CENTER FOR THEORETICAL BIOLOGY

Health Sciences Center

State University of New York at Buffalo

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for year 1966

412 Michael Hall
State University of New York
Buffalo, N. Y. 14214

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INTRODUCTION

This grant has been used principally as "seed" money to promote the activities of a number of working parties, as indicated later in this report. Thus we have supported secretaries and other support staff whose help would result in acceleration of research progress, paid graduate student stipends, brought in outside consultants, paid a variety of faculty salaries, and in this way have catalysed the formation of working parties which involve about 30 faculty members, 12 post-doctoral fellows and 7 graduate students.

We have also supported a summer workshop on Transport Theory (June - July, 1966), and assisted in a symposium on Drugs Affecting Immunity (September 1966).

In this way the grant has promoted a large amount of interdisciplinary interdepartmental activity which is having a valuable effect upon the organisation and capacity of the university. Twelve departments now participate in the work of the Center.

The Center will move into a new set of offices in the fall of 1967.

J. F. Danielli

COMMITTEES

Executive Committee

Chairman — J. F. Danielli

Members — A. I. McMullen, Irving H. Shames, Fred M. Snell, and Dov Tamari

General Purposes Committee

Chairman — H. Collins (alternate P. Ford)

Members — P. Ford, P. Weber, R. Wagner, K. Maher

The general purposes committee is concerned with provision of all support services, including secretarial, accounting, space allocation, supplies, equipment, conference services, etc.

Seminar, Library & Preprint Committee

Chairman — Cora Saltarelli

Members — A. I. McMullen, N. Leibovic, R. J. Good, D. Triggle, R. A. Jensen

Faculty - Graduate Student Committee

Chairman — Fred Ridley

Members — Mary Danielli, P. Ford

Working Parties

Statistical Mechanics

Chairman - V. Vaidhyanathan

Members - F. Snell, D. C. Mickulecky, R. Spangler, S. Ohki

Consultant - R. Aranow

Quantum Biochemistry

Chairman - R. Rein

Members - N. Fukuda, P. Hochman, S. Svetina, M. Davids, J. Harlos

Consultants - F. Harris, N. Goel

Theory of Macromolecules

Chairman - A. I. McMullen

Members - D. MacGillivray, R. Rein, I. Marinsky*

Consultants - M. Ycas, N. Goel

Theory of Surfaces & Membranes

Chairman - J. F. Danielli

Members - R. Good, D.A. Cadenhead, S. Ohki, M. Phillips, A. Goldup, I. Shames

Transport Phenomena

Chairman - C. Paganelli

Members - D. Mickulecky, S. Ohki, V. Vaidhyanathan, R. Spangler*, F. Snell

Cytoplasmic Inheritance

Chairman - J. F. Danielli

Members - K. Jeon, J. Moran, J. Lorch

Consultant - M. Ycas

Receptor Isolation

Chairman - D. Triggle

Members - M. May, J. Moran, J. F. Danielli

Systems Theory & Relational Biology

Chairman - R. Rosen

Members - K. N. Leibovic, J. F. Danielli, J. Myhill, A. Rallston

Models of the Visual Pathway and the Central Nervous System

Chairman - K. N. Leibovic

Members - M. Danielli, J. Abernethy, P. Bright, G. Lord, D. Faber, G. Allen, W. Ulvang, W. Noell, R. Rosen, R. Spangler, M. Licker

Cancer Chemotherapy

Chairman - A. Mittleman

Members - R. Jones, W. Meeker, J. Ambrus, U. Kim, J. F. Danielli, E. Mihich, D. Triggle, T. Bardos, N. Fukuda

FACULTY AND SUPPORTING STAFF

CENTER FOR THEORETICAL BIOLOGY

		Main Field of Interest
James F. Danielli	Director	Membrane phenomena, cell theory, cytoplasmic inheritance, relational biology
	PROFESSORS	
Eric A. Barnard, Ph.D.	Biochemical Pharmacology, Biochemistry	Active centers of enzymes; properties of enzymes in cells
Robert J. Good, Ph.D.	Chemical Engineering	Surface chemistry and physics
Joseph G. Hoffman, Ph.D.	Physics	Quantitative measurement of heat released by mammalian tissue cells
Akira Isihara, D.S.	Physics	Statistical mechanics
Arnold I. McMullen, Ph.D.	Theoretical Biology Unit	Theoretical aspects of the physics of intra and intermacromolecular interactions
David Pressman, Ph.D.	Roswell Park Memorial Institute	Biochemistry and immunology
Irving H. Shames, Ph.D.	Interdisciplinary Studies, Engineering	Continuum mechanics
Fred M. Snell, Ph.D.	Biophysics	Transport and membrane phenomena, nonequilibrium thermodynamics, theoretical biology
Dov Tamari, Ph.D.	Mathematics	Algebra; Furthering mathematical thought in biology
Sol W. Weller, Ph.D.	Chemical Engineering	Heterogenous and homogeneous catalysis; chemical reaction kinetics

ASSOCIATE PROFESSORS

Robert Abbott, Ph.D.	Interdisciplinary Studies, Engineering	Surface physics; physisorption and chemisorption of molecules and macromolecules on solid surfaces
G. R. Blakely, Ph.D.	Mathematics	Population studies
David A. Cadenhead, Ph.D.	Chemistry	Surface chemistry-monolayer studies and molecules or biological interest
Mac S. Hammond, Ph.D.	English	Linguistics and poetics
K. Nicholas Leibovic, Ph.D.	Biophysics	Processes of communication and control in biological systems, especially the cerebral nervous system
Donald C. Mikulecky, Ph.D.	Biophysics	Membrane phenomena; nonequilibrium thermodynamics transport across biological membranes
Charles Paganelli, Ph.D.	Physiology	Transport across biological membrane
Armin H. Ramel, Ph.D.	Biochemical Pharmacology	
Robert Rein, Ph.D.	Research, Theoretical Biology Unit	Quantum chemistry of organic and biomolecules
Robert Rosen, Ph.D.	Mathematics and Biophysics	Biological systems analysis
David J. Triggle, Ph.D.	Theoretical Biology Unit	Theories and mechanisms of drug-receptor interactions, receptor isolation
V. S. Vaidhyanathan, Ph.D.	Theoretical Biology Unit	Statistical mechanics, membrane transport, interfacial physics, mathematical biophysical chemistry

ASSISTANT PROFESSORS

Moises Derechin, MD, Ph.D.	Biochemical Pharmacology	Protein structure. Relation between configuration and activity
Kwang W. Jeon, Ph.D.	Theoretical Biology Unit	Cytology and cell physiology
A. D. MacGillivray, Ph.D.	Mathematics	Perturbation theory, including its application to macromolecular systems
John F. Moran, Ph.D.	Theoretical Biology Unit	Mechanisms of Drug Action, Deuterium isotope; Effects in biological systems; receptor isolation
Dorita A. Norton, Ph.D.	Biophysics	X-ray studies in sterols
Shinpei Ohki, Ph.D.	Theoretical Biology Unit	The structure and the permeability of membranes
Cora G. Saltarelli, Ph.D.	Interdisciplinary Studies, Engineering	Physiology and genetics of pathogenic yeasts; Bioengineering

RESEARCH ASSOCIATES

John Abernethy, Ph.D.	Biophysics	
Shym S. Chatterjee, Ph.D.	Theoretical Biology Unit	Medicinal organic chemistry
Mary Danielli	Center for Theoretical Biology	Anthropological studies bearing on man's control of environment and of his reaction to it.
Nobuo Fukuda, MD	Theoretical Biology Unit	Quantum biochemistry; cancer chemotherapy

RESEARCH ASSOCIATES, Cont'd

Norman Lazarus, MD	Biochemistry	Biochemistry
Marian May, Ph.D.	Theoretical Biology Unit	Estrogen receptor isolation and identificati
Michael Phillips, Ph.D.	Chemistry	Surface chemistry and related phenomena of biological interest
Fred Ridley, Ph.D.	Theoretical Biology Unit	Medicinal organic chemistry; Heterocyclic synthesis; drug-receptor interactions
Joan Lorch Staple, Ph.D.	Theoretical Biology Unit	Nucleo-cytoplasmic relationships in protozoa and other cells
Maureen Triggle	Theoretical Biology Unit	Medicinal organic chemistry relating to folic acid antagonists and to analgetics
Darold C. Wobschall Ph.D.	Roswell Park Memorial Institute	Electrical properties of membranes and organic semiconductors

RESEARCH INSTRUCTORS

Peter Bright, Ph.D.	Biophysics	Theoretical foundations of transport phenomena for the study of neuronal membranes
David Shear, Ph.D.	Biophysics	Kinetics and thermo-dynamics of coupled chemical reactions; muscle contractions

VISITING PROFESSORS

Alan Goldup, Ph.D.	British Petroleum	Lipid bilayers
Hugo Martinez, Ph.D.	University of California	Embryology
Paul Weiss, Ph.D.	Rockefeller University	Developmental biology, specifically neurogenesis

CONSULTANTS

S. Svetina, Ph.D.	Roswell Park Memorial Institute	Intermolecular forces, cell-cell interaction; quantum and statistical mechanical study of DNA
Narendra Goel, Ph.D.	University of Rochester	Statistical mechanics
Martynas Ycas, Ph.D.	Upstate Medical Center (Syracuse)	Molecular biology and cell physiology

SUPPORTING STAFF

Harry Collins	Laboratory Manager
Priscilla Ford	Administrative Assistant
Robert Wagner	Accountant
Patricia Weber	Secretary to Director
Kathleen Maher	Principal Secretary
Tom Maddocks	Instrument maker
Charles J. Volk	Photographer and Model Builder
Evelyn Wood	Artist

RESEARCH ASSISTANTS AND TECHNICIANS

Lorraine Powers	Theoretical Biology Unit	Technician
Eleanor Sattler	Theoretical Biology Unit	Technician
Judith Trice		Literature searcher

SECRETARIES

Mildred Andrews	Doris Mertens
Ursel Busch	Alice Richards
Enez King	Mary Speilman

FELLOWS (Graduate Student Assistants)

Howard Allen	Theoretical Biology Unit and Biology Department
John Borst	Mathematics
Michael Davids	Mathematics
Richard Demchak	Chemistry
Joseph Goren	Biochemistry
Paul Jarrell	Mathematics
John Winkleman	Mathematics

Listed are individuals who have received financial support from this grant:

James F. Danielli	- Director & Professor of Theoretical Biology
Robert Rein	- Professor
D.A. MacGillivray	- Professor
Robert Abbott	- Associate Professor
Harold King	- Associate Professor
Hugo Martinez	- Visiting Professor
Robert Rosen	- Visiting Professor
Peter Bright	- Research Associate
Nobuo Fukuda	- Research Associate
Gary Russell	- Research Assistant
Vincent Gallucci	- Graduate Assistant
Paul Jarrell	- Graduate Assistant
John Winkleman	- Graduate Assistant
James Harlos	- Graduate Assistant
Michael Davids	- Graduate Assistant
James Kelly	- Graduate Assistant
John Borst	- Graduate Assistant
John Abernethy	- Research Assistant
Frank Harris	- Consultant
W. S. McCullogh	- Consultant
Robert Smith	- Computer Programmer
Thomas Maddocks	- Laboratory Mechanician
Harry Collins	- Technical Specialist
Penelope Barnard	- Technical Abstractor
Priscilla Ford	- Administrative Assistant
Ursel Busch	- Secretary
Clara Mroz	- Secretary
Virginia Muniak	- Secretary
Judith Trice	- Secretary
Alice Richards	- Secretary
Joyce Chait	- Typist
Robert Wagner	- Accountant

INDIVIDUAL REPORTS

In the following pages reports are listed of the work of all members of the Center who have in any way benefitted by support from this grant.

R. Abbott, Associate Professor in Department of Interdisciplinary Studies, School of Engineering

The four months of half-time support furnished by the Theoretical Biology Center to me were utilized in several ways. Familiarization with areas currently under investigation by members of the Center (and by others, as well) was brought about by attendance at lectures and seminars sponsored by the Center, and by personal contact. Background reading was also undertaken, mostly in the field of statistical mechanics of macromolecules. Finally, some time was spent on a preliminary theoretical treatment of pre-exponential term effects (including entropy and vibrational terms) on the field desorption of biological macromolecules (the transfer RNA's in particular).

E. A. Barnard, Professor

Department of Biochemistry, School of Pharmacy

Research Projects Undertaken

The following theoretical projects have been undertaken in this period.

a. Theoretical work on design of low molecular weight compounds having enzymic properties (artificial enzymes) and related experimental work.

b. Theoretical and experimental analysis of techniques for labeling of receptor-type structures in cells.

c. Assembly of a data retrieval system for the field of enzyme structure and function. In this project, a complete cross-referenced library of all current publications in molecular enzymology has been established.

John Abernethy, Research Instructor

Department of Biophysics, School of Medicine

Research Project Undertaken

Mathematical modeling of physiological systems

Meetings Attended

American Physiological Society, Houston, Texas, "Inert Gas Tension in Urine: Possible Evidence for Concurrent Multiplication", September, 1966.

R. Blakely, Associate Professor

Department of Mathematics
College of Arts & Sciences

Research Project

The application of Liapunov methods and homogeneous polynomial transformations to problems in ecology and population genetics, involving natural selection. 25% of my time has been spent on topics related to biology.

Peter Bright, Research Instructor

Department of Biophysics
School of Medicine

Research Projects Undertaken:

a. Facilitated transport of oxygen through hemoglobin solution.

b. Some difficulties in the theoretical foundations of transport phenomena.

c. The role of chemical reactions to the macroscopic equations of electrophysiology.

Publications:

Bright, P. F., "Brain Momentum and Experimental Concussion", Aerospace-Medical Research Laboratory (AMRL), Memorandum B-80 (1964).

Bright, P. F., "Relations Between Component and System Behavior", Submitted to Bionics Symposium (1966).

Bright, P. F., "The Basic Flow Equations of Electrophysiology in the Presence of Chemical Reactions; Part I. Development of the Equations", to be published, Bull. Math. Biophys. (1966).

Bright, P. F., "The Basic Flow Equations of Electrophysiology in the Presence of Chemical Reactions; Part II. A Practical Application Concerning the Voltage and pH Effects Accompanying the Diffusion of O Through Hemoglobin Solution", to be published, Bull. Math. Biophys. (1966).

Meetings Attended:

Gordon Research Conference on Interaction and Transport, June 20-24, 1966, Andover, N. H.

Summer Workshop in Transport Theory, June 27-July 6, 1966, State University of New York at Buffalo, Buffalo, New York

Biological Systems Symposium, Case Institute, Cleveland, Ohio, October 19-21, 1966.

Gave Seminar, "Difficulties in the Theoretical Foundations of Transport Phenomena, May 19, 1966 (210 Winspear)

Gave Seminar, "Facilitated Transport of Oxygen Through Hemoglobin Solution", December 5, 1966 (223 Sherman).

D. A. Cadenhead, Associate Professor

Department of Chemistry
College of Arts and Sciences

Together with

M. C. Phillips, Postdoctoral Fellow

Center for Theoretical Biology

R. Demchak, Graduate Student

Department of Chemistry

Studies of the Properties of Monolayers of Synthetic Compounds of Biological Significance

Various monolayers of pure synthetic materials of biological interest, including phospholipids and sterols, have been studied on a film balance which allowed continuous recording of the spreading pressure and surface potential with changes in area of the film. Among the various substances have been various glycerides: the diglycerides 1, 3 Dipalmitin, 1, 2 Dimyristin; the triglycerides tripalmitin, triolein also 1,2-Dimyristoyl-3-Cephalin and 1,2-Dimyristoyl-3-Lecithin. The sterols (acetate derivatives) oestradiol and oestratriol have also been studied. Most of these studies represent original work on the pure synthetic substances and in all cases the physical state of these monomolecular films

have been examined in greater detail than hitherto reported in the scientific literature. In addition, a study was made of the condensation which occurs on mixing cholesterol in monolayers of substances which give expanded films when spread alone at the air-water interface. By varying the nature of these amphipathic molecules it was possible to effect changes in the condensing action of the cholesterol. The condensations at various film pressures have been examined in terms of the changes in the partial molecular areas of the film components as the amount of cholesterol in the mixed film is increased. Discontinuities in these plots have been found to be due to changes in phase of the expanded monolayer component and not to formation of surface complexes as has previously been suggested. Measurements were made over a range of temperatures and the excess free energies, entropies and enthalpies of mixing calculated. The significance of these parameters has been evaluated.

Attention has also been paid to the effects of substrate additions such as glycerol and to low temperature effects. Evidence suggests that the fluidity or permeation of such monolayers is controlled by a variety of parameters in a qualitatively predictable fashion - a conclusion which cannot but have relevance in bilayer or membrane theory. Several

publications resulting from this work are envisaged in the near future.

James F. Danielli - Professor, Unit of Theoretical Biology, School of Pharmacy

Research Projects:

1) Structure of lipid membranes
2) Cell control phenomena in Amoeba
3) Theory of cells

Two results have been obtained which are of general interest.

1) The analysis of the structure of lipid bilayers has been extended, in consultation with F. Fowkes, S. Ohki and A. Goldup. The principal point which has emerged is that the assymetric organisation of the hydrocarbon (CH_2) chains of lipids is primarily responsible for the properties of lipid membranes. Since the polarisability of the chains is not symmetrical, and the chains are oriented, the dispersion forces between a monolayer of oriented chains (CH_2^o) and a liquid composed of randomly oriented chains (CH_2^r) are significantly high, giving rise to a surface free energy of about 10 ergs/cm^2 at the interface CH_2^o/CH_2^r. Thus if a thick membrane is thinned to a bilayer, there is a sharp diminution of free energy at the bilayer thickness due to disappearance of the interface CH_2^o/CH_2^r. Also, if the membrane is thinned below the bilayer thickness, since the density of the lipid must remain approximately constant, new interface which is

CH_2/H_2O must be formed in proportion to the deviation from bimolecular thickness. This new interface has a high surface free energy, $\backsim 50$ ergs/cm^2. Hence the sharp drop in free energy at bimolecular thickness is followed by an even more precipitate rise as the thickness is further diminished. Hence there is a remarkably sharp minimum in free energy at the bilayer thickness.

Thus lipid bilayers are a natural unit of structure in the same sense as the α helix of proteins and the double helix of DNA are natural units. And we see clearly why the lipid layer of cell membranes, the myelin figures formed by pure lipids dispersed in water, and the artificial bilayers discovered by Rudin & Mueller, are bimolecular in thickness. Many of the properties of such membranes can now be simply explained. Furthermore, the anisotropy of the chains must be considered in many studies e.g. the optical birefringence is a consequence of the assymetry of polarisability, and in calculating membrane thicknesses from optical studies or from capacitance measurements, the use of the bulk values (i.e. values for CH_2^r) for refractive index and dielectric constant is incorrect. Thus all bilayer thickness values published to date based on these measurements are probably in error by a factor of 20-50%.

2) Studies have been made of a number of characters of Amoeba proteus over a period of 17 years. These organisms divide every 2-3 days. They undergo no form of mating or meiotic process, so that the only genetic changes in clones occur by mutation, accidental loss of genes, or infection. They are highly polyploid, so that they should show marked genetic stability. Nevertheless, over the period of observation (about 2500 generations) there has been marked phenotypic drift. E.g. the shape of an amoeba when moving may be "stable" over a few months or even years, but over the period in question the cumulative drift results in a totally new shape. Similarly, a cytoplasm which can accept nuclei from another clone readily at one period may become completely incompatible with the nuclei of the second clone. These results seem likely to be of major value in evaluating the evolution of micro-organisms, the development of symbiosis and in understanding pathogenicity.

Publications:

Life Sciences 4, 705-711 (1965) - The estrogenic activities of 16α, 17α- and 16β, 17β-epoxy-1,3,5(10)-estratriene-3-ol. M. May, B. Johnson, J.F. Danielli and S. Gilani.

Claude Bernard Symposium (Paris; June 28 - July 3, 1965) published as proceedings of this symposium; "The Problem of Receptors in Relation to Regulation of the Milieu Interieur" J.F. Danielli.

Arch.Ital.di Patol. e Clin.dei Tumori, Vol.VIII, Fasc.3-4(1965) "The Selective Antitumor Action of Some Alkylating Sulfonamides". P.J. Barnard, J.F. Danielli, R. Hawkins, P.Hebborn, A. Muggleton, D. Triggle and M. Triggle.

J.Theoret.Biol. 11, 465-477 (1966); Electrostatics of Membrane Systems-I.: "A Non-statistical Approach to Cellular Membrane Systems". R. Friedenberg, A. Blatt, V. Gallucci, J.F. Danielli and I. Shames.

In press. "Permeability Phenomena in Relation to Drug Action; 1965. J.F. Danielli.

J.Theoret.Biol. 12, 439-441 (1966) "On the Thickness of Lipid Membranes" J.F. Danielli.

Meetings attended:

1965

June 24-25 - Gave lecture on "The Cell as a Molecular Machine" at the University of Milan, Dept.of Pharmacology.

June 28 - July 3 - Represented the State Univ.of New York at Buffalo & the Royal Society in attendance at the symposium at College de France to celebrate the 10th Anniversary of the publication of Claude Bernard's book on experimental medicine. Gave talk on "The Problem of Receptors in Relation to Regulation of the Milieu Interieur"

Oct. 27 - Gave a talk entitled "Theoretical Studies of Bimolecular Lipid Leaflets" at the Dept.of Physiology, University of Michigan, Ann Arbor.

Nov.22-23 - Attended Conference on Communications for Biology at Cherry Hill, New Jersey.

Nov.26-27 - Attended "The Future of Biology" Symposium sponsored by the State University of N.Y. & Rockefeller Univ.(at Rockefeller Univ.). Gave talk "What Special Units Should be Developed for Dealing With the Life Sciences and What Specializations of Program Are Most Likely to be Needed in the Future?"

Dec. 2-4 - Attended Medicinal Chemistry Symposium at the Univ.of Tennessee. Gave a paper entitled "Programs in Cell Biology Which Will Facilitate Drug Design"

1966

Feb.22-24 - Attended and served as Chairman of Membrane Structure Session at the 10th Annual Meeting of Biophysical Society at Statler-Hilton Hotel in Boston, Mass.

Mar. 22 - Visited London, England, to attend Symposium on "Membrane Transport" at the Royal Society of Medicine.

May 5-7 - Attended opening of Henry Moses Research Institute at Montefiore Hosp. & Medical Center, New York City. Gave paper on "Recent Studies on the Physical State of Cell Plasma Membranes".

June 8 - Attended the Canadian Federation of Biological Societies in Vancouver, B.C. Gave talk on "Physics and Physical Chemistry of Lipid Bilayers"

July 17 - Aug. 18 Directed Summer Colloquium entitled "Theoretical Biology of the Cell" sponsored by the National Aeronautics & Space Administration under the auspices of the American Institute of Biological Sciences.

Sept. 9 - Chaired session at International Symposium on Atherosclerosis and Reticuloendothelial System in Como, Italy.

Sept.11-15 - Chairman of Symposium of International Society for Cell Biology held in Cambridge, England on "Formation and Fate of Cell Organelles". Also gave paper on "Theory of Formation of Pauci-molecular Membranes".

Sept.20-23 - Attended International Symposium on Immunity, Cancer, and Chemotherapy in Buffalo.

Oct. 25 - Visited Chemical Institute of Canada (Toronto Section). Gave an address "Cell Biology and Chemotherapy".

Oct.29-30 - Attended meeting of Commission on Undergraduate Education in the Biological Sciences (CUEBS) in Washington, D.C.

Mary Danielli, Research Associate

Center for Theoretical Biology

Attended Colloquium of Malagasy students at Broadstairs, England, summer 1965, auspices Friends' Service Council. General cultural discussion.

In 1946 I did anthropological field work in Madagascar as Horniman Student of the Royal Anthropological Institute, London and a student of Prof. J. H. Hutton, D. Sc., C. S. I. at Cambridge University, England. I collected information concerning the mechanisms whereby primitive man expresses and codifies awareness of his relationship to his environment. A half dozen papers, groundwork for my main thesis, were published. After bringing up my family, commenced in 1947, I began to return to this thesis in summer 1965.

In resuming work further information was seen to be needed and personal contact had to be established with sources in Madagascar. I have to work through educated Malagasy who still have kinsfolk in rural districts and are in sympathetic relationship with them. With the help of the Malagasy Ambassador in London and his wife, of the Anglo-Malagasy Society (largely a trade society), of the Society of Friends (who have a missionary concern in Madagascar and have always been

especially friendly and cooperative towards my work) and also of the London Missionary Society (who have an Oxford scholar in the mission field there), and through picking up friends made over the years in London among Malagasy students in England and France, I have succeeded over the past two years in establishing contact with the sources of information.

The Friends' Service Council now runs an annual Colloquium for Malagasy students, lawyers, doctors, teachers, pastors, etc., and in 1965 I was able to attend for a short time at one of these on my visit to England on other business. This visit introduced me to two persons who have given me quite exceptional help: one by persuading a friend to do research in Madagascar among his relatives and friends (not vitiated by contamination with western scholarship), which are communicated directly to me, as well as running some independent inquiries of his own on which he reports.

Through these contacts two questionnaires on Malagasy customs have been constructed, translated into French and Malagasy, and distributed in Madagascar, France, and England. Some answers have already been received. A paper "Famadihana" (on the bone turning ceremonial of Imerina, Madagascar) has been dispatched to the Academie Malgache in Tananarive. A

proposal relative to the foundation of a Folk Archives in Madagascar has also been sent to various bodies and individuals and to the Academié Malgache in Tananarive.

M. Derichin, Department of Biochemistry
School of Pharmacy

A computer program for the processing of sedimentation equilibrium data obtained by the method of Van-Holde and Baldwin has been devised.

This program yields the molecular weight, the diffusion coefficient and the sedimentation velocity of any pure macromolecule in solution, for molecular weights from about 300 to over 1 million.

This program carries out calculations by least square fitting whenever slopes of sets of data are required but no standard deviations are obtained as yet since all the available core for the Watfor compiler has been used. An expansion of the present program for the calculation of standard deviations in addition to all others mentioned above is presently in progress for use with the Ibsys compiler.

After this expansion is completed the program would be suitable for publication.

A. Goldup, Research Associate

Center for Theoretical Biology

A research programme on lipid bilayers is currently in the course of preparation. Initially it is proposed to measure the electrical and transport properties of phospholipid bilayers (egg lecithin) but later the scope will be extended to cover membranes of simpler chemical composition as well as excitable membranes similar to those currently under investigation by Mueller and Rudin. Attempts will be made to develop satisfactory theories accounting for the formation, stability and transport properties of live membranes. The prime objective of these studies will be to obtain a clearer understanding of the underlying physical chemistry of bilayers thus providing a better foundation from which to approach problems relating to natural membranes.

R. J. Good, Professor

Department of Chemical Engineering
School of Engineering

Research Achievements:

1. Collaborated in an explanation of a curious effect in which an oil droplet penetrates an echinoderm egg. The "line tension" at a triple interface was held to be responsible.
2. Extended the theory of wetting of low-energy surfaces to include a rigorous treatment of adsorbed films.
3. Collaborated in measurements of liquid--liquid interfacial tension, which show that the Harkins drop-weight method for interfacial tension may be in error by 3%.

Publications since June, 1965:

1. "Line Tension and the Penetration of a Cell Membrane by Oil Drop." With N. L. Gershfeld. Journal of Theoretical Biology, October, 1966.
2. "Estimation of Surface Energies from Contact Angles". Nature, 212, October 15 (1966).
3. "Intermolecular Forces," in "Treatise on Adhesion," R. L. Patrick, ed., Marcel Dekker Co., N. Y., December, 1966.

Meetings:

1. Summer Colloquium on Theoretical Biology, Ft. Collins, Colorado, July-August, 1966.
2. Symposium on "Wetting," Bristol University, Bristol, England, September, 1966.

K. W. Jeon, Research Associate

Unit for Theoretical Biology
School of Pharmacy

with

J. Moran, Assistant Professor

Department of Biochemistry
School of Medicine

I. J. Lorch, Research Associate

Unit for Theoretical Biology

H. Allen, Graduate Student

Department of Biology

Studies on the Physical Basis of Cytoplasmic Inheritance, and on Cellular Regulation

a. Investigation of Immunological response of amoeba clones derived from single cells injected with cytoplasmic homogenates of another strain. It has been found that 40% of such strains show changes in their immunological responses, the changes being unstable.

b. Investigation of cytoplasmically transmitted differences between strains of amoebae. The characters studied include: streptomycin sensitivity, actinomycin sensitivity, growth rates at different temperatures, responses to calcium ion deprivation, rate of attachment, reaction to starvation, and specific bacterial infection.

c. Investigation on the cellular basis of spanning in amoeba. It has been found that spanned amoebae possess structural differences from normal amoebae, detectable under the light microscope.

A. Muggleton and J. F. Danielli read a paper entitled "Nuclear and cytoplasmic control of alternative states in Amoeba, with reference to life span" at the 21st Annual Meeting of the Society of General Physiologists, in September 1966.

Publications:

a. "A modified oil chamber for micrurgy on large cells" by K. W. Jeon, in press in Exp. Cell Res. (1966).

b. "Cytoplasmic inheritance in Amoebae: Modification of immunological response by micro-injection of heterologous cytoplasmic homogenates" by K. W. Jeon, I. J. Lorch, J. F. Moran, A. Muggleton, and J. F. Danielli, submitted for publication in Exp. Cell Res. in November.

c. "Inheritance of the 'Life-spanning' Phenomenon in Amoeba Proteus" by Audrey Muggleton and J. F. Danielli, submitted for publication.

H. F. King, Assistant Professor

Department of Chemistry
College of Arts and Sciences

Intermolecular Forces Between Water and Hydrocarbons

This work was done under the auspices of Professor J. F. Danielli in consultation with Dr. S. Ohki. Biological interest in the problem centers on its applications to theories of hydrophobic bonding. The problem has been approached here as a general problem in the theory of intermolecular forces. Although the period of financial support consisted officially of 2 1/2 months during the summer of 1966, work along these lines is being continued by Dr. King.

The interaction of a single methane molecule with a single water molecule was considered. As a first step, accurate quantum mechanical wave functions for the individual molecules were computed using the Hartree Fock method. These are remarkable in that they are the most accurate wave functions available today for these molecules according to the energy criterion. Two alternatives were considered for the second step. The first alternative is to compute the molecular interaction by a Hartree Fock calculation for the entire 20-electron system followed by an analysis of the electron correlation energy. Some progress has been made here, but it has been set aside for the future. The second alternative

consists of a more conventional analysis in terms of electrostatic multipole, Van der Waals, and repulsive interactions. Multipole moments have been computed for methane using the computed wave function and a computer program has been written to compute multipole interactions for various conformations.

This work is continuing. This work is reported in part in a paper submitted to the Journal of Chemical Physics.

K. Nicholas Leibovic, Associate Professor

Department of Biophysics, School of Medicine

Research Projects Undertaken:

1. Effect on the integrated response of the extent of center and surrounding mechanisms in the receptive field: computer simulation studies.
2. Critical review of the anatomy and physiology of the lateral geniculate body in relation to information processing.
3. A model of size discrimination in vision.
4. Computer simulation of a 3-component receptive field model.
5. Visual masking and interference phenomena in the visual pathway.
6. The quantization of visual information
7. A model of information input and transmission in the eye.

Publications:

1. "A Note on Visual Integrative Mechanisms", Bulletin of Mathematical Biophysics, Special Issue, 27, 1965.
2. "A Model for Information Processing with Reference to Vision", J. Theor. Biol., 11, 1966.
3. "Observations on some Experiments on Visual Masing", to be published in J. Gen. Psych.

Papers given and Meetings Attended:

1. "Information Input & Transmission in the Visual Pathway", Biophysical Society, 10th Annual Meeting, February, 1966

2. "Models of Visual Function", C.T.B. Seminar, March 1966.

3. "Mathematical Models in Biophysics", Basic Sciences Seminar, March, 1966.

4. "The Quantization of Visual Information", 2nd International Biophysics Congress, Vienna, September, 1966.

5. "Analysis of a 3-Component Visual Receptive Field Model", with R. A. Spangler, 2nd International Biophysics Congress, Vienna, September, 1966.

6. Gordon Research Conference on Biomathematics, July 10-23, 1965, Andover, N. H.

7. Biophysical Soc. Annual Meeting, February 23-25, 1966, Boston, Mass.

8. Gordon Research Conference on Biomathematics, July 11-15, 1966, Andover, N. H.

9. 2nd International Biophysics Congress, September 5-9, 1966, Vienna, Austria

10. Visits to (a) Prof. Reichard's Laboratory, Max Planck Inst., Tübingen, (b) Prof. Bauman at Saestendijk, Holland; (c) Prof. Schanten's Inst. for Perception Research, Eindhoven, Holland; (d) Prof. Campbell, Physiological Laboratory, Cambridge (e) Dr. Mackay's Laboratory at Keele, Staffordshire, England, during Sept. 12-23, 1966.

11. Biological Systems Symposium, Case Institute, Cleveland, Ohio, October 19-21, 1966.

D. A. MacGillivray, Assistant Professor

Department of Mathematics
College of Arts & Sciences

A. No previously described projects have been substantially altered.

1. Work is continuing on the theoretical study of DNA denaturation, using the full nonlinear Poisson-Boltzmann equation.

   Investigators: Prof. A. I. McMullen, Mr. J. Swift, A. D. MacGillivray

2. Work is continuing on the investigation of asymptotic solutions of the Poisson-Boltzmann equation.

   Investigators: Mr. J. J. Winkleman, A. D. MacGillivray

B. Projects which have begun in the past few months are

1. Study of the dependence of activity coefficients on ionic strength. This is of importance for the desalination problem.

   Investigators: Mr. J. Swift, A. D. MacGillivray

2. Theoretical study of the action of Lysozyme has just begun. This is a problem of very great interest, and we hope the expertise developed in our study of the DNA problem will enable us to make some basic contributions.

   Investigators: Prof. A. I. McMullen, A. D. MacGillivray

Publications since June, 1965.

1. MacGillivray, A. D., and Winkleman, J. J. "On an Asymptotic Solution of the Poisson-Boltzmann Equation - the Moderately Charged Cylinder." J. Chem. Phys., 45, 1966.

2. MacGillivray, A. D., and McMullen, A. I. "A Theoretical Study of the Role of Salt Concentration in the Melting of DNA." J. Theoret. Biol., 12, 1966.

3. MacGillivray, A. D., and McMullen, A. I., "On the Influence of Ionic Strength on the Melting Temperature of DNA", J. Theoret. Biol., 12, 1966.

4. MacGillivray, A. D., "A Variational Principle for Polyelectrolyte Theory, with an Illustrative Application", Preprint #9, T.B.C., SUNY/B, 1966.

5. MacGillivray, A. D., and McMullen, A. I., "A Variational Approach to the Dynamics of the Helix-Coil Transition". Preprint #11, T.B.C. SUNY/B, 1966.

List of Meetings Attended:

1. Symposium on Physical Chemistry of DNA, 40th National Colloid Symposium, University of Wisconsin, June, 1966.

2. Second International Biophysics Congress, Vienna, Austria, Sept. 1966.

A. I. McMullen, Professor

Unit for Theoretical Biology
School of Pharmacy

G. Russell, Graduate Student

J. Harlos, Graduate Student

Research Projects:

1. There has been some concentration on the RNA codon-anticodon interaction and on DNA membrane interaction from a semi-quantitative aspect.

During discussions with Dr. F.H.C. Crick in the Molecular Biology Summer School, Spetsai, this year, and in a subsequent communication, the question of the possibility of calculating interaction energies of the codon-anticodon interaction was raised. In particular, the "wobble" hypothesis of Crick pointed some interesting variations on this interaction. It was suggested to Dr. Rein that Q-M calculations on the stacking interactions of the codon-anticodon mechanisms on the lines of Nash and Bradley (biopolymers, 3, 261, 1965) but with the sophistication of the "wobble" geometry included, might be fruitful. Simultaneously, the writer instituted a model building program to attempt to define this geometry more exactly. According to Dr. Crick, no one has yet carried this out, although possibly sufficient data on the transfer

RNA loop is available to enable part of the model to be built. It would seem from Dr. Crick's work and from preliminary models that the electrostatic free energy difference of "wobbling" interactions might well be significant.

2. An original procedure, based on the variational calculus, has been developed with Dr. MacGillivray, for the treatment of electrostatic energy calculations, including nonlinear (Poisson-Boltzman) ion distributions. Dr. MacGillivray's observation (in press, J. Chem. Phys., 1966) that the Poisson-Boltzmann equation can be derived from a variational principle, has enabled the application of this principle to the case of the helix-coil transition. The result has been a very good correlation of the calculated T_m in various salt concentrations with the experimental data (MacGillivray and McMullen, 1966).

This application is awaiting the arrival of x-ray co-ordinate data (from Dr. D. C. Phillip of Oxford University) on lysozyme, in order to attempt to derive the electrostatic free energy charges, during the lysozyme + NAG interaction.

Dr. Perutz, (University of Cambridge), is willing to

supply similar coordinate data on horse oxyhaemoglobin, when this is available, but feels that, at present, such data are insufficiently accurate for the purpose.

3. Some preliminary approach to the problem of the stability of the "electrostatic micelle" has been made with a view to understanding aspects of soap and lipid aggregates and configurational transition in solutions.

In preliminary attempts to devise models for soap, phospholipid and other micellar aggregates, including that of the membrane, a computer program to determine the relationship between area and volume of ellipsoids containing different numbers of molecules of defined sizes, was devised. By considering the net charge on the polar head groups and assuming a value for binding forces other than purely electrostatic, it was hoped to determine which configuration would be the most favorable electrostatically in various ionic concentrations. To find the electrostatic potential ϕ, it is necessary to find a general solution to the equation.

$$\nabla^2 \Phi = - \frac{M_o}{\epsilon_o} \exp \frac{e\Phi}{kT}$$

This has not yet been achieved.

Publications:

1. "Quantum Mechanical Interfacial 'trigger' Action in Macromolecular Replication". A. I. McMullen. Theoretical Biology Center (TBC) Preprint No. 1. J. Chem. Phys. (1965), 43, p. S230. This describes a model of DNA replication involving interaction with a membrane.

2. "A Theoretical Study of the Role of Salt Concentration in the Melting of DNA". Coauthor A. D. MacGillivray. TBC Preprint No. 2. Journal of Theoretical Biology, 12, 75 (1966). This work represents a considerable improvement on calculations of electrostatic energy of molecular models representing DNA and takes into account some degree of discreteness of the charges of the molecule. It is confined to the same regions of reliability, however, as any calculation which employs the linearized Poisson-Boltzmann distribution of ions.

3. "On the Influence of Ionic Strength on the Melting Temperature of DNA". Coauthor A. D. MacGillivray. TBC Preprint No. 3. Journal of Theoretical Biology 12, 260 (1966). This represents an application of the previous work to explain the logarithmic relationship with ionic strength obtained experimentally and uses a simple statistical theory.

4. "The Influence of Ionic Strength on the Rate of Unwinding of DNA". Coauthor A. D. MacGillivray. TBC Preprint No. 4. This is an application of the absolute reaction rate theory of Eyring to explain experimental data on the rate processes of the unwinding of DNA. This theoretical concept is awaiting the discovery of further experimental information on fast reaction rates before publication.

5. "A Variational Approach to the Dynamics of the Helix-Coil Transition". Coauthor A. D. MacGillivray. 40th National Colloid Symposium, Wisconsin (June, 1966). This describes a semi-direct method from the calculus of variations for the calculation of the electrostatic energy of DNA in various configurations.

6. "Theoretical Studies of Models Concerned with Possible Mechanisms of Replication of DNA". Coauthors R. Rein, M. Pollak. 2nd International Congress of Biophysics in Vienna, September, 1966. This describes the calculation of binding energies within a model of the replication

plane (two base pairs) of DNA.

7. "A Theory of DNA Membrane Interaction". A. I. McMullen. 2nd International Congress of Biophysics in Vienna, September, 1966.

8. "A Theoretical Consideration of the Effect of Ionic Strength on the Helix-Coil Transition". Coauthor A. D. MacGillivray. 3rd meeting FEBS, Warsaw (1966).

Meetings Attended:

40th Colloid Symposium of A.C.S., Wisconsin, June, 1966. To present a paper (MacGillivray and McMullen).

2nd. International Biophysics Congress, Vienna, September, 1966. To present two papers (McMullen and Rein; McMullen and Pollak) and to chair one of the sections.

D. C. Mikulecky, Assistant Professor

Department of Biophysics
School of Medicine

Research Projects Undertaken:

1. The physical meaning of nonsymmetrical coefficient matrices in irreversible processes.
2. The concentration dependence of the electroosmotic coefficient in wide pore membranes.
3. A study of the parameters governing periodic phenomenon in membranes.
4. Studies of the relationship between transport properties and type of phospholipid in phospholipid membranes models.
5. A generalization of Carie's theorem: The effect of symmetry in the boundary conditions.

Publications:

1. Caplan, S. R. and Mikulecky, D. C., "Transport Processes in Membranes", Ion Exchange, J. Marinsky (Ed.), Marcell-Dekker Publ. Co., in press (1966).

2. Mikulecky, D. C., "Sodium-Potassium Ion Exchange Equilibria for Fragmented Human Erythrocyte Ghosts", Nature, 205:706 (1965).

3. Mikulecky, D. C. and Caplan, S. R., "The Choice of Reference Frame in the Treatment of Membrane Transport by Non-Equilibrium Thermodynamics", in press (1966).

4. Mikulecky, D. C., Snell, F. M., "The Meaning of Assymmetry in Phenomenological Coefficients", Biophysical Society Abstract (1966).

5. Mikulecky, D. C., "Biological Aspects of Transport", submitted for publication (1966).

Meetings attended:

1. N.Y.A.S. - Biological Membranes: Recent Progress, October, 1965.
2. Inst. for Fluid Dynamics and Applied Mathematics, Univ. of Maryland: Symposium on the Dynamics of Fluid and Plasmas. Oct. 7-9, 1965.
3. Biophysical Society, February, 1966.
4. Gordon Research Conf.: Interaction and Transport in Physical, Chemical and Biological Systems, June 20-24, 1966.
5. Summer Workshop in Transport Theory, June 27-July 6, 1966, State University of New York at Buffalo, Buffalo, N. Y.

Papers read:

1. "The Meaning of Nonsymmetric Coefficient Matrices in Irreversible Processes" at Biophysical Society, February, 1966.
2. "The Choice of Reference Frame in the Treatment of Membrane Transport by Non-Equilibrium Thermodynamics II: Phenomenological Equations for a Wide Pore Model" at Gordon Research Conference, June 20-24, 1966.

Dorita A. Norton, Assistant Professor

Institute of Crystallography
Roswell Park Memmorial Institute and
Department of Biophysics, School of Medicine

Research Projects Undertaken:

1. Steroid structure and function.
2. Crystal and molecular structure determinations.
3. Steroid complexes with other biologically important molecules.
4. Change transfer complexes and structural functional relationships.

Publications:

1. Norton, D. A. and Haner, V. A., "Crystal Data (I) for some Biol Acid Derivatives", Acta Cryst., 19:477 (Sept., 1965).

2. Ohrt, J. M., Haner, V. A. and Norton, D. A., "Crystal Data (I) for some Halogenated Steroids", Acta Cryst., 19:280 (Aug., 1965).

3. Ohrt, J. M., Haner, V. A., and Norton, D. A., "Crystal Data (II) for some Androstanes", Acta Cryst., 19:479 (Sept., 1965).

4. Wobschall, D. and Norton, D. A., "Iodine Complexes with Cyclohexanone and Related Compounds", Amer. J. Chem., 87:3559 (1965).

5. Ohrt, J. M., Haner, V. A., and Norton, D. A., "Crystal Data (I) for some Pregnane-Related Compounds", Acta Cryst., 19:869 (Nov., 1965).

6. Egar, C. and Norton, D. A., "Androgenic Steroid Complexes with p-Bromophenol" Nature, 208:997 (Dec., 1965).

7. Norton, D. A. and Ohrt, J. M., "Introduction to Steroid Molecular Stocking", J. Theor. Biol., 11:140 (1966).

8. Haner, V. A. and Norton, D. A., "Crystal Data (I) for some Cholestrone Derivatives", Acta Cryst., 20:930 (1966).

Meetings attended:

1. VII International Congress and Symposium of the International Union of Crystallography, July 12-21, 1966, Moscow, Russia.

S. Ohki, Assistant Professor

Unit for Theoretical Biology
School of Pharmacy

Research Projects:

1. The expanded phase of monolayers has been treated as a two-dimensional lattice gas, using lattice gas theory. The phase transition points for the transition L_1 to condensed phase have been analyzed from the statistical mechanical point of view, and comparison made with experimental data.
2. Studies are in progress on the oil-in-water $\rightleftharpoons$ water in oil transition.

Publications:

1. Rectification by a Double Membrane, J. Phys. Soc., Japan, Vol. 20, 1674 (1965).
2. Application of the Lattice Gas Theory to Lipid Monolayers, J. Theor. Biology (in press).

Meetings Attended:

Colloquium in Theoretical Biology, Fort Collins, July-August, 1966.

R. Rein, Associate Research Professor

Unit for Theoretical Biology, School of Pharmacy

This report includes collaborative work with

G. Clark, Chemistry Department, Buffalo
F. Harris, Chemistry Department, Stanford
M. Pollak, Physics Department, Riverside
M. Anbar, Weizmann Institute, Israel
P. Claverie, Institute de Biologie Physico-Chimique, Paris
L. Weiss, Department of Experimental Pathology
Roswell Park Memorial Institute
S. Svetina, Research Associate
N. Fukuda, Research Associate
M. Davids, Graduate Student, Mathematics Department
H. Win, Chemistry Department
J. Harlos, Chemistry Department

Summary of Research Achievements:

The principal objective of the Quantum Group was the evaluation of molecular interaction energies, necessary for the formulation of a theory from first principles of the order disorder transition in Biological macromolecules, in particular the description of the helix-coil transition in DNA.

Some of the more important problems to be solved in connection with the above objectives are:

1. Improved calculation of the complete electronic structure (including both σ and π electrons) of bio-molecules. With parallel development of

appropriate advanced molecular orbital methods suitable for this type of calculations.

2. Development of improved methods for calculation of interaction energies between neighboring large molecules.
3. Using the above methods, the calculations of the hydrogen bond, stacking and non nearest neighbor correlation energies in DNA.
4. The calculation of the solvation energies for the helix and for the bases in the randum coil.
5. Effects originating from the phosphate charges, and interactions within ions of the media.
6. Refinement and testing of existing statistical models, using results in 3, 4 and 5 and attempting correlations with experimental data.

Substantial results have been arrived in connection with problems 1, 2 and 3. These results have been presented in 11 publications and 14 meeting papers. Some of the most outstanding results are:

1. The development of the Extended Huckel Theory and integral approximations in molecular orbital theory, which represents a groundwork for an improved description of the electronic structure of large

molecules. On this project, we greatly benefited from the collaboration with Dr. F. E. Harris, who is an outstanding authority in this field.

2. In collaboration with Dr. M. Pollak and more recently with Dr. Pierre Claverie, we completed the formulation of methods for calculation of all the interaction energy components in DNA.

3. We have already performed the calculation of Hydrogen bond energies of the nucleotide bases which successfully matches with experimental quantities. We are in the phase of simplifying the calculations at the stacking and non nearest neighbor interaction energies, which will be particularly useful in connection with testing of statistical models.

We are now in the beginning phase of projects 4, 5 and 6 and with the existing background we hope to make a rapid progress which may provide interesting insight into the mechanism and factors involved in the helix-coil transition process in DNA and ultimately to offer a complete theoretical description of this process.

Publications of R. Rein and Collaborators, since June 1965.

1. On the Hydrogen Bonding Schemes Between Purines and Pyrimidines, Coauthor M. Pollak. J. Theoretical Biol. 11, 490-494 (1966).

2. Integral Approximations for Molecular Orbital Theory. Coauthor F. E. Harris. Thioretica Chimica Acta. 6, 73 (1966).

3. Approximations of Molecular Integrals. Coauthor F. E. Harris. Accepted for publication in Nature.

4. Calculation Explains Mutation. Reported by the Editor. Chem. & Eng. News, April 15, 1966, p. 39.

5. Iterative Extended Huckel Theory. Coauthors N. Fukuda, H. Win, G. Clarke, F. E. Harris. J. Chem. Physics, scheduled for publication Dec. 15, 1966.

6. Studies of Hydrogen Bonded Systems. Part III. Potential energy surface, tunneling and tautomeric equilibria in the N-H...N and O...H-N bonds of the Guanine-Cytosine base pair. Coauthor F. E. Harris. J. Chem. Physics, 44, (1966).

7. Studies of Hydrogen Bonded Systems, Part IV Radiation-induced tunneling and tautomeric equilibria in the guanine-cytosine base pair. Coauthor F. E. Harris. J. Chem. Phys., 45, 1797 (1966).

8. Molecular Orbital Studies of Intermolecular Interaction Energies. Part I. Methods and application in helical polymers. Coauthor M. Pollak. Submitted for publication in J. Chem. Phys.

9. Molecular Orbital Studies of Intermolecular Interaction Energies. Part II. Approximations concerned with Coulomb interaction and comparison of the two London schemes. Coauthor M. Pollak. Submitted for publication J. Chem. Phys.

10. On the Nature of Calcium Originating from the bones A Double Tracer Study. Coauthors G. A. Rodan, M. Parran, M. Anbar. Submitted to American Journal of Physiology.

11. On the Calculation of Van der Wals, London, Interactions in a monopole-bond Polarisability approximation with application to interaction between purine and pyrimidine bases. Coauthor P. Claverie. Ready for publication.

Meeting Papers

12. Semi-Empirical Study of Hydrogen Bonding Between Purine and Pyrimidine Bases. Coauthor F. E. Harris. International Symposium on the Quantum Theory of Atoms and Molecules and Solid-state Physics, Annual Progress Report, (1965-66), p. 55.

13. Studies of Intermolecular Interactions in DNA By a Perturbation Method in the Monopole Approximation. Coauthor M. Pollak. Ibid, p. 56.

14. Semi-Empirical Treatment of the Overlap Energy in DNA. Coauthor M. Pollak, Ibid, p. 57.

15. A Study of π-Electron Intermolecular Interactions, with some Application to Biopolymers. Coauthor M. Pollak. Bull. Am. Phys. Soc., Vol. 11, No. 1, (1966).

16. Some Remarks on Interaction Energies Between Bases in Nucleic Acids. Coauthor M. Pollak. Abstracts Am. Biophys. Soc., 10th annual meeting, (1966) p. 15.

17. On the Applicability of Molecular Exciton Theories to DNA. Coauthor M. Pollak. Abstracts Am. Biophys. Soc., Ibid.

18. Radiation-induced Tunneling in the Guanine-cytosine Base Pair. Coauthor F. E. Harris. Abstracts Am. Chem. Soc. Meeting, 151st. annual meeting (1966).

19. On the Hydrogen Bonding Scheme between Purines and Pyrimidines. Coauthor M. Pollak. Abstracts Am. Chem. Soc. Meeting, Ibid.

20. Theoretical Studies of Models Concerned with Possible Mechanisms of Replication of DNA. Coauthor M. Pollak, A. I. McMullen. Abstracts 2nd. Intl. Biophysics Congress, (1966), p. 138, Vienna, Austria.

21. Stacking Energies between Bases in a DNA Configuration. Coauthor M. Pollak. Abstracts, Ibid, p. 139

22. Iterative Extended Huckel Theory. Coauthors N. Fukuda, G. Clarke, H. Win and F. E. Harris. Abstracts Am. Chem. Soc. Meeting, (1966).

23. Application of Iterative Extended Huckel Theory. Coauthors G. Clarke, H. Tieckelmann, H. Win, N. Fukuda and F. E. Harris. Abstracts, Ibid.

24. Iterative Extended Huckel Theory. Coauthors, G. Clarke, H. Win, N. Fukuda, F. E. Harris. Ohio Symposium on Molecular Structure and Spectroscopy, (1966), p. 60, Abstracts.

25. Integral Approximations. Coauthor F. E. Harris. Abstracts Am. Chem. Soc. Meeting, (1966).

List of Meetings Attended

1. 2nd. Annual Biophysics Meeting in Vienna in 1966 acted as Chairman of the following sections:
   a. Nucleic Acid Interaction.
   b. Nucleic Acid Theoretical
2. International Symposium for Quantum Theory of Atoms and Molecules, Sanibel Island, Jan. 1966.
3. American Physical Society Meeting in Jan. 1966, New York.
4. Biophysical Society, January 1966, Boston.
5. American Chemical Society, March 1966, Pittsburgh.
6. Presentation of Colloquium in leading scientific laboratories.

a. Laboratoire Chimique Quantique, Institute de Biology Physico Chimique, Paris, France.

b. Weizmann Institute of Science, Rehovoth, Israel.

c. Department of Quantum Chemistry, Uppsala, Sweden.

d. Quantum Chemistry Group, Dept. of Chemistry, Johns Hopkins University

R. Rosen, Associate Professor

Department of Mathematics
College of Arts & Sciences, and Department of Biophysics
School of Medicine

Research Projects Undertaken:

1. Biomathematics and modeling in biological systems.
2. Abstract systems as sequential machines. Optimality theory and principles in biology.

Scientific Meetings

1. Sanibel Island Symposium on Quantum Theory. Sanibel Island, Florida, 1/18/66-1/22/66.
2. Gordon Research Conference on Biomathematics. Andover, New Hampshire, 7/11/66-7/13-66.
3. Colloquium on Theoretical Biology. Fort Collins, Colorado, 7/17/66-8/18/66.
4. Case Institute Symposium on Biological Aspects of System Theory. 10/20-10/21/66. Cleveland, Ohio.
5. American Society for Cell Biology Annual Meeting. 11/17/66-11/19/66. Houston, Texas.
6. Biophysical Society Annual Meeting. 2/23/66-2/25/66. Boston, Mass.

Publications:

1. "Some Comments on Re-establishability", Bull. Math. Biophysics, 27SI: 11 (1965).

2. "Mongraph: Optimality Principles in Biology" London: Butterworth and Co. Ltd., in press.

3. "Abstract Biological Systems as Sequential Machines III: Some Algebraic Aspects". Bull. Math. Biophysics 28 (1966), 141-148.

4. "A Note on Replication in (M, R)-Systems". ibid. 149-151.

Invited Lectures and Papers

1. 1/19/66. Sanibel Island Symposium. "Quantum Theory as a Tool in Theoretical Biology.

2. 4/18/66. Booth Computing Center, Cal. Tech. "Relational Biology".

3. 4/21/66. Research Lab. of Electronics, Stanford. "Relational Biology and System Theory."

4. 7/11/66. Gordon Research Conference, Biomathematics. "Biological Evolution as Pattern Recognition".

5. 8/11/66. Theoretical Biology Colloquium, Fort Collins. "Towards a Comprehensive Cell Theory".

6. 11/25/66. Committee on Math. Biol., U. of Chicago. "Alternate Realizations of the Two-Factor Theory".

Contributed Papers:

1. Biophysical Society. 2/25/66. "On the Physical Basis of the Meiotic Pairing Forces".

I. H. Shames, Professor

Department for Interdisciplinary Studies
School of Engineering

V. Gallucci, Graduate Student

A. J. Blatt, Graduate Student

Research Project

Work which was commenced with R. Friedenberg on the organization of polar groups at lipid membrane surfaces was continued, with consideration given to the presence of an interfacial layer of protein. It was assumed that the protein was in the β configuration, and could be represented, in its effect on the orientation of lipid polar groups, by a set of dipoles representing the C=O and NH groups. The organization of the lipid polar group was then studied by means of a generalized computor program, and found to be more stable than in the absence of protein.

Publications

1. "A Non-statistical Approach to Cellular Membrane Systems", R. Friedenberg, J. F. Danielli and I. H. Shames, Journal of Theoretical Biology, 1966.

David Shear, Research Associate

Department of Biophysics
School of Medicine

Research Projects:

1. "An Analog of the Boltzmann H-Theorem (A Liapunov Function) for Systems of Coupled Chemical Reactions", submitted for publication to the Journal of Theoretical Biology. Preprinted as TBC Preprint No. 13
2. The behavior of the free energy of chemical reaction systems near equilibrium.

Meetings Attended:

1. Biophysical Society 10th Annual Meeting, February 23-25, 1966, Boston, Mass.
2. Gordon Research Conference on Interaction and Transport in Physical, Chemical, and Biological Systems, June 20-24, 1966, Andover, New Hampshire.
3. New York Heart Association Symposium on the Contractile Process, December 9-10, 1966, New York City.
4. Summer Workshop in Transport Theory, June 27-July 6, 1966, State University of New York at Buffalo, Buffalo, New York

Fred M. Snell, Professor

Department of Biophysics, School of Medicine

Research Projects:

1. Computer simulation of the facilitated transport of oxygen by hemoglobin.
2. Geometric considerations of membranes and their effect on transport phenomena. Snell and Spangler.
3. Models in transcellular transport process. Snell, Spangler, Mikulecky.
4. Development of a macroscopic phenomenological theory of transport based on molecular frictional coefficients. Snell and Spangler.
5. A statistical mechanical interpretation of partial molecular stress tensors. Snell.
6. An investigation of the physical meaning of asymmetry among phenomenological transport coefficient. Snell and Mikulecky.
7. Development of control theory applicable to biological systems. Snell.

Meetings Attended:

1. Symposium of the International Society of Cell Biology, June 21-25, 1965, Frascati, Italy.
2. Symposium on Biophysics and Physiology of Biological Transport, June 15-18, 1965, Frascati, Italy.

3. 10th Annual Biophysical Society Meeting, Boston, Massachusetts, February, 1966.

4. Chairman, Gordon Research Conference, "Interaction and Transport in Physical, Chemical and Biological Systems", June 20-24, 1966, Andover, New Hampshire.

5. Conducted Summer Workshop in Transport Theory, June 27-July 6, 1966, State University of New York at Buffalo, Buffalo, New York.

6. NAS-National Research Council Symposium on "Physical Bases of Circulatory Transport: Regulation and Exchange", Aspen, Colorado, September 14-17, 1966.

7. Fourth Annual Symposium on Biomathematics and Computer Science in the Life Sciences, Houston, Texas, March 24-26, 1966.

Publications:

1. Snell, F. M., "Facilitated Transport of Oxygen Through Solutions of Hemoglobin", J. Theor. Biol., 8:469 (1965).

2. Gabrieli, E. R., Yeostros, S. J., Doganer, Y., and Snell, F. M., "Reticuloendoethelial System Phagocytic and Catabolic Activity", Arch. Path., 80:24 (July, 1965).

3. Gabrieli, E. R. and Snell, F. M., "Reflection of Reticulo-endothelial Function in Studies of Blood Clearance Kinetics", J. Reticuloendo. Soc., 2:141 (July, 1965).

4. Snell, F. M., Shulman, S., Spencer, R. P., and Moos, C., Biophysical Principles of Structure and Function, Addison-Wesley Publ. Co., Reading, Mass., (1965).

5. Spangler, R. A. and Snell, F. M., "Equation of Transport in Terms of Molecular Frictional Coefficients", 2nd Int'l. Congress on Biophysics, Vienna, September 5-10, 1966.

6. Snell, F. M., "Phenomenological Formulation of Transport Equations and Their Application", Proceedings of Conf. "Physical Bases of Circulatory Transport: Regulation and Exchange", Aspen, Colorado, September 14-17, 1966, Saunders Publ. Co., Philadelphia, Pa.

7. Snell, F. M. and Spangler, R. A., "A Phenomenological Theory of Transport in Multicomponent Systems", submitted for publication.

8. Snell, F. M., 'Reciprocal Relations Among Transport Coefficients", J. Phys. Chem., 69:2479 (June, 1965).

9. Snell, F. M. and Stein, Barry, "Onsager Reciprocal Relations in Complex Membranes", J. Theor. Biol., 10:177 (1966).

10. Snell, F. M., "The Nature of Coupling of Transport Processes", Submitted for publication in special issue of Protoplasm (1965).

11. Snell, F. M. and Chowdhury, T. K., "Intracellular Potentials in Frog Skin and Toad Bladder", in Symposia of the International Society for Cell Biology, Catherine B. Warren, ed. (1966).

12. Chowdhury, T. K. and Snell, F. M., "A Microelectrode Study of Electrical Potentials of Frog Skin and Toad Bladder II", The Physiologist, 8:134 (1965).

13. Chowdhury, T. K. and Snell, F. M., "Further Observations on the Intracellular Electrical Potential in Frog Skin and Toad Bladder", Biochim. et Biophys. Acta, 112:581 (1966).

14. Chowdhury, T. K. and Snell, F. M., "Ionic Diffusion as a Basis of Bioelectric Potentials", Biophysical Society, "Discussion Only Session", Membrane and Transport Phenomena (1966).

15. Spangler, R. A. and Snell, F. M., "Macroscopic Equation of Transport in Terms of Molecular Frictional Coefficients", Biophysical Society, "Discussion Only Session", Membrane and Transport Phenomena (1966).

16. Mikulecky, D. C. and Snell, F. M., "The Meaning of Asymmetry on Phenomenological Coefficients", Biophysical Society, FD-5 (1966).

17. Snell, F. M., "Biophysics" (Book review on Nonequilibrium Thermodynamics in Biophysics by A. Katchalsky and P. F. Curran) Science, 151:1378 (March 18, 1966).

18. Spangler, R. A. and Snell, F. M., "Transfer Function Analysis of Chemical Kinetics Systems", J. Theor. Biol., Submitted for publication (1965).

19. Spangler, R. A. and Snell, F. M., "Transfer Function Analysis of an Oscillatory Model Chemical System", J. Theor. Biol., Submitted for publication (1965).

20. Thrall, Robert M. and Snell, Fred M., "Joint Efforts of CUEBS and CUPM", Abstract, Fourth Annual Symposium on Biomathematics and Computer Science in the Life Sciences, Houston, Texas (March 24-26, 1966).

Robert A. Spangler, Assistant Professor

Department of Biophysics, School of Medicine

Research Projects:

1. Geometric considerations of membranes and their effect on transport phenomena. Spangler and Snell.
2. Models in transcellular transport process. Snell, Spangler and Mikulecky.
3. Development of a macroscopic phenomenological theory of transport based on molecular frictional coefficients. Snell and Spangler.

Meetings Attended:

1. 2nd Int'l. Congress on Biophysics, Vienna, September 5-10, 1966.

Publications:

1. Spangler, R. A. and Snell, F. M., "Transfer Function Analysis of a Chemical Kinetic System", submitted for publication.
2. Spangler, R. A. and Snell, F. M., "Transfer Function Analysis of an Oscillatory Model Chemical System", submitted for publication.
3. Snell, F. M. and Spangler, R. A., "Transport Characteristics in Tubular Invaginated Membranes", submitted for publication.
4. Spangler, R. A. and Snell, F. M., "A Dual Wavelength, Dual Beam Microspectrophotometer", Biophys. Soc. Abst., FH-11 (1965).

5. Spangler, R. A. and Snell, F. M., "Equation of Transport in Terms of Molecular Frictional Coefficients", 2nd Int'l. Congress on Biophysics, Vienna, September 5-10, 1966.

6. Snell, F. M. and Spangler, R. A., "A Phenomenological Theory of Transport in Multicomponent Systems", submitted for publication.

NOTE: Recipient of a Research Career Development Award for a 5-year term from the Public Health Service. Will spend one year (Sept., 1966-Sept., 1967) in the laboratories of Professor Aaron Katchalsky at the Weismann Institute, Rehovoth, Israel.

D. J. Triggle, Associate Professor.

Unit for Theoretical Biology
and
Department of Biochemical Pharmacology
School of Pharmacy

Post-Doctoral Fellows

M. May
F. Ridley
S. S. Chatterjee

Research Projects:

1. Kinetic isotope effects in enzyme reactions.
2. Irreversibly acting analgetic agents.
3. Design of compounds that irreversibly intercalate in DNA.
4. Conformational analysis of the acetylcholine receptor.

Much work has been done alkylating agents, including alkylating analogs of folic acid, which may be of value in chemotherapy. Work has continued on studies related to the isolation of the nor-epinephrine α receptor. Perhaps some of the most interesting work lies in the area of quantitative pharmacology (publications 16 and 17 and unpublished work) where we have demonstrated that tissue response is directly proportional to the number of available receptors and that maximum response occurs when 100% of the receptors are available for occupation.

Additions to Publications:

1. 2-Halogenoethylamines as Potential Folic Acid Antagonists I. Synthesis and Biological Activity of Ethyl-N-[2-amino-4-hydroxy-6-methyl-5-pyrimidyl)-3-(2-chloro)-propyl]-p-aminobenzoate. A. M. Triggle and D. J. Triggle, J. of Pharmaceutical Sciences, 54, 795 (1965).

2. Potential Folic Acid Antagonists. I. The Antitumor and Folic Acid Reductase Inhibitory Properties of 6-Substituted 2,4-Diamino-5-arylazopyrimidines. J. Hampshire, P. Hebborn, A. M. Triggle, D. J. Triggle and S. Vickers, J. Med. Chem., 8, 745 (1965).

3. A Study of Comparative Chemical and Biological Activities of Alkylating Agents. T. J. Bardos, N. Datta-Gupta, P. Hebborn and D. J. Triggle, J. of Med. Chem., 8, 167 (1965).

4. N^4-(2-Bromoethyl)-N^4-ethylsulfanilamide, a Monofunctional Nitrogen Mustard with Antitumor Action. P. Hebborn and D. J. Triggle, J. of Med. Chem., 8, 541 (1965).

5. The Selective Antitumor Action of some Aliylating Sulfonamides. P. J. Barnard, J. F. Danielli, R. Hawkins, P. Hebborn, A. Muggleton, D. Triggle and A. M. Triggle, Archivio Italiano de Patologia e Clinica dei Tumori, VIII, 141 (1965).

6. Intramolecular Participation in Ester Hydrolysis by the Diazonium Group. D. J. Triggle and S. Vickers, Chemical Communications, 544 (1965).

7. The Mechanism of Interaction of 2-Halogenoethylamines at the Noradrenaline Receptor. H. Kimelberg, J. F. Moran and D. J. Triggle, J. Theoret. Biol. 9, 502 (1965).

8. The Reactions of 2-Halogenoethylamines at the Noradrenaline Receptor-Storage Complex. H. Kimelberg and D. J. Triggle, J. of Theoret. Biol. 9, 313 (1965).

9. 2-Halogenoethylamines and Receptor Analysis. D. J. Triggle, Adv. in Drug Res., 3, 173 (1965).

10. The Estrogenic Activities of 16α, 17α- and 16β, 17β-Epoxy-1, 3,5(10)-Estratriene-3-OL. M. May, B. J. Johnson, D. J. Triggle, J. F. Danielli and S. S. H. Gilani, Life Sciences, 4 (1965).

11. The Synthesis of Nitrogen-Containing Steroids, I. Diels-Alder Adducts of Steroids and 4-Phenyl-1,2-4-triazoline-3,5-dione[1]. S. S. H. Gilani and D. J. Triggle, J. Org. Chem., 31, 2397 (1966).

12. 2,4-Diamino-6-substituted-5-(4-carbethoxyphenylazo)pyrimidines as irreversible Inhibitors of Folic Acid Reductase. J. Hampshire, P. Hebborn, A. M. Triggle and D. J. Triggle, J. Pharm. Sci., 55, 453 (1966).

13. Rate-determining Step in the Action of L-Amino-acid Oxidase. D. J. Triggle and J. F. Moran, Nature, 211, 307 (1966).

14. 6-Substituted 2,4-Diamino-5-(4-carbethoxyphenylazo pyrimidines as Potential Precursors of Tetrahydropteridine Antimetabolites. M. Chadwick, J. Hampshire, P. Hebborn, A. M. Triggle and D. J. Triggle, J. Med. Chem. 9, 874 (1966).

15. Chemical Aspects of The Autonomic Nervous System. D. J. Triggle, Academic Press, November, 1965.

Papers Scheduled for Publication (accepted and in proof).

16. Studies on The Adrenergic α-Receptor. I. J. F. Moran, M. May, H. Kimelberg and D. J. Triggle, J. Mol. Pharm. 1967 (January).

17. Studies on the Adrenergic α-Receptor. II. M. May, J. F. Moran, H. Kimelberg and D. J. Triggle, J. Molec. Pharmacol. 1967 (January).

18. 5-Substituted Pyrimidines. II. A. M. Triggle and D. J. Triggle, J. Med. Chem. 1967 (January).

19. Participation by the Diazonium Group in Carbonyl Reactions. I. S. Vickers and D. J. Triggle, J. Chem. Soc. (Spring, 1967).

20. The Analgesic and Hypothermic Activities of some N-Substituted α-5,9-Dimethyl-6,7-Benzomorphans. M. May and D. J. Triggle, Nature (Spring, 1967).

V. S. Vaidhyanathan, Associate Professor

Unit for Theoretical Biology
School of Pharmacy

Research Problems:

1. Molecular theory of interfacial phenomena (collaboration with Frank Buff of Rochester).
2. Theory of transport coefficients.
3. Compartmental systems.
4. Thermodynamic functions of two-dimensional systems (collaboration with Dr. Montroll's group at Rochester).

Meetings Attended:

1. International Symposium on Membrane Phenomena, Frascati, 1965.
2. Conference on Recent Advances in Physical and Mathematical Sciences, New York, November 1965.
3. American Chemical Society, Pittsburgh, April, 1966.
4. Gordon Conference on Physical Interactions in Biological Systems, June 1966.
5. Summer Colloquium in Theoretical Biology, Fort Collins, July-August 1966.
6. Biophysics Congress, Vienna, September 1966.

Publications (Since June, 1965):

1. Statistical Mechanical Theory of Electrolyte Diffusion Inside a Charged Membrane, J. Theor. Biol., 8, 344 (1965).

2. Statistical Theory of Transport of Electrolytes Across A Charged Membrane, J. Theor. Biol., 9, 478 (1965).

3. On the Criteria of Active Transport, J. Theor. Biol., 9 489 (1965).

4. Some Comments on Steady State Transport of Ions Across A Charged Membrane, J. Theor. Biol., 10, 159 (1966).

5. Molecular Theory of Nerve Potentials, coauthor, Hannah M. Phillips. J. Theor. Biol., 10, 460 (1966).

6. Some Theoretical Aspects of Biological Transport, Proceedings of International Conf. Cell Biology, Rome, (1965).

7. Theory of Mechano-elective Membrane Transducers, J. Theor. Biol., 12, 000, (1967).

8. Mobile Ion Interactions in Membrane Phase, coauthor, Hannah M. Phillips, J. Theor. Biol., 12, 000, (1967).

9. Molecular Theory of Membrane Potential, J. Phys. Soc. of Japan, 21, 1363 (1966).

10. Concentration Profiles and Steady State Fluxes of Permeable Molecules in a Membrane System, Abstract of # 353, IInd International Biophysics Congress, Vienna, (1966).

11. A Contribution to the Theory of Stability of Bimolecular Lipid Films I, To be published.