drug, chlorothiazide has been under study. Results are too preliminary for any definite statement at this time.

e) Significance to HEART Research: The understanding of the intimate details of renal tubular transport of electrolyte is central to a solution of the problem of cardiac, renal and hepatic edema and rational management of this problem will indubitably be advanced as our insight into the mechanism of its production expands. There is at present a crying need for compounds which are effective diuretics when given by mouth and the discovery of such a compound will represent a significant therapeutic advance.

f) Proposed Course of Project: As diuretic agents of preliminary promise become available, they will be subjected to intensive study as outlined above.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-170
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$11,400	$35,365	$46,765	.6	.7	1.3

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	145

13. BUDGET ACTIVITY:-

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-170
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-171
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies on the Function of Single Nephrons in Necturus Maculosus
PROJECT TITLE

7. Thos. J. Kennedy, Jr.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Project: The study of the operation performed by the nephron in the formation of urine.

Objectives: The objectives of this program are to study in as intimate detail as possible the mechanisms whereby the nephron modifies glomerular filtrate into the final urine. Classical clearance techniques permit the evaluation of the chemical compositon of both the initial material (glomerular filtrate) presented to the nephron as well as the final material, urine, elaborated by the nephron. However, there is no method evaluating what happens along the course of the nephron other than a direct approach to the various segments of this structure.

Methods: The general technique used is micromanipulative. The nephrons of the kidney of necturus can be visualized with proper lighting and microscopy. Micromanipulators have been built to which micropipettes may be attached for sampling of tubular urine at various levels of the nephron. Segments of the nephron can be isolated between blockades of oil or mercury and the intervening nephron can be perfused. Microelectrodes may be introduced into the tubular lumen for measurement of potential differences across membranes or for the measurement of pH. Ultramicrochemical analytical methods are used to determine the chemical composition of the urine collected from the puncture sites.

Major Findings: Some measurements of the transluminal potential gradient have been made. A large amount of effort has been expended in an attempt to fabricate a microflame photometer for measurement of sodium and potassium in the microsamples, and chemical methods for the measurement of chloride and of inulin have been developed for the sample sizes which we expect to encounter.

Significance to HEART Research: The transport of electrolytes and water across the renal tubule is altered in heart failure. Recognition of the nature and cause of this alteration requires understanding of normal mechanisms of electrolyte transport. Once the normal mechanisms are understood, the possibility of characterization of the abnormalities seen in heart failure becomes more likely. Rational therapy based on sound physiological premises should follow.

Proposed Course of Project: Over the next year the plan is to carry out a number of exploratory experiments and select lines of study that appear, on the basis of preliminary work, most promising. A systematic study of electrical potential gradients along the nephron will be undertaken and the effort thereon of various compounds known to modify electrolyte transport will be studied. In addition, it will be of interest to study simultaneously the relationship between changes in electrolyte transport and D.C. potential changes. If technically feasible, acute changes in the composition of tubular urine will be induced by perfusion of isolated segments of nephron with solutions of composition different from that of glomerular filtrate. A study of the feasibility of insertion of a microglass electrode for pH determination will also be made.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-171
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,800	$3,876	$11,676	.5	.4	.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-171
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NH1-172
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The Renal Excretion of Phosphate in the Chicken
PROJECT TITLE

7. Douglas G. Davidson
PRINCIPAL INVESTIGATOR

8. Norman Levinsky, Robert W. Berliner
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To investigate a possible specific phosphaturic effect of the parathyroid hormone. If the hormone has a specific renal effect of increasing the renal excretion of phosphate, it should be theoretically possible to demonstrate a unilateral rise in phosphate excretion when the hormone is administered in one leg of the chicken.

Methods Employed: Utilizing the unique circulation of the kidney in the chicken which has been discussed in previous reports, separation of glomerular and tubular effects is facilitated. Renal phosphate excretion was studied by intravenous infusion of 2.5 and 25 micromoles per minute of sodium phosphate. The infusion contained inulin to measure GFR. Renal tubular secretion of phosphate was demonstrated by bilateral phosphate excretion forty to sixty per cent in excess of filtered load. In other experiments parathyroid extract, 0.5 to 2.5 units per hour per kilo, was infused continuously into one leg vein. No constant or large changes in plasma phosphate concentration or in the GFR of

either kidney occurred. In several experiments unilateral phosphate secretion was demonstrated with excretion of 20 to 100 per cent more phosphate than the filtered load.

Major Findings: 1. Tubular secretion of phosphate. a) The filtration rates were measured by the clearance of alkali-stable inulin. b) With systemic phosphate loading, the excretion of phosphate by the kidney has been found to substantially exceed the filtered load of phosphate. These findings have been taken as secure evidence of phosphate secretion by the chicken kidney.

2. The effect of parathyroid hormone ("Parathrone"-Lilly) on phosphate excretion. When the hormone is administered in the leg of the chicken there is a unilateral increase in the rate of phosphate excretion. The effective dosage range of the hormone is 1, 3, and 5 units per hour per chicken. The average weights of the chickens studied were two kilo. With suitable rates of hormone administration unilateral secretion of phosphate has been demonstrated. At higher levels of hormone administration there is a contralateral rise in phosphate excretion. The mechanism by which the parathyroid hormone increases the rate of phosphate excretion is not known.

Significance to HEART Research: The problem is of importance insofar as it helps to define the normal mechanisms of electrolyte excretion.

Proposed Course of Project: a) Investigation of the effects of feeding and starvation on the basal rate of phosphate excretion by the chicken kidney. b) Radioactive phosphate will be utilized in an attempt to elucidate the mechanism of phosphate excretion.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-172
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,800	$3,383	$10,183	.2	.8	1.0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-172
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-173
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Effect of the Chronic Administration of Pitressin in the Dog
PROJECT TITLE

7. Robert W. Berliner
PRINCIPAL INVESTIGATOR

8. Douglas G. Davidson, Norman Levinsky
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To determine the mechanism by which dogs accommodate to the chronic administration of supra-maximal amounts of pitressin and water. The information secured should provide evidence concerning the factors which influence the action of pitressin on urine concentration.

Methods Employed: 1. Conventional balance techniques have been utilized. The diet was synthetic, the daily portion containing 30 cal/kilogram, 24 meq of NaCl and 15 meq of KCl. Controlled water intake was made possible by the daily administration of known amounts of intravenous

fluids. Following a suitable control period of 5 to 7 days, 10 units of pitressin tannate in oil were given daily. A sharp rise in urine concentration occurred, and simultaneously there was a progressive fall in plasma osmolality. After three or four days of daily administration of pitressin tannate in oil the urine concentration began to decline and leveled off at near control values. The plasma osmolality ceased to fall. The glomerular filtration rates during the period of accommodation were near double those of the control values. A marked rise in Na^+ excretion occurred during the first 3 to 5 days of pitressin administration. This was followed by a period of minimal NaCl excretion. This study has been completed in three dogs.

Major Findings: The findings have been utilized to define more closely the accommodation of the dog to the chronic administration of pitressin. a) A marked and sustained rise in glomerular filtration rate, b) the excretion of a less concentrated urine at control levels of solute excretion, c) an initial increase of salt excretion followed by a period of salt conservation.

Significance to HEART Research: Continuous excessive release of pitressin is a common occurrence in advanced cardiac failure and a number of other severe disease states. Elucidation of its consequences is therefore of considerable importance.

Proposed Course of Project: 1. Attempt to correlate changes in urine concentration with changes in glomerular filtration rate by daily measurements of glomerular filtration rates during the administration of pitressin tannate in oil.

2. Continue experiments with simultaneous administration of DOCA and P.T.O.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-173
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$19,300	$9,654	$28,954	1.2	1.2	2.4

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-173
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-174
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Mathematical Formulations of the Relationship between Solute, Sodium, and Water Excretion
PROJECT TITLE

7. Mackenzie Walser
PRINCIPAL INVESTIGATOR

8. John Stephenson, Jack Orloff
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To evaluate the consequences of various mechanisms for renal reabsorption of solute and water by means of assuming the given mechanism to be operative throughout the tubule, and then obtaining the resultant relationship by integrating from one end of the tubule to the other. 2. To test alternative theories of solute and water reabsorption by comparing the prediction of such formulations with observed data.

Methods Employed: The relationship between sodium excretion and total solute excretion observed in patients with various disorder subjected (for other reasons) to mannitol diuresis has been compared to the relationship predicted upon the basis of a mathematical formulation. The latter is obtained from the assumption that sodium reabsorption is proportional to sodium concentration in the tubular fluid.

Patient material: obtained from other projects.

Major Findings: The correspondence between the observations and predictions has been found to be close in most instances, lending support to the assumption.

Significance to HEART Research: The findings shed light upon some of the factors regulating sodium excretion by providing a quantitative test of the hypothesis that sodium reabsorption is concentration-dependent.

Proposed Course of the Project: Further studies of a similar nature are planned.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-174
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$20,500	$10,289	$30,789	1.4	1.1	2.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	1	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-174
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-175
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The Effect of Chlorothiazide in the Chicken
PROJECT TITLE

7. Jack Orloff
PRINCIPAL INVESTIGATOR

8. Floyd Rector, Douglas G. Davidson
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

Concurrent studies of the drug in patients is being undertaken by Drs. Kennedy and Berliner.

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Project: The effect of chlorothiazide in the chicken.

Objectives: A new diuretic agent, chlorothiazide, has recently been released for investigative purposes. It is said to produce effects similar to mercurial diuretics in low dosages and to inhibit carbonic anhydrase at higher dosages. The mechanism of action of the drug is being studied in the chicken.

Methods Employed: Drugs infused into a leg vein perfuses only the peritubular capillaries of the homolateral kidney and is not filtered by the glomerulus until after it has entered the systemic circulation. The presence of separate ureters emptying directly to the exterior permits the collection

of urine separately from each kidney. Hence, it is possible in the chicken to differentiate between effects on glomerular filtration and specific tubular effects of the drug.

A moderate osmotic diuresis to maintain adequate urine flows is produced by the infusion of mannitol into the systemic circulation via a wing vein. The glomerular filtration rate, urine flow, urine pH and excretion of sodium, potassium and chloride on the infused and control sides are compared during control periods and during the infusion of graded doses of chlorothiazide. To determine whether chlorothiazide has a specific effect on potassium secretion, similar experiments will be performed in which a high level of potassium secretion is maintained by the infusion of potassium chloride into the wing vein.

Major Findings: A. Chlorothiazide has been shown to produce a specific unilateral effect on chloride excretion on the side of the infusion. The minimum effective dose is approximately 0.1 mgm/kilo body weight/hour.

B. At all dosage levels studied (0.25 - 25.0 mgm/kilo/hr.) the diuresis appears to be predominantly due to an increase in Na^+ and Cl^-. Dosages of 2.5 mgm/kilo/hour or more appear to inhibit carbonic anhydrase slightly as manifested by an increase in urine pH. (from 5.5 to 6.5). However, it does not appear to be as potent as Diamox in this regard.

Significance to HEART Research: The studies in a general way relate to the problem of edema formation in heart disease and nephrosis. If it is possible to elucidate the mechanism of action of this diuretic this may provide information concerning the problem of chloride excretion in general.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-175
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$16,300	$8,160	$24,474	.8	1.4	2.2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-175
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-176
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Renal Diluting Function in Nephrosis
PROJECT TITLE

7. Mackenzie Walser
PRINCIPAL INVESTIGATOR

8. Jack Orloff
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To determine the response to water-loading in nephrotics as a function of solute excretion and filtration rate (GFR), and the effect thereon of steroid therapy.

Methods Employed: Sustained water diuresis is maintained during superimposed osmotic diuresis with mannitol or acetazoleamide. Filtration rate (inulin) and the rate of excretion of solute and electrolytes is measured.

Patient material: 6 normal control-subjects have been subjected to the above procedure as well as 8 patients with the nephrotic syndrome.

Major Findings: As compared with normal subjects or patients with nephrogenic diabetes insipidus, the patients with the nephrotic syndrome exhibit normal or enhanced diluting function per unit of glomerular filtrate. Steroid therapy did not alter the relationship between urine flow and solute excretion per unit of glomerular filtrate although in some patients considerable change in filtration rate occurred.

Significance to HEART Research: The data are consistent with the interpretation that the diluting function of the remaining tubules in patients with nephrosis is normal, and that glomerular flow per nephron unit is normal or increased. Steroid therapy apparently increases the number of functioning nephrons rather than increasing flow in the remaining nephrons. These conclusions, if substantiated by further work, are significant in understanding the pathogenesis of the nephrotic syndrome and the mechanism of steroid-induced remission. They are also relevant to the problem of the mechanism of urinary dilution.

Proposed Course of Project: After one or two more experiments this project will be completed.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-176
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,400	$3,735	$11,135	.2	.9	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-176
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-177
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The Graded Effect of Purified Vasopressin and Urinary Solute on the Excretion of Solute-Free Water
PROJECT TITLE

7. Jack Orloff
PRINCIPAL INVESTIGATOR

8. Henry N. Wagner, Jr., Douglas G. Davidson
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

Similar studies in man are being performed by Dr. Wagner and are discussed elsewhere.

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Project: The graded effect of purified vasopressin and urinary solute on the excretion of solute-free water.

Objectives: To elucidate the mechanism of urinary concentration.

Major Findings: (a) It has been found that solute-free water excretion rises in association with an increase in solute excretion.
(b) The excretion of solute-free water is decreased progressively by the administration of purified arginine vasopressin in dosages varying from 0.5 to 5.0 mU/kilo/hour.
(c) During the administration of submaximal amounts of vasopressin, at low levels of solute excretion, the urine was hypertonic, but as solute excretion increased, the urine became hypotonic to plasma. When sufficient quantities of ADH were administered, the urine remained hypertonic to plasma despite the magnitude of the increase in solute excretion.

Significance to HEART Research: The problem is of importance insofar as it affords information concerning the normal mechanism of maintenance of water balance.

Proposed Course of Project: To determine whether the transition from hypertonic to hypotonic urine during solute excretion occurs when ADH activity is initially maximal. It may not be feasible to perform these studies other than in dogs with diabetes insipidus.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-177
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$15,200	$7,601	$22,801	1.2	.5	1.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	1	3	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

(Use reverse and additional pages, if necessary)

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NH1-177
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-178
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The role of the autonomic nervous system in the control of sodium excretion in man
PROJECT TITLE

7. Henry N. Wagner, Jr.
PRINCIPAL INVESTIGATOR

8. ---
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To determine the factors which influence the excretion of electrolytes, chiefly sodium, in man

Patient Material: Five patients with the syndrome of idiopathic postural hypotension, anhidrosis and impotence. Normal persons and persons with unrelated diseases as controls.

Major Findings: The five patients with diffuse hypofunction of the autonomic nervous system have an enhanced ability to excrete sodium as compared to normal persons.

Significance to HEART Research: In contrast to patients with congestive states who have a decreased ability to excrete sodium, the patients with autonomic nervous system hypofunction have an enhanced ability to excrete sodium when the extracellular fluid volume is expanded. The studies are of significance in leading to an understanding of the mechanisms of congestion of all types, including congestive heart failure.

Proposed Course of the Project: (a) To determine the role of the glomerular filtration rate, venous pressure, change in serum proteins, changes in hematocrit, and other factors in determining the rate of sodium excretion.

(b) To determine the effect of administration of various steroids with aldosterone-like properties on the sodium excretion of patients with autonomic hypofunction.

(c) To more clearly define the role of the autonomic nervous system in controlling sodium excretion.

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October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-178
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$13,600	$6,765	$20,365	1.0	.6	1.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-178
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI_179
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Mechanisms of Fluid and Electrolyte Retention in Experimental Cardiac Failure.
PROJECT TITLE

7. James O. Davis
PRINCIPAL INVESTIGATOR

8. Wilmot C. Ball, Jr., M. Jay Goodkind, Dr. Robert C. Bahn, Dept. of Pathological Anatomy, Mayo Clinic, Rochester, Minnesota
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

Research complements work done by Bartter and associates (Serial #301)

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Project: Increased secretion of aldosterone by the adrenal cortex in dogs with cardiac failure and in dogs with thoracic inferior vena cava constriction and ascites.

Objectives: To determine whether aldosterone is secreted at an increased rate in dogs showing chronic Na retention.

Methods Employed: The concentration of aldosterone is determined in adrenal vein blood from (1) normal dogs, (2) dogs with heart failure and (3) dogs with thoracic inferior vena cava constriction and ascites. Also, the rate of flow of blood from the adrenal gland is determined so that the minute output of aldosterone can be calculated. To determine the concentration of aldosterone in adrenal vein blood, the blood is extracted and chromatographed; all chromatographic fractions are assayed for aldosterone-like activity.

Major Findings: A. Studies using nembutal anesthesia. When adrenal vein blood was obtained from dogs under nembutal anesthesia, no aldosterone was detected in 300 cc. of blood from each of three normal dogs. However, the rate of aldosterone secretion was 6 γg/hour for a dog with caval constriction and ascites and 4 γg/hour for a dog with heart failure.

B. Studies using local anesthesia. In this series of dogs, adrenal vein blood was collected using local anesthesia and during transfusion of blood to replace the blood removed. Aldosterone secretion was 0,3, and 5 γg/hour for three normal dogs, 7 and 16 γg/hour for two dogs with thoracic caval constriction and 5, 20 and 25 γg/hour for three dogs with heart failure. Three hundred cc. of peripheral blood from one of the dogs with caval constriction and one of the dogs with heart failure showed no detectable aldosterone.

The data demonstrate increased secretion of aldosterone in dogs with thoracic caval constriction and in dogs with right heart failure.

Significance to [redacted] Research: This finding provides a very important link in the chain of events from the heart to the kidney in elucidation of the mechanisms of Na retention in congestive heart failure.

Proposed Course of Project: This project is complete. The mechanism whereby the adrenal cortex is stimulated to secrete aldosterone is the next logical problem. Also, the possibility of decreased rate of degradation of aldosterone by the liver as a secondary mechanism for increased circulating aldosterone should be investigated.

Project II.

Project: Aldosterone and Na excretion in urine from hypophysectomized dogs with thoracic inferior vena cava constriction and ascites.

Objectives: To determine the role of the anterior pituitary gland in the control of aldosterone production.

Methods Employed: The urinary excretion of aldosterone was studied by extraction of urine with an organic solvent, methylene chloride. The solvent is evaporated and the residue dissolved in absolute ethanol. The extract is injected into adrenalectomized assay dogs to characterize the effect on Na and K excretion. Potency is determined from a dose-response curve. It has been shown previously that the biologically active agent is aldosterone.

Dogs with thoracic caval constriction and ascites were subjected to hypophysectomy. In the first experiment, no therapy was given during the post-hypophysectomy period, but in the second group of animals (Experiment II) ACTH was administered in an attempt to prevent the changes resulting from hypophysectomy. In a third group of dogs (Experiment III) the pituitary gland was removed first and then the thoracic inferior vena cava was constricted.

Major Findings: Experiment I. A marked decrease in the urinary excretion of aldosterone occurred within 5-10 days after hypophysectomy. When aldosterone dropped to the normal level, Na excretion invariably increased. In some instances, aldosterone excretion did not return completely to normal and Na excretion remained low. Later in the course, aldosterone output returned to normal in the latter instances and Na excretion increased.

Experiment II. ACTH failed to prevent the fall in aldosterone excretion and rise in Na output which followed hypophysectomy of dogs with caval constriction and ascites. Reconstriction of the thoracic inferior vena cava with a resultant increase in inferior vena caval pressure was followed by restoration of aldosterone output to the high pre-hypophysectomy level, marked Na excretion and ascites formation.

Experiment III. In this experiment the pituitary gland was removed first and then the thoracic inferior vena cava was constricted. Urinary aldosterone excretion increased, marked Na retention occurred and ascites formed. The adrenal cortex of these two dogs was markedly atrophic but the atrophy was limited to the two inner layers; the zona glomerulosa appeared normal.

It is concluded that the pituitary gland is not essential for increased aldosterone excretion, Na retention and ascites formation.

Significance to HEART Research: The present data provide information on the relation of the anterior pituitary gland to aldosterone excretion in urine from dogs with experimental ascites. The findings also furnish valuable information on the fundamental relationship of the pituitary to the adrenal cortex.

Proposed Course of Project: To determine the effect of hypophysectomy on aldosterone output both thyrotropin and growth hormone should be given as replacement therapy. Also, the effect of thyroidectomy upon aldosterone excretion by dogs with caval constriction should be studied.

Project III.

Project: Effect of hemorrhage on the urinary excretion of aldosterone and sodium in dogs.

Objectives: To investigate the role of aldosterone in the retention of sodium following hemorrhage.

Methods Employed: Same as in Project II.

Major Findings: An increase in urinary aldosterone-like activity was associated with sodium retention following hemorrhage. A similar amount of activity characteristic of aldosterone was obtained by placing normal dogs on a low Na intake which was equivalent to the net Na intake produced by bleeding. The latter finding makes it unnecessary to hypothesize that factors other than Na loss are responsible for increased aldosterone output.

Significance to HEART Research: The data show the important role of aldosterone in homeostasis.

Proposed Course of Project: Project completed.

Project IV.

Project: Functional changes during high output failure produced by daily hemorrhage in dogs with pulmonary artery constriction.

Objectives; To determine the relationship of changes in cardiovascular and renal hemodynamic function to Na excretion during the development of high output heart failure.

Major Findings: Seven dogs with constriction of the PA and 6 normal dogs were bled 15-25 cc/kg. daily until a severe anemia developed. Five of the 7 dogs with PA constriction developed signs of right heart failure, but no evidence of cardiac decompensation was observed in the normal dogs made severely anemic. Mean right atrial pressure (RAP) inceased from 90/140 to 140/240 mm water but otherwise normal animals. Sodium retention occurred only in the dogs with PA constriction and ascites formation was associated with an RAP of 140 mm. water or above (normal RAP was 10-70 mm. water). Cardiac output increased to a similar extent (1.0-2.9 L./min.) in the two groups of animals. In dogs with PA constriction, C_{Cr} increased in some animals and decreased in others whereas C_{PAH} increased in 4 of 5 dogs. In the normal dogs made anemic, C_{Cr} was decreased or unchanged while C_{PAH} was increased or unaltered. The increase in RPF was apparently marked since the extraction ratio done on one of the dogs with PA constriction was 65%.

It is concluded that the most consistent differences between the two groups of animals in their responses to bleeding were in the effects on RAP and Na excretion; RAP increased and Na retention occurred only in dogs with PA constriction.

Significance to HEART Research: The data support the "backward failure" concept of the pathogenesis of congestive heart failure.

Proposed Course of Project: Project is complete.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-179
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$23,800	$9,834	$33,634	1.3	1.8	3.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-179
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Davis, James O., Howell, David S., Goodkind, M.Jay, and Hyatt,Robert E.: Accumulation of ascites during maintenance of adrenalectomized dogs with thoracic inferior vena caval constriction of a high Na diet without hormone therapy. Am. J. Physiol. 185:230,1956.

2. Davis, James O.,Goodkind, M.Jay, Pechet, Maurice M. and Ball, Wilmot C.,Jr.: Increased excretion of aldosterone in urine from dogs with right-sided congestive heart failure and from dogs with thoracic inferior vena cava constriction. Amer. J. Physiol. 187:45, 1956.

3. Goodkind, M.Jay, Hyatt, Robert E. and Davis, James O.: Failure of large doses of desoxycorticosterone acetate to block the natriuretic action of mercury in adrenalectomized dogs with thoracic inferior vena caval constriction and ascites. Amer. J. Physiol. (Accepted for publication)

4. Goodkind, M. Jay, Davis, James O., Ball, Wilmot C. Jr., and Bahn, Robert C.: Alterations in cardiovascular and renal hemodynamic function following hypophysectomy in the dog. Amer. J. Physiol. (Accepted for publication)

5. Davis, James O.: Some aspects of the physiology of aldosterone. J. National Medical Association. (Accepted for publication).

~~17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:~~

6. Ball, Wilmot C.,Jr., Davis, James O. and Goodkind, M.Jay: Ascites formation without Na intake in dogs with congestive heart failure and in dogs with thoracic inferior vena cava constriction. Amer. J. Physiol. (Accepted for publication).

17. List Honors and awards to personnel relating to this project during calendar year 1956.

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-180
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Method and Apparatus for Automatic Titration of Chloride
PROJECT TITLE

7. Ernest Cotlove
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Project: Development of method and apparatus for rapid, precise and automatic titration of chloride.

Objectives: The object of this project is to develop a simple, rapid, precise and sensitive method that will permit a detailed investigation of tissue chloride contents, cellular chloride content and exchangeability of chloride.

Methods Employed: The analytic method is based on titration of chloride by silver ion. The silver ion is generated at a constant rate from silver wire by electrolysis. The end-point is detected amperometrically by the sudden rise in diffusion current (due to free silver ion) between two stationary silver electrodes in a stirred medium. A meter-relay, set to be actuated by the current rise just past the end-point, stops a timer. The titration is thus entirely automatic. The elapsed time minus the over-titration time for relay actuation (as measured by a blank sample) is a direct measure of chloride content.

Major Findings: The apparatus and method have been further improved and simplified so that results are obtainable from the timer reading by simple calculation. The recording and measurement of the titration curve can be eliminated. Accurate results are obtainable in biological fluids (plasma, urine, tissue extracts) without prior preparation of the sample other than addition of acid reagent mixture. The procedure is rapid (about a half-minute) accurate (to within 1% or better), sensitive (to as little as one-quarter microequivalent of chloride), and can be performed by personnel without special training.

Significance to HEART Research: A simple, rapid and accurate method for determination of chloride in biological materials will be of value, since chloride is the predominant anion in extracellular fluid, and current methods are slow and depend on operator skill and judgment. The analysis of chloride in tissues in particular has presented problems. The present method should be of great usefulness not only in specialized research problems but also in clinical laboratories involved in patient care.

Proposed Course of the Project: The method is being applied to the problems for which it was developed, namely a study of tissue chloride. It is also being used in a number of other projects requiring analysis of chloride in biological fluids. The plans will be released to manufacturers who might be interested in producing it for research and clinical laboratories.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-180
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,600	$2,604	$8,204	.2	.5	.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

This project is being conducted in collaboration with Dr. Robert L. Bowman and Mr. Hillary Trantham, Laboratory of Technical Development, NHI.

(Use reverse and additional pages, if necessary)

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-180
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-181
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Kidney & Electrolyte Metabolism
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Absorption of Drugs by the Intestine
PROJECT TITLE

7. Dr. C. Adrian M. Hogben
PRINCIPAL INVESTIGATOR

8. Dr. Lewis S. Schanker (Lab. of Chemical Pharmacology)
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: The rates of movement of diverse compounds across the gastrointestinal tract will permit characterization of membrane permeability and significant physical chemical factors.

Methods Employed: A saline solution containing the drug is perfused through the rat intestine in situ. The decreased concentration of the drug leaving the intestine provides a measure of absorption and an apparent permeability coefficient. The steady state distribution of a drug is determined by injecting the drug intravenously and then perfusing the intestine with a drug concentration that establishes equilibrium.

Major Findings: A survey of a large number of acidic and basic drugs indicates that there are limiting ionization constants determining absorption from an unbuffered solution in the intestinal lumen. In the case of acids, the pKa is 2.5; for bases the pKa is 8.5. In no instance has there been evidence of competition between drugs. The rate of absorption is proportional to concentration.

Among those drugs which are rapidly absorbed, there are small but significant differences in absorption rates. While these differences parallel the lipid:water partitions in some cases, there is lack of agreement in others. Similar findings have been encountered in other biological membranes thought to have an essentially lipoid matrix.

The absorption of these drugs has been examined at several pH's ranging from 4 to 8. Qualitatively the rates of absorption are modified in the direction expected if these drugs were absorbed in the uionized form. Quantitatively the rate of absorption does not change as much as the change in concentration of the unionized form, e.g., the absorption of salicylate changes from 64% at pH4 to 11% at pH8.

The dependence of absorption on intestinal lumen pH and the limiting pKa's determining rapid absorption have been clarified by determining the steady state distribution between plasma and intestinal lumen. When the intestinal lumen has a pH of 6.5 the plasma to lumen ratio of salicylic acid is 30:1 and of quinine is 1:30. These observations and others can be interpreted on the basis of the intestinal lumen having a virtual pH of 5.5 and the steady state being determined by both the rapid movement of the unionized moiety and the slow movement of the ionized moiety.

Significance to HEART Research: This study will provide for the first time a quantitative picture of gastrointestinal absorption of drugs. Analysis of factors governing weak electrolyte transfer will contribute information to the study of electrolyte exchange across the gut. Investigation of factors other than permeability are significant for other aspects of gastrointestinal physiology such as fat absorption.

Proposed Course of Project: Extend our understanding of pH dependence of drug absorption by further steady state experiments. Analyze the absorption of different regions of the intestine. Scrutinize the rates of absorption of poorly absorbed drugs.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI-181
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,700	$2,684	$8,384	.4	.3	.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	0

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

(Use reverse and additional pages, if necessary)

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-181
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Shore, P.A., Brodie, B. B. and Hogben, C.A.M. Gastric secretion of drugs - a pH partition hypothesis. J. Pharm. & Exp. Therap. (In press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-182
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. THE SEQUENCE OF VENTRICULAR CONTRACTION IN HUMAN BUNDLE BRANCH BLOCK.
PROJECT TITLE

7. Eugene Braunwald, M. D. & Andrew G. Morrow, M. D.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To ascertain whether or not the ventricles contract simultaneously or not in the presence of EKG findings of bundle branch block.

Methods Employed: Simultaneous left and right ventricular pressures were determined in both normal individuals and those with bundle branch block.

Major Findings: In five patients with left bundle branch block there was no delay in contraction. In some patients with right bundle branch block there was delay and in others there was not. In those with the delay there was always right ventricular hypertrophy.

Significance to HEART Research: The significance of the EKG pattern of bundle branch block is open to question and these studies should do much to clarify the clinical problem.

Proposed Course of Project: The studies will be continued in patients with and without bundle branch block.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NMI - 182
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,800	$21,219	$28,019	.3	.4	.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	380

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-182
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-183
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. THE USE OF DYE DILUTION CURVES FROM THE LEFT HEART AND AORTA FOR THE LOCALIZATION OF LEFT TO RIGHT SHUNTS AND THE DETECTION OF VALVULAR INSUFFICIENCY.
PROJECT TITLE

7. Andrew G. Morrow, M. D., Eugene Braunwald, M. D. & Herbert Tanenbaum, M. D.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To assess the usefulness of left heart and aortic indicator dilution curves in the localization of left-to-right shunts and the detection of valvular insufficiency.

Methods Employed: Dye curves were made by injection into the left atrium, left ventricle and at various sites in the aorta in patients with a variety of cardiovascular lesions.

Major Findings: A normal curve results when the injection is made distal to the origin of the shunt or when no insufficiency is present. An abnormal curve is obtained proximal to a shunt or in the presence of valvular insufficiency. The two types of abnormal curves are distinct.

Significance to HEART Research: The precise localization of left-to-right shunts is often a difficult clinical problem. The present technique promises to be of great aid in this diagnostic problem.

Proposed Course of Project: Studies will be continued as outlined.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 183
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$15,400	$48,096	$63,496	.7	.7	1.4

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	573

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

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Part C: Honors, Awards & Publications

15. NRL-183
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

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Part A. Project Description Sheet

1. NHI-184
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. EVALUATION OF LEFT ATRIAL PRESSURE CONTOURS IN DIFFERENTIATING MITRAL STENOSIS AND MITRAL INSUFFICIENCY.
PROJECT TITLE

7. Andrew G. Morrow, M. D., Edward H. Sharp, M. D., Eugene Braunwald, M. D. & J. Alex Haller, Jr., M. D.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To evaluate the usefulness of left atrial pressure pulses in the assessment of the severity of mitral insufficiency.

Methods Employed: Left atrial pressure was measured preoperatively in patients with mitral valve disease and the resulting curves analyzed by many methods.

Major Findings: Best differentiation occurred when the slope of the y descent of the left atrial V wave was related to the mean left atrial pressure. By this technique patients with mitral stenosis and mitral insufficiency were easily distinguished.

Significance to HEART Research: Rheumatic mitral valve disease constitutes the largest group of patients with acquired valvular disease. The selection of the patients for operation is greatly facilitated by the method outlined.

Proposed Course of Project: Studies will be continued and the results correlated with operative and autopsy findings.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 184
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$25,600	$79,218	$104,818	1.6	.5	2.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	1	3	1140

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-184
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-185
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. EXPERIMENTAL PRODUCTION OF GRADED VALVULAR MITRAL STENOSIS IN DOGS.
PROJECT TITLE

7. C. S. Weldon, M. D. & Joseph W. Gilbert, M. D.
PRINCIPAL INVESTIGATOR

8. Surgical Laboratory, NHI
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objective: To develop a direct vision approach to the mitral valve in order to produce experimental mitral stenosis and evaluate this technique for possible clinical application in the treatment of mitral insufficiency.

Methods Employed: The interior of the left atrium is exposed in animals by an incision on the right inferolateral border of the left atrium. The animal is supported during this time on the heart-lung machine during a period of elective cardiac arrest. Hypothermia has been employed in some but with low survival.

Major Findings: The valve can be safely exposed for 20-30 minutes and graded mitral stenosis produced by direct vision suture of the leaflets.

Significance to HEART Research: The treatment of mitral insufficiency remains a major unsolved problem in clinical cardiac surgery. It is believed that the technique described will provide a method for its successful repair.

Proposed Course of Project: Animal experimentation will be continued and human autopsy material studied to determine the best operative technique.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 185
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$15,800	$6,695	$22,495	.7	.8	1.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-185
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-186
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. THE REACTIVITY OF CARDIAC MUSCLE TO ADRENERGIC AGENTS AFTER BILATERAL THORACIC SYMPATHECTOMY.
PROJECT TITLE

7. Theodore Cooper, M. D.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To determine the effects of thoracic sympathectomy on the sensitivity of the heart to adrenergic drugs.

Methods Employed: The contractile force of the heart has been measured after varying doses of adrenalin and noradrenalin in the normal and sympathectomized dog.

Major Findings: Thus far, no changes in the sensitivity of the heart have been found after sympathectomy.

Significance to HEART Research: The results indicate that there would be no "supersensitivity" of the heart to adrenalin after sympathectomy in the human.

Proposed Course of Project: The study will be continued as outlined.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 186
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$9,700	$4,091	$13,791	.	.	.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-186
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-187
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. STUDIES ON THE EXCITABILITY OF VENTRICULAR HEART MUSCLE DURING HYPOTHERMIA WITH AND WITHOUT PROCAINE BLOCKADE OF THE CAVAL-ATRIAL JUNCTION.
PROJECT TITLE

7. Leo R. Radigan, M. D., Thomas A. Lombardo, M. D. & Theodore Cooper, M. D.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To determine if anesthetic block of the atrial caval junction protects the heart from ventricular fibrillation due to electrical stimuli.

Methods Employed: It has been shown that atrial caval infiltration in hypothermic animals protects the heart against ventricular fibrillation secondary to right ventriculotomy. In the present study the effects of the block were determined in preventing VPC's following electrical stimulation.

Major Findings: The preliminary results indicate that the procedure does not seem to protect against electrical stimulation. However, regulation of heart rate, pH and other factors must be carefully controlled.

Significance to HEART Research: Ventricular fibrillation is a dreaded complication of operations involving hypothermia. A successful means of preventing it would be a valuable adjunct in clinical surgery.

Proposed Course of Project: The project will be continued with the extensions outlined above.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 187
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$35,600	$14,878	$50,478	2.2	.8	3.0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	1	3	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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Part C: Honors, Awards & Publications

15. NHI-187
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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Part A. Project Description Sheet

1. NHI-188
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. INTRAPULMONARY TRANSPLANTATION OF AUTOGENOUS THYROID TISSUE PER COURNAND CATHETER.
PROJECT TITLE

7. Richard Sanders, M. D. & Joseph W. Gilbert, M. D.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objective: To determine if functioning gland tissue can be transplanted to the lung.

Methods Employed: Autogenous thyroid tissue has been injected into the pulmonary arteries in dogs and the lung studied histologically one month later.

Major Findings: Thus far, no identifiable thyroid tissue has been found in the segments of the lung.

Significance to HEART Research: The lung did seem to be an ideal vascular bed for the auto- or homotransplantation of many tissues.

Proposed Course of Project: The project will be continued with tracer studies and perhaps with other acinar tissue.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 188
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$12,000	$5,021	$17,021	.7	.2	.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-188
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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Calendar Year 1956

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-189
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. REVERSAL OF THE CARDIAC EFFECTS OF SEVERAL SYMPATHOMIMETIC AMINES BY DIGITALIS GLYCOSIDES DURING HYPOTHERMIA
PROJECT TITLE

7. Marion DeV. Cotten, Ph. D. & Theodore Cooper, M. D., Ph. D.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To determine the effects of digitalis and allied compounds on the response of the heart to vaso-pressor agents at normal and lowered boy temperatures.

Methods Employed: Contractile force of the heart was determined by a strain gauge arch and the various compounds under study were administered in both warm and hypothermic animals.

Major Findings: Digitalis and allied compounds blocked or reversed the pressor effects of adrenalin or noradrenalin when the animal's temperature was 30° but not at 37°.

Significance to HEART Research: Many patients receiving digitalis must undergo operations with hypothermia. It is important to know the responsiveness of these hearts if resuscitation is necessary.

Proposed Course of Project: Studies will be continued with further observations and more compounds.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 189
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$21,500	$8,927	$30,427	1.1	.9	2.0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-189
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-190
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. CLINICAL APPLICATION OF NITROUS OXIDE IN THE DETECTION OF LEFT-TO-RIGHT INTRACARDIAC SHUNTS.
PROJECT TITLE

7. Andrew G. Morrow, M. D., Richard Sanders, M. D. & Eugene Braunwald, M. D.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To determine the usefulness of blood nitrous oxide levels in the detection of left-to-right shunts.

Methods Employed: Blood levels of nitrous oxide are determined in various cardiac chambers and the arterial system. Calculation of the comparative levels reveals an index which is the measure of the shunt present.

Major Findings: A "nitrous oxide index" of 0.2 or greater has been found diagnostic of the presence of a shunt. The procedure is a useful screening test when performed with the catheter tip in the pulmonary artery.

Significance to HEART Research: The precise localization of left-to-right shunts is a continuing problem in the assessment of patients with congenital heart disease. The present method is much more sensitive than conventional cardiac catheterization techniques.

Proposed Course of Project: Clinical studies will be continued and a detailed analysis of the studies performed is being made.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 190
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,800	$33,950	$44,750	.7	.2	.9

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	1140

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

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Part C: Honors, Awards & Publications

15. NE-190
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-191
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. TRANSBRONCHIAL LEFT HEART CATHETERIZATION
PROJECT TITLE

7. Andrew G. Morrow, M. D., Edward H. Sharp, M. D. & Eugene Braunwald, M. D.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To utilize the technique of transbronchial left heart catheterization in the assessment of a variety of forms of cardiovascular disease.

Methods Employed: The left atrium is punctured bronchoscopically and a catheter is then passed into the left atrium and left ventricle where pressures are recorded and indicator solutions injected.

Major Findings: The technique has been proved safe in nearly 500 studies. As a tool the method has been useful in studies concerning bundle branch block, pressure-volume relationships in the left heart, the assessment of

Significance to HEART Research: This technique and its applications represent one of the significant steps in recent years in the clinical management and investigation of patients with heart disease.

Proposed Course of Project: The project will be continued and expanded along the lines indicated.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. MHY - 191
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$14,500	$45,267	$59,767	.3	1.3	1.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	2	2	1577

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

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Part C: Honors, Awards & Publications

15. NHI-191
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

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Part A. Project Description Sheet

1. NHI-192
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. STUDY AND APPLICATION OF THE MELROSE PUMP OXYGENATOR
PROJECT TITLE

7. Edward H. Sharp, M. D., Clarence Weldon, M. D., Joseph W. Gilbert, M. D. & Andrew G. Morrow, M. D.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To perfect the Melrose heart and lung machine and adapt it for safe and practical clinical use.

Methods Employed: The Melrose machine was purchased and used in 55 animals subjected to total cardiac bypass. Many changes were found necessary in the machine and in the manner in which it was used.

Major Findings: Perfusion rates of more than 3000 cc./min. are practical and the animal's oxygen and other metabolic requirements can be kept normal. 80% survival in animals can now be obtained with the open left or right heart.

Significance to HEART Research: The development of a practical and safe heart-lung machine is necessary for the treatment of many forms of congenital and acquired heart disease.

Proposed Course of Project: Continued animal experimentation will be carried out with particular emphasis upon exposure of the mitral and aortic valves. Clinical application will be increased with emphasis upon ventricular septal defects and mitral insufficiency.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 192
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$32,600	$13,576	$46,176	1.2	2.0	3.2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	2	4	60

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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Part C: Honors, Awards & Publications

15. NHI-192
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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Part A. Project Description Sheet

1. NHI-193
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. EXPERIMENTAL CLOSURE OF RUPTURED SINUS OF VALSALVA ANEURYSMS
PROJECT TITLE

7. R. Robinson Baker, M. D., Hans Erik Hanson, M. D. & Andrew G. Morrow, M. D.
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To develop a method for the closure of fistulae between the aorta and right heart.

Methods Employed: Fistulae were created in dogs between the right atrium, right ventricle and aorta. They were then closed by means of a plastic sponge prosthesis introduced via the aorta.

Major Findings: The operation was technically successful in animals and has recently been used successfully in the treatment of two patients with this form of heart disease.

Significance to HEART Research: Although cardio-aortic fistulae are rare they usually lead to rapid and progressive heart failure.

Proposed Course of Project: Continued clinical use of the technique is planned and the method has been extended to such that it is useful in other forms of congenital heart disease.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 193
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$28,500	$51,218	$79,718	1.7	.8	2.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	1	3	118

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-193
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-194
SERIAL NUMBER

2. HEART
INSTITUTE OR DIVISION

3. SURGERY
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. CARDIAC OUTPUT DETERMINATIONS AND CALCULATION OF AORTIC AND MITRAL VALVE SIZE DURING SURGERY AND LEFT HEART CATHETERIZATION.
PROJECT TITLE

7. Herbert L. Tanenbaum, M. D.
PRINCIPAL INVESTIGATOR

8. Andrew G. Morrow, M. D. & Eugene Braunwald, M. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objective: To measure cardiac output during left heart catheterization, calculate aortic valve and mitral valve size from pressure and flow data and to do similar determinations during mitral and aortic valve surgery.

Methods Employed: Cardiac output obtained by dye dilution curves injecting Evans blue dye into left ventricle. Pressure measured in the conventional way and valve size calculated from the above information by use of Gorlin's hydraulic formulae.

Patient Material: 11 patients during left heart catheterization.
3 patients at surgery.

Major Findings: Pressure gradients vary directly with changes in square flow hence the importance of measuring both simultaneously. Valve area gives a relative estimation of degree of valvular stenosis and benefit following surgery.

Significance to HEART Research: Better definition of dynamics of mitral and aortic valve disease.

Proposed Course of Project: Collect more data. Relate valve areas to symptoms and other objective findings pre- and postoperatively. Establish bronchoscopic approach to left heart catheterization as valid means of defining more closely mitral and aortic valve disease.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 194
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$16,000	$49,511	$65,511	.7	.8	1.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	196

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-194
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI 195
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Development of Methods for Measurement of Blood Flow
PROJECT TITLE

7. Robert L. Bowman
PRINCIPAL INVESTIGATOR

8. Frank W. Noble
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

NONE

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: To develop an efficient method of blood flow measurement that produces a minimum disturbance in the system being measured.

Methods Employed: Physical techniques that offer the possibility of application to the problem are applied as they come to attention. At present the application of a magnetic and radio frequency field is used to induce the nuclei of the hydrogen atoms to precess and the energy absorbed by the interaction is utilized to indicate the effect. This effect is slow and time dependent so that in flowing systems the amplitude of the effect is changed by the flow. No mechanical or electrical contacts are necessary for the system to operate.

Major Findings: It has been relatively easy to obtain flow signals by this method and they have been relatively free of temperature, viscosity and salinity effects. It would appear that non-contacting flow systems can be made utilizing the principle noted.

Significance to HEART Research: Measurement of blood and body fluid flows without introduction of interfering probes or tubes offers a method of study that will minimize the influence of the method on the measurand.

Proposed Course of Project: To develop the method into a practical device and to examine its possibilities in relation to measurement of concentration and content of other elements.

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October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NRI - 195
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$11,400	$5,708	$17,108	.7	.9	1.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-195
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI - 196
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Microanalytic Methods for Alkali Metals in Micropuncture Samples
PROJECT TITLE

7. Dr. Robert L. Bowman
PRINCIPAL INVESTIGATOR

8. Dr. T. J. Kennedy, Jr.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To develop an accurate dependable method of analysis of samples of 0.0001 and .01 ml containing 50×10^{-12} to 150×10^{-10} moles of Na and 50×10^{-10} to 5×10^{-10} moles of K.

Methods Employed: Micropuncture samples are sealed into quartz capillary sample tubes and the tubes evacuated. These tubes are then lit by inducing an electrodeless discharge to occur due to a powerful microwave field. The field is produced by a specially developed tunable cavity of high efficiency. Analysis of the sample is made by spectrophotometric scanning of the emitted light and recording the intensity of the spectral lines. A specially constructed photometer extends the spectral sensitivity to the near infra-red.

Major Findings: The sensitivity of the method appears to exceed our requirements and this sensitivity extends to Lithium, Cesium and Rubidium, as well as Na and K. Halide bands due to Cl. may provide for the determination of Cl. at the same time.

Significance to HEART Research: This problem is designed to provide methods for analysis of the material obtainable from secretory and excretory systems involved in the regulation of electrolyte balance.

Proposed Course of Project: To work out the method to provide a practical accurate method for analysis of minute samples of body fluids.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 196
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$18,300	$9,161	$27,461	.5	2.5	3.0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	3	4	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. CRP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI - 196
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI - 197
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Development of a Mechanical Pump
PROJECT TITLE

7. Dr. Selwyn McCabe
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To construct a small and relatively simple pump for use in open heart surgery. The pump must be capable of working two pressure systems simultaneously.

Methods Employed: A prototype machine has been made. There are two parts - an activating mechanism at a distance from the actual pump. The pump is four chambered and uses four semilunar type valves. Its action is similar to the heart - the myocardial action being mimicked by fluid under compression "contracting" two "ventricular" (sacs). The pumping is dependent upon "venous return" i. e., a cam comes in contact when the ventricles are

appropriately filled to the desired output and the activating mechanism thus comes into play ejecting the ventricular contents. The two pressure systems are dependent on the peripheral resistance and the stroke volume. The total output can be controlled by either increasing the stroke volume or by increasing venous return and thereby speeding the action of the pump. "Diastole" can be shortened or lengthened by this same action. Some control of the length of "systole" can be obtained by increasing the revolutions of the power motor. Thus the pressure curves can be simply controlled. If the "venous" pressure on one side of the system becomes elevated then the receiving "ventricle" will be filled rapidly and displacing the fluid outside the sac will therefore fire off the power mechanism with a resultant increase in pump rate. Thus no overloading occurs.

Significance to HEART Research: A simple easily controlable and relatively small by-pass heart pump has been made. The pump tests the use of the artificially made semilunar valves and points to their advantages for use in artificial pump systems. The machine can be used for demonstrating the hearts action and the problems that arise when valves are damaged, etc. "Heart Sounds" 1, 2 and 3rd can be heard at the same time as the valves can be observed. It seems the machine is therefore useful for teaching purposes.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NRI - 197
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,000	$3,030	$9,030	.5		.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	-	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-197
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-198
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Development of Prosthetic Heart Valves
PROJECT TITLE

7. Dr. Selwyn McCabe
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To continue to develop prosthetics to be used in the replacement of diseased heart valves.

Since the semilunar tricuspid valve has prooved its efficiency both in nature and during our mechanical tests in the laboratory it seems only necessary to find a satisfactory material and design that will withstand the dangers of clotting and the rigors of time. Such a valve can be inserted at the

site of the original diseased valve - in the aortic site below the coronaries - and even the mitral valve can be replaced with this type valve as dynamically shown by the work of Dr. Murray of Toronto.

Methods Employed: Semilunar type valves have been assembled in plastics. Concurrently an investigation into all types of speculatively suitable materials has been in progress. The valves constructed have undergone tests in two pumps. They pass all the mechanically necessary criteria - namely, they are sufficient, have no practical impedance to flow or stenotic effect, withstand pressures well beyond the range demanded in nature.

Major Findings: The semilunar type valve has by its performance warranted consideration as the kind to replace diseased or congenitally aberrant heart valves. Success seems hinged on details of valve structure and problems of clotting with fibrin formation. The latter involves the consideration of the materials.

Significance to HEART Research: With the advent of open heart surgery, the success in the repair of congenital defects, the modified approach and success of the third coronary artery as outlined by Dr. Sidney Smith, the field of heart surgery will inevitably be pointed toward the replacement of the valves. Intensive research by this department is directed in this direction. Valves, theoretically and mechanically suitable for replacement of all hopelessly diseased heart valves, have been constructed. Their fabrication is reasonably straight forward.

Proposed course of Project: Continued search and testing for suitable materials. The use of human tissues is also under investigation. The long term trials in dogs to determine whether the designed valves will be tolerated. Speculated approaches to the insertion of the valve will be tested.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 198
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,000	$3,030	$9,030	.5		.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	-	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI - 198
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-199
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Drying and Hydration Studies of Proteins and Tissues
PROJECT TITLE

7. John L. Stephenson
PRINCIPAL INVESTIGATOR

8. Murray Eden
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To obtain information on the nature of the solid-liquid interface in protoplasm, particularly its area and hydration structure.

Methods Employed: By simultaneous recording of the weight and temperature of a sample being dried after rapid freezing, the probability of a water molecule, originating from the interface between the exterior dried shell and the still solidly frozen interior, escaping through the dried shell without returning to the interface, can be measured. Utilizing the transport theory which we have developed, this probability can be used to compute the envelope of the surface area per unit volume of the dry shell which is available for collision.

Major Findings: The previously described apparatus has been calibrated on water; giving results within the estimated magnitude of experimental error, and measurements have been begun on gelatin. The preliminary data on gelatin give an estimate of the order of 100 square meters per gram of dry gelatin. Gas adsorption techniques have given an estimated area of about 300 square meters per gram of dry weight of collagen. This difference is not unexpected and is in the anticipated direction, since the kinetic flow method should exclude certain kinds of area--for example, that interior to macromolecules or to crystalline micells.

Significance to HEART Research: This study shows promise of providing a method for characterizing the coarseness of molecular aggregates in gel structures - and so of measuring one very important aspect of protoplasmic structure. In addition, the drying data are of use in the design of drying apparatus for drying biological material such as blood and plasma from the frozen state.

Proposed Course of Project: Drying data on a variety of proteins and tissues are being compiled. The theory by which surface areas are computed from the raw drying data is being extended. In connection with this theoretical development, experimental studies of gas flow through mazes of known geometry are planned.

Attempts are also being made to refine the technique so that drying rates of samples of dry weight less than one microgram can be determined. Here, there are two possibilities: One is the use of a specially designed torsion balance mounted in the drying chamber; the other is by measuring the rate at which heat is supplied to the sample. The importance of this refinement is so that the drying rates of samples sufficiently small that no ice crystal formation occurs (as judged by electron microscopic studies) can be measured.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 139
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$8,000	$4,017	$12,017	.4	.7	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	-	1	1	None

13. BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION	
REVIEW & APPROVAL		PROFESSIONAL & TECHNICAL ASSISTANCE	
BIOLOGIC STANDARDS			

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-199
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI - 200
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Development of a Self-Balancing Potentiometer
PROJECT TITLE

7. John L. Stephenson
PRINCIPAL INVESTIGATOR

8. Frank W. Noble
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To develop a potentiometer type circuit of high sensitivity and rapid response, for the measurement of rapid cooling curves, occuring in one second or less and having rapid transients in various parts of the curve.

Methods Employed: The signal to be measured is applied to a galvanometer. The motion of the light spot of the galvanometer is amplified with a photoelectric following system consisting of a single photomultiplier and one power tube. A fraction of this signal is used to counteract the motion of the galvanometer. The entire signal is used to drive an appropriate recording system: recording milliammeter, speedomax, oscilloscope.

Major Findings: The previously described instruments have been used in daily laboratory work for over a year now and have performed satisfactorily. The general theory of such instruments has been developed somewhat more extensively than has so far appeared in the literature and correlates satisfactorily with the performance of our specific instruments and should in the future greatly facilitate the design of instruments for particular problems.

Significance to HEART Research: The instrument will be of use in recording a variety of bioelectric phenomena and is more sensitive and stable in the frequency range d.c. to 500 cps than conventional electronic amplifiers.

Proposed Course of Project: Except for publication the project is completed.

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October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 200
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,500	$3,735	$11,235	.4	.6	1.0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	0	1	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-200
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-201
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Electron Microscopy
PROJECT TITLE

7. John L. Stephenson
PRINCIPAL INVESTIGATOR

8. Murray Eden
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To further theapplication of electron microscopy to cytological problems.

Methods Employed: Thin sections of biological material fixed by freezing, then dried, are examined in the electron microscope. Various staining procedures to heighten contrast have been tried.

Major Findings: The original project has been essentially completed; that is, procedures have been developed for the freezing and drying of biological tissues for electron microscopy which apparently avoid

ice-crystal formation. During this year several trips were made to North American Philips Company to investigate the possibility of applying emission microscopy to biological material. Without doubt the method has possibilities both in regard to thermal emission from incinerated specimens and photon induced emission from tissue sections.

Significance to HEART Research: These techniques should open up new approaches in the submicroscopic pathology of cardiovascular disease.

Proposed Course of Project: If some sort of suitable collaborative arrangement can be made with an electron microscopist further correlations of freezing and electronmicroscopic data are planned. At the present time, because of limitations of personnel, no further investigation of emission microscopy is planned.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 201
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,600	$2,819	$8,419	.4	.2	.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	-	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

This has been a cooperative study with Dr. Isadore Gersh, Department of Anatomy, University of Chicago.

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-201
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Two papers from Dr. Isadore Gersh's laboratory have been accepted for publication:

I. Gersh, I. Isenberg, J. L. Stephenson, W. Bondareff, "Submicroscopic Structure of Frozen-Dried Liver Specifically stained for Electron-Microscopy. Part I. Technical", Anatomical Record.

I. Gersh, I. Isenberg, W. Bondareff, J. L. Stephenson, "Submicroscopic Structure of Frozen-Dried Liver Specifically Stained for Electron Microscopy. Part II. Biological". Anatomical Record.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-202
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Physics of Ultra-rapid Freezing of Water, Colloidal Solutions and Protoplasm.
PROJECT TITLE

7. John L. Stephenson
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

None

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: (1) To investigate the basic physics of the rapid freezing process in water, colloidal solutions and protoplasm. (2) To apply this information to the analysis of hydration phenomena in protoplasm. (3) To extend the range of application of freezing and drying as a method of fixation and preservation of biological material.

Methods Employed: The rate of cooling of various systems is measured with small embedded thermocouples. The output of these thermocouples is amplified and recorded from a cathode ray oscilloscope. From the theoretical analysis of these curves the properties of various coolants and various constants relating to ice crystal formation during cooling can be determined.

Major Findings: The recording techniques have been improved; particularly a variety of methods of constructing microthermocouples and microcalorimeters have been devised including vacuum evaporation of metals. Additional cooling studies on water in small capillary tubes (0.2 mm diameter) have confirmed the earlier results that if water is cooled below about -100 to -130°C in less than 2/100 of a second, heat release indicative of the phase transformation of ice to water is not observed. We have interpreted this as meaning that water solidifies in a metastable vitreous state. The theory of rapid cooling and of ice crystal formation during rapid cooling has been further developed. An experimental study was also made of the effects of freezing under pressure. Red blood cells were frozen under pressures of 35,000 lbs. per square inch, high enough so that on freezing water goes into ice II instead of the usual ice I. In this transformation there is a volume contraction instead of a volume expansion. The purpose of the experiment was to test the hypothesis that the cause of protoplasmic damage on freezing at ordinary pressures is the volume increase. It was found that on freezing and thawing under pressure complete hemolysis occurred.

Significance to HEART Research: These studies on freezing provide basic information which can be used to improve and extend freezing and drying as a method for preserving and storing biological materials such as arterial grafts, plasma, biologicals and whole blood. Secondly, they give information on the type of changes which may occur in protoplasm during freezing and drying and so provide a basis for extrapolating from data (such as microspectrometric and electron microscopic) obtained on frozen dried material to the living state. Finally, as discussed below, they may in themselves provide fundamental information on the organization of aqueous gels including protoplasm.

Proposed Course of the Project: The principal immediate problem is to demonstrate conclusively by calorimetric and volumetric studies during warming that samples whose cooling curves do not appear to show release of the latent heat of crystallization are actually vitrified during the cooling. Experiments which it is hoped will show this have been planned. A second problem to be explored is whether in aqueous gels it is possible to correlate ice-crystal formation during freezing with the hydration of the macromolecules. It has been observed that in certain parts of cells such as nuclei, ice crystals are particularly likely to form during rapid freezing - - whereas in certain other structures such as mitochondria, ice crystals are rarely observed. These differences probably have some relation both to the degree of aggregation of the colloidal particles and the thermodynamic activity of the water in the different regions. If this relation could be determined it would be possible to get information on both the colloidal morphology and the activity of the water.

Form No. ORF-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NEI - 208
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,800	$2,398	$7,198	.2	.5	.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	-	1	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-202
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

John L. Stephenson, "Ice-Crystal Growth During the Rapid Freezing of Tissues", Journal of Biophysical and Biochemical Cytology, July 25, 1956, Vol. 2, No. 4, pp. 45-52.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-203
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Infra-Red Microspectrometry
PROJECT TITLE

7. John L. Stephenson
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

None

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: To develop an infra-red spectrometer suitable for obtaining absorption spectra of tissues and cells.

Methods Employed: Infra-red radiation from a monochromator is passed through a reflecting microscope into a suitable detector, thus permitting absorption spectra of microscopic samples to be obtained.

Major Findings: A Perkin-Elmer infra-red spectrometer has been acquired and set up.

Significance to HEW Research: If techniques can be developed, should be useful in the study of intracellular metabolism and organization.

Proposed Course of Project: It is planned to use the Perkin-Elmer instrument to investigate the effects of dehydration on the absorption spectra of proteins. Because of the very large absorption of water in the 3 micron region, of the spectra, k greater than 700 cm^{-1}, infra-red absorption should be a very sensitive measure of the amount of water bound to tissue. In addition, with changes in the degree to which water is bound to protein there are shifts in the wavelength of the absorption maximum. If the methods can be developed in proteins, there is some possibility of utilizing them on individual cells because spectra can be taken on areas of about 100 square micra.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 203
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,200	$3,594	$10,794	.2	1.0	1.2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-203
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-204
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Development of a Method of Separating Erythrocytes by Their Density
PROJECT TITLE

7. Murray Eden
PRINCIPAL INVESTIGATOR

8. David Chalfin
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

None

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: To determine what properties of red blood cells affect their density. In particular, to ascertain whether there is a change in the density of erythrocytes with age.

Methods Employed: A gradient density tube has been devised consisting of layers of varying concentrations of serum albumin, made isotonic and adapted to pH 7.4. The whole blood is layered on top of the tube and the tube centrifuged to equilibrium. Radioactive iron is employed as a tracer to determine the function of age vs. density.

Major Findings: Normal human blood shows a wide distribution of density. In a given individual there are only minor day to day fluctuations. There is a statistically significant increase in density with age for the human erythrocyte.

Significance to HEART Research: It is hoped this will contribute to an understanding of the aging of red blood cells. Further, if the separation of young from old cells can be done readily, it may increase the lifetime of stored blood.

Proposed Course of Project: Efforts will be made to ascertain whether the separation of cells by age is sufficiently sharp as to permit correlations of various properties of blood cells, e. g., ion fluxes with the age of cells.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 204
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$16,600	$8,315	$24,915	1.2	.5	1.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-204
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-205
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Development of a Probabilistic Model for Growth
PROJECT TITLE

7. Murray Eden
PRINCIPAL INVESTIGATOR

8. ---
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

None

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: To construct a minimal information, stochastic, two-dimensional model of a growing organism and to study the properties of the model.

Methods Employed: Combinatorial analysis and probability theory are the basis for most of the analysis. A high speed digital computer is necessary for certain of the computations.

Major Findings: A measure of the effect of environmental factors on the growth pattern of an organism has been devised using the techniques of information theory. The growth properties of a very simple system, analogous to tissue culture growth, has been studied.

Significance to HEART Research: Theoretical studies of this sort are intended to throw some light on the nature of the process that specifies and limits the patterns of growth and repair.

Proposed Course of Project: An attempt will be made to formulate more complicated models as analog to embryonic processes, e. g., development to the blastular stage. The results of the simpler model will be extended to larger numbers of cells.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 205
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,300	$2,185	$6,485	.2	.4	.6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	-	1	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

Dr. Hale Trotter, Princeton University

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-205
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"The Form of the Frequency Distribution Curve of Cell and Nuclear Sizes", J. T. Bonner and M. Eden, Experimental Cell Research, II, p. 265, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-206
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Development of a Micro Glass Electrode
PROJECT TITLE

7. Murray Eden
PRINCIPAL INVESTIGATOR

8. ---
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To develop a glass electrode small enough to be embedded into living organisms for some length of time. To ascertain how small a glass electrode can be made that will function as an adequate sensing element for the measurement of pH.

Methods Employed: Micro glass electrodes are fabricated from special pH responsive glass using techniques similar to those required for the preparation of micro dissection apparatus. Measurements are made with extremely sensitive amplifiers.

Major Findings: Techniques have been devised to circumvent most of the difficulties encountered in the preparation of workable micro glass electrodes. The vibrating reed electrometer amplifier has proven ideally suited to the measurement of the potentials produced by the electrode system.

Significance to HEART Research: Such electrodes may be used to study the acidity in small capillaries or in kidney tubules and ultimately within cells.

Proposed Course of Project: Equipment for evaporating films of insulation onto the body of the electrodes, and efforts will be made to coat the electrodes to within 50 microns of the tip, so as to decrease the sensitive area of the glass.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 206
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$3,800	$1,903	$5,703	.2	.3	.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	-	1	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-206
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-207
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Development of Equipment for Studies of Adsorption
PROJECT TITLE

7. Murray Eden
PRINCIPAL INVESTIGATOR

8. ---
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To develop methods for determining the thermodynamic properties associated with the adsorption of water on biological substances.

Methods Employed: Samples of biological materials e. g., protein solutions are placed in a thermostated bath. The vapor pressure of the solution is measured by a pressure transducer. A known amount of the water is removed by pumping and the pressure measurement is repeated until the sample is completely dried.

Major Findings: Studies with carbonic acid anhydrase and trypsin indicated that they are not irreversibly inactivated by reducing the water vapor pressure to an extremely low level.

Significance to HEART Research: All biological materials as they exist in the tissues are surrounded by a more or less tight layer of water molecules. Many of the functions of cells seem to depend on the properties of membrane or cell wall. The membrane structure in turn is influenced by the degree of hydration.

Proposed Course of Project: The procedure will be repeated at elevated temperatures at which there is measurable denaturation and the energy of inactivation determined.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 207
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$2,400	$1,198	$3,598	.2	-	.2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	-	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-207
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-208
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. Electronics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Catheter Tip Pressure Gauge
PROJECT TITLE

7. Frank W. Noble
PRINCIPAL INVESTIGATOR

8. ----------
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

Objectives: To develop and evaluate a new type of catheter tip pressure gauge for use in cardiac catheterization procedures.

Methods Employed: A new type of catheter tip gauge has been investigated and found to be promising. A high frequency sound wave is introduced into one lumen of a double lumen catheter. The cross sectional area of the sound path is varied by a diaphragm attached to the far end of the catheter. The sound returns through the second lumen. Pressure applied to the diaphragm modulates the sound waves in accordance with the instantaneous value of the pressure so that the return lumen

supplies an amplitude modulated sound to the receiving apparatus. The receiving system amplifies and demodulates the wave, yielding an output voltage proportional to the instantaneous value of the pressure on the diaphragm.

Major Findings: The frequency response of the gauge has been measured by the use of a magnetic sine wave pressure generator and found to be uniform from zero to 100 cycles per second. The linearity has been measured and found to be fair.

Drift in sensitivity and base line has been traced to the variation in sound transmission with temperature of the air in the catheter. It was computed that the properties of the air would produce about 1% decrease in transmission per degree centigrade. The measured amount was in good agreement with this figure. Compensation for this effect could be obtained if a material having a very large positive temperature coefficient of expansion could be found. A catheter made of such a material would expand by an amount just sufficient to counteract the effect of the changing properties of the air.

Significance to HEART Research: A pressure gauge attached to the tip of a catheter would greatly improve the accuracy of pressure measurements made during cardiac catheterization.

Proposed Course of the Project: Several schemes for overcoming the temperature effect are under consideration. A second sound path not including the valve but otherwise experiencing the same changes with temperature could provide the answer. As a last alternative, a different gas might be found in which the temperature effect is much less than the effect in air.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 208
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,500	$2,255	$6,755	.2	.5	.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	-	1	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-208
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

This instrument was described at the annual meeting of the Federation of American Societies for Experimental Biology, which was held in Atlantic City, New Jersey, April 15-20, 1956.

A more recent paper was given at the Conference on Electronic Instrumentation in Biology and Medicine sponsored by the Institute of Radio Engineers, The American Institute of Electrical Engineers, and the Instrument Society of America. The conference was held in New York City on November 7-9, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-209
SERIAL NUMBER

2. National Heart Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. Electronics
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Computer for a Catheter Tip Flowmeter
PROJECT TITLE

7. Frank W. Noble
PRINCIPAL INVESTIGATOR

8. Donald L. Fry
OTHER INVESTIGATORS

9. **IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).**

10. **PROJECT DESCRIPTION (SEE INSTRUCTIONS):**

Objectives: To provide means for recording the velocity of blood flow in the aorta using a sensing element on the tip of the catheter.

Methods Employed: It can be shown that the pressure difference between two points along the axis of flow is the sum of two components:

$$p = A\frac{dv}{dt} + Bv \qquad (1)$$

where p is the pressure difference, v is the velocity, and A and B are constants. P is obtained from a differential pressure gauge, A is calculated, and B must be determined from the boundary conditions. A special analog computer is required to solve Equation 1 for velocity at every instant.

Major Findings:

A. Simple analog computer has been built to solve Equation (1). It makes use of the fact that the line current supplying a parallel connection of resistance and capacitance is of the same form as equation (1), i. e.

$$I = C \frac{de}{dt} + \frac{1}{R} E \qquad (2)$$

Since it is inconvenient to supply a current to the computer, we have connected a large resistance in series with the input and supplied an input voltage. We now have

$$KE_i = C \frac{de_o}{dt} + \frac{1}{R} E_o \qquad (3)$$

When K is a constant, the voltage E_i is obtained from the differential pressure gauge via a Sanborn Strain Amplifier. The voltage E_o, which is proportional to v in equation (1), is connected to a Sanborn D. C. Amplifier and recorded.

A modified computer has been designed and built to operate with the new model of the Sanborn Recorder. Since the new Sanborn equipment incorporates voltage regulation, it is hoped that the drift problem will be reduced.

Significance to HEART Research: A velocity flowmeter operating from a sensing element in the tip of a catheter would be of value in clinical research.

Proposed Course of Project: The computer in its present form is rather involved in its operation and is subject to baseline drift problems. We propose to investigate the use of an electro-mechanical link between the Strain Amplifier and the computer in an attempt to simplify and improve the performance of the device.

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October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 209
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,500	$2,255	$6,755	.2	.5	.7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57		1	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

NHI 108

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October 1956
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-209
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NHI-210
SERIAL NUMBER

2. [illegible]t Institute
INSTITUTE OR DIVISION

3. Laboratory of Technical Development
LABORATORY, BRANCH, OR DEPARTMENT

4. [illegible]tronics
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. [illegible]t Coupled Electrokymograph
PROJECT TITLE

7. [illegible]ble
PRINCIPAL INVESTIGATOR

8. [illegible]. Boone, Harold T. Dodge
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION (SEE INSTRUCTIONS):

[illegible]: To provide an electrokymograph having response down to true [illegible] frequency. This is a desirable feature because it prevents distortion of the record due to action of coupling capacitors. It also makes it possible to obtain accurate calibration of [illegible]ions or densities.

Methods Employed: The instrument has been improved and rebuilt in final form. Two copies of the final design have been built by the NIH Instrument Shop. After testing here, these models will be loaned for clinical testing to:

Dr. M. J. Oppenheimer, Temple University Medical School, Philadelphia, Pennsylvania

Dr. Gordon Ring, University of Miami Medical School, Miami, Florida

Major Findings: This instrument is superior to the commercial instrument in regard to speed, accuracy, and ease of calibration.

Significance to HEART Research: The Electrokymograph is already established as a useful instrument for studying the characteristic motions of the heart border in health and disease. It is hoped that the D. C. response feature of this new instrument will enhance the usefulness of the Electrokymograph by decreasing errors and allowing for easy calibration.

Proposed Course of Project: The instrument will be evaluated by Drs. Oppenheimer and Ring. Alterations and improvements will be made during the clinical tests. Finally, details of the instrument will be published.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NHI - 210
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$9,700	$4,862	$14,562	.7	.4	1.1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	-	1	None

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NHI-210
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None