Center for Theoretical Biology

Report on NASA Grant NGR 33-015-016

for 1969

Faculty of Health Sciences

State University of New York at Buffalo

4248 Ridge Lea Road

Amherst, N. Y., 14226

CONTENTS

INTRODUCTION

During the year considerable progress has been made in the development of theory related to exobiology, and this development has been notably assisted by the Colloquium on Theoretical Biology of the Cell which was held at Fort Collins in the summer, sponsored by NASA and AIBS.

Perhaps the most notable single development has been that, (under pressure from the theoreticians!) our associated Cell Biology Laboratory has succeeded in reassembling living cells from isolated membranes, nuclei and cytoplasms. This is the first successful cell synthesis, and opens the way into a variety of programs which involve the design and synthesis of cells for special purposes. One of these is the design of an organism which can live on Mars. This study is being conducted together with members of the staff of the Department of Geology at Buffalo. This association has in turn led to formation of a team at Buffalo which is working with Biospherics, Inc., in a rigorous study of control experiments and instrument design for the Viking flights to Mars.

Arising from our successful development of the theory of lipid bilayers is a membrane design which has been suggested to the Office of Saline Water. Development work on this is expected to start in the fall of 1970.

The work of the past year can be summarised by saying that the maturation of the theoretical work previously supported by this Grant has resulted in a series of developing studies relevant to exobiology, and is also leading to substantial contributions to the solution of some terrestrial problems.

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Perhaps the most notable single development has been that, (under pressure from the theoretical) our associated cell biology laboratory has succeeded in maintaining living cells from isolated membranes, nuclei and cytoplasm. This is the first successful cell synthesis, and opens the way into a variety of programs which involve the design and construction of cells for special purposes. One of these is the design or re-design of cells for special purposes. This nearly is being undertaken jointly with members of the staff of the Department of Geology at Indiana. This association has in turn led to formation of a team at Illino which is working with simulation. Here, in a relatively short of control experiments and underground design for the Illino facility is to have.

Arising from our successful development of the theory of lipid bilayers is a membrane design which has been successfully to the Office of Saline Water. Development work on this is expected to start in the fall of 1970.

The work of the past year can be summarized by saying that the maturation of the theoretical work previously supported by this Grant has resulted in a series of developing research relevant to ecobiology, and is also leading to substantial contributions to the solution of some terrestrial problems.

REPORT OF THE EXTERNAL ADVISORY COMMITTEE
November 11, 1969

E. A. Pollard
Mones Berman
Terrell L. Hill
Otto Schmitt
Martynas Ycas

INTRODUCTION

The Center for Theoretical Biology continues to be a unique and refreshingly different group with a characteristic individual approach to biology. In our opinion, it adds stature to the scientific program at the State University of New York at Buffalo. The group is clearly able to relate to other science departments and also to act responsibly as concerns problems the University has to face and solve.

At the present time, when the University faces major new construction prior to an increase in enrollment and therefore in the recruitment of new faculty, there is a considerable advantage to the strategy of building up theoretical competence throughout science. Strengthening of the Center for Theoretical Biology would be a move in accord with this strategy. Moreover, since the membership and active participation in the Center for Theoretical Biology is largely by individuals with faculty appointments in other departments, the understanding of theory throughout science is important to guarantee the availability of individuals of distinction to work in the Center.

MISSION ORIENTED RESEARCH

The situation in general support of science today is changing because one rapid period of expansion is clearly ending and this suggests that some new approaches be made in all science departments. Theoretical Biology lends itself to cooperative and consulting programs with Engineering and Medical Departments in which the theoretical ideas and advice on the program can come from, for example, the Center for Theoretical Biology. In this connection, we note with satisfaction, the use of membrane theory to devise artificial membranes for a desalination program undertaken by the Department of Chemical Engineering.

EXPERIMENT IN THE MIDST OF THEORY

A center for theory should not be in a vacuum as regards experiment. The amoeba nuclear transplant and linear algae work makes sense as both are related to cellular theory in one case and multicell theory in the other.

ACTIVE ENZYME SITES

The loss of one faculty member has cut back on the potential to study the theory of active enzyme sites. This is to be regretted.

COMPUTER FACILITIES AND THE CENTER FOR THEORETICAL BIOLOGY

Many Universities are facing a sharp problem with regard to computer facilities. These have grown and overall support by grants has ceased. The tendency is to adopt a hard line and to require that only supported projects get computer time for which they pay. If this is done the

utilization of the computer may become very much sub-optimal. An alternative which we recommend, is for the University to permit and indeed encourage skilled personnel such as those in the Center to participate in the use of the computer, for they are effective and efficient in their use of its time, and to show faith that the results forthcoming will earn the right to support in the future. In any event, some time on the computer should be made available to the Center on the grounds that the computer is to them what a library is to a Department of English.

APPOINTMENT OPPORTUNITIES AND THE DIRECTION OF RESEARCH

The External Advisory Committee feels that the appointment of only two or three first class men would take the status of the Center from very good to excellent. The work of the senior staff was briefly personally reviewed with the Director. There was some feeling that somewhat more coherence within and between the various programs induced without regimentation, would strengthen the Center for Theoretical Biology.

II. ORGANIZATION OF THE CENTER FOR THEORETICAL BIOLOGY

Director: James F. Danielli

Assistant Director: Robert Rosen

EXECUTIVE COMMITTEE: Maintains relationship between various departments, provides guidance for programs of the Center, and determines budget policies.

James F. Danielli - Chairman

Eric Barnard
Harry T. Cullinan, Jr.
Seymour Geisser
John S. King
Daniel Murray
Robert Rosen
Fred Snell
Robert Spangler
Dov Tamari
David J. Triggle
Sol Weller
Ta-You Wu

ACADEMIC COMMITTEE: Determines the academic policy of the Center, academic research programs, teaching activities, and postdoctoral training.

James F. Danielli - Chairman

Robert Rosen - Co-Chairman

David Cadenhead
Moises Derechin
Jon R. Hamann
Kwang Jeon
K. N. Leibovic
Robert Rein
Robert Spangler
David Triggle
V. S. Vaidhyanathan

Elected Representatives:

Luigi Bianchi - Assistant Professor
John Borst - Graduate student
Peter Bright - Postdoctoral
Marian May - Secretary

SEMINAR, LIBRARY, PUBLICATIONS COMMITTEE: Schedules seminars, special lecture series and symposia, administers the library, publishes the Quarterly Bulletin from the Center.

Kwang Jeon - Seminars

Luigi Bianchi - Library
Noreen Ritchie

Marian May - Publications
Ruth Kuhfahl

BUDGET COMMITTEE: Meets quarterly to discuss appropriations and expenditures of funds provided for the Center.

James F. Danielli - Chairman

Harry Collins
Margaret Riester
Robert Rosen
David J. Triggle

GENERAL PURPOSES COMMITTEE: Meets once a month and is responsible for all services, supplies, rooms, complaints, etc.

Harry Collins - Chairman
Kay Maher
Marian May

EXTERNAL ADVISORY COMMITTEE: This is a group of distinguished outside consultants who meet once a year at the Center to evaluate the progress of the Center and advise on future plans.

Mones Berman
H. W. Emmons
Terrell L. Hill
Ernest C. Pollard
Otto Schmitt
Martynas Ycas

FRONTIERS OF RESEARCH COMMITTEE: The function of this study group is to consider the aspects of biology not presently under study in the Center, particularly novel aspects, and to make recommendations as to whether a serious research effort should be made by the Center in such novel areas. This committee is in the process of being reorganized.

James F. Danielli - Chairman

SUB-COMMITTEE ON EDUCATION:

James F. Danielli--Chairman
Jon R. Hamann
K. N. Leibovic
Robert Rein
Robert Rosen

III. FACULTY AND FIELDS OF INTEREST

Professors:

Thomas Bardos	Cancer chemotherapy
Eric A. Barnard	Active centers of enzymes, properties of enzymes in cells
Lyle Borst	Physics
James F. Danielli	Membrane phenomena, cell theory, cytoplasmic inheritance, relational biology
Robert J. Good	Surface chemistry and physics
Mac Hammond	Linguistics and poetics
Joseph G. Hoffman	Quantitative measurement of heat released by mammalian tissue cells
Arnold Mittelman	Cancer chemotherapy
Donald Parsons	Membranes and surfaces
David Pressman	Biochemistry and immunology
Robert Rein	Quantum chemistry of organic and biomolecules
Irving Shames	Continuum mechanics
Fred Snell	Transport and membrane phenomena, nonequilibrium thermodynamics, theoretical biology
Dov Tamari	Algebra; furthering mathematical thought in biology
David J. Triggle	Theories and mechanisms of drug-receptor isolation
Ludwig von Bertalanffy	Systems theory
C. H. Waddington	Developmental and evolutionary biology

Sol W. Weller	Heterogeneous and homogeneous catalysis; chemical reaction kinetics
Marvin Zelen	Statistics

Associate Professors:

Robert Abbott	Surface physics; physisorption and chemisorption of molecules and macromolecules on solid surfaces
George R. Blakley	Population studies
David A. Cadenhead	Surface chemistry, monolayer studies and molecules of biological interest
Peter Hebborn	Anti-inflammatory agents, cancer chemotherapy
K. Nicholas Leibovic	Processes of communication and control in biological systems especially the central nervous system.
A. Dean MacGillivray	Perturbation theory, including its application to macromolecular systems
Dorita A. Norton	X-Ray studies in sterols
Charles Paganelli	Transport across biological membrane
Robert Rosen	Biological systems analysis
V. S. Vaidhyanathan	Statistical mechanics, membrane transport interfacial physics, mathematical biophysical chemistry

Assistant Professors:

Luigi M. Bianchi	Central nervous system and sensory communication
Moises Derechin	Protein structure, relation between configuration and activity

Jon R. Hamann	Relational systems
Kwang W. Jeon	Cytology and cell physiology
Marian May	Estrogen receptors
John F. Moran	Mechanisms of drug action; deuterium isotope effects in biological systems; receptor isolation
Shinpei Ohki	Structure and permeability of membranes
Cora G. Saltarelli	Physiology and genetics of pathogenic yeasts; biochemistry
Robert A. Spangler	Irreversible thermodynamics, biological transport processes
Joan Lorch Staple	Nucleo-cytoplasmic relationships in protozoa and other cells
V. C. Swamy	Pharmacology of adrenergic receptors.
Darold C. Wobschall	Electrical properties of membranes and organic semiconductors.

Research Associates:

Robert Beckwith	Musicology, psycholinguistics
Peter B. Bright	Theoretical foundations of transport phenomena for the study of neuronal membranes
Shym S. Chatterjee	Medicinal organic chemistry
Mary Danielli	Anthropological studies bearing on man's control of environment and of his reaction to it.
Richard Gordon	Form and pattern generation
James Harlos	Cancer research
Michael Kleiner	Cancer research

S. R. McLean	Medicinal organic chemistry
M. S. Sheshadri	Statistical mechanics
Frank Tsien	Monomolecular films

Graduate Assistants

Howard Allen	R. Jarvis
Ehud Artzy	J. S. Jayanthinathan
Barry Avner	R. Kendall
Francis Bellino	Joseph Miao
John Borst	Thomas Mathieson
K. Chang	George Pack
Philip Cota	Joel Pursner
Richard Demchak	James Rabinowitz
Peter Engler	V. Renugopalakrishnan
S. Fridjonsson	Nassir Sabah
Arthur Hedley	Robert Sayre
Kenneth Jacobson	Edward Shapiro

Mrs. Wu

Visiting Professors:

Franco Conti	Action potential
Nobuo Fukuda	Simulation study of biological systems
Robert Lebovitz	Neural and non-neural membranes
Otto Rössler	System theory and kinetics

Consultants:

Narendra Goel	Statistical mechanics
Sasa Svetina	Intermolecular forces, cell-cell interaction, quantum and statistical study of DNA
Miriam Weller	Psychiatric social worker
M. H. F. Wilkins	Biophysics
Martynas Ycas	Molecular biology and cell physiology

Administrative Staff:

James F. Danielli	Director
Robert Rosen	Assistant director
Harry Collins	Laboratory Manager
Dennis DeGweck	Computer Programmer
Shirley Drescher	Model Builder
Eliza Ferby	Technician
Priscilla Ford	Administrative Assistant (to April)
David Garrison	Technician
Lee Gordon	Secretary, Journal of Theoretical Biology
Evelyn Hammond	Secretary - part time (from September)
Ruth Harvey	Secretary
Carole Hayden	Technician
Ruth Himmel	Secretary
Kwang Jeon	Academic Co-ordinator
Ruth Kuhfahl	Secretary
Thomas Maddocks	Instrument Maker (to September)
Kathleen Maher	Administrative Assistant (from April)
Marian May	Assistant to the Director, Writer
Claude Miller	Instrument Maker (from September)
Lorraine Powers	Technician
Carol Retzer	Secretary to the Director
Alice Richards	Secretary - part time (to June)
Margaret Riester	Accounts secretary
Noreen Ritchie	Literature searcher

Eleanor Sattler	Technician
Vickie Skowronski	Technician
Hsin-yu Wang	Computer programmer
Robert Wagner	Accountant
Evelyn Wood	Artist

ANNUAL REPORT FROM THE WORKING PARTY ON NUCLEAR AND CYTOPLASMIC INHERITANCE

1. DEFINITION OF FIELD OF INTEREST:

Study of cell physiology using the amoeba as a model system.

2. FINANCIAL SUPPORT:

NSG 501 and NGR 33-015-016 from NASA.

3. FACULTY AND OTHER PARTICIPANTS:

K. W. Jeon	Working party chairman, Research Assistant Professor, School of Pharmacy (Center for Theoretical Biology)
J. F. Danielli	Professor, School of Pharmacy (Center for Theoretical Biology)
I. J. Lorch	Research Assistant Professor, School of Pharmacy (Center for Theoretical Biology)
Student participant:	Technicians:
Howard Allen	Lorraine Powers Eleanor Sattler

4. RESEARCH PROGRAM:

The work carried out during the past year can be divided into three major areas as follows:

A) Assembly of viable cells from dissociated cell components: There has been an increasing interest on the problem of experimental synthesis of living cells. However, the approach has been largely theoretical in most cases. We realized that the first step toward achieving such a goal would be to reassemble a cell from its individual components, and that we already had the necessary techniques available for

the reassembly of Amoeba. We have completed a preliminary study in which we have shown that a new viable amoeba may be produced using the membrane of one cell, cytoplasm from one or more other cells, and the nucleus from a third cell. We are in the process of isolating clear cytoplasmic organelles in a viable state.

B) Studies on the strain-specific nuclear cytotoxicity: Recently we discovered that the amoeba nucleus from one strain has a specific antimitotic and lethal effect on other strains of amoebae, including those of different genera when introduced into the latter. We further learned that such an effect is caused by a diffusible substance released from the grafted nucleus. We have succeeded in partial identification of the nuclear toxic factor, and have been using the isolated factor in studies of cellular synthetic activities and cell division. Our results obtained so far indicate that the factor is a high molecular weight protein and we are continuing in our effort to identify the exact chemical nature of the protein and to elucidate its mode of action. Meanwhile, we believe that this lethal phenomenon plays an important role in determining strain or species specificity in general and is related to cell variation and differentiation.

C) Continued studies on the roles of nucleus and cytoplasm in determining cell characters in amoebae: We have continued our studies on the mechanisms for phenotypic changes that occur among our strains of amoebae in continuous culture. The characters we used as genetic markers are the response of

amoebae to anti-amoeba serum and rate of attachment to the substratum. We have found out from our experiments using the techniques of nuclear transplantation and cytoplasmic injection, that the characters of fast attaching and negative response to anti-amoeba serum are dominant over those of slow attaching and positive response respectively. We have also learned that these dominant characters can be conferred to other cells under the influence of both cell nucleus and cytoplasm. When such a character was conferred by the nuclear influence, that change was permanent, while any change induced by the cytoplasmic influence was transient. Changes in inter-strain compatibility were also studied.

D) Studies on hexosamine metabolism in amoebae: With a continued partial financial support from the Center, H. Allen has studied the hexosamine metabolism with special reference to the cell surface. Both glucosamine and galactosamine were present, and chemical analyses showed that glycoproteins are components of the cell surface rather than acidic mucopolysaccharides. Tracer studies showed that amoebae take up glucosamine and convert it to expected intermediates. The results suggested that a glycoprotein surface precursor pool sufficient to synthesize a complete surface is present with about 30% of the cellular hexosamine bound to non-surface glycoproteins.

5. PUBLICATIONS:

K. W. Jeon (1969) Nuclear-cytoplasmic relations in lethal amoeba hybrids, Exptl. Cell Res. 55, 77.

I. J. Lorch and K. W. Jeon (1969) Reversible effect of actinomycin D. on nucleoli of A. discoides, Nature 221, 1073

I. J. Lorch (1969) The rate of attachment of amoebae to the substratum, J. Cell Physiol. 73, 171.

K. W. Jeon and I. J. Lorch (1969) Lethal effect of heterologous nuclei in amoeba heterokaryons, Expt. Cell Res. 56, 233

K. W. Jeon and I. J. Lorch (1969) Strain-specific mitotic inhibitor produced by free-living amoebae, J. Cell Biol. 43, 60a.

K. W. Jeon (1969) Short-term preservation of viable amoeba nuclei in vitro, J. Cell Biol. 43, 60a

I. J. Lorch (1969) A comparison of movement of amoebae enucleated at different stages of their life cycle, J. Cell Biol. 43, 82a.

I. J. Lorch and K. W. Jeon (1969) Character changes induced by heterologous nuclei in amoeba heterokaryons, Exptl. Cell Res. 57.

K. W. Jeon and I. J. Lorch (in press) Strain-specific mitotic inhibition in large mononucleate amoebae, J. Cell. Physiol.

6. PAPERS AND SEMINARS PRESENTED: MEETINGS ATTENDED

July 13-August 15, Summer Colloquium on Theoretical Biology, Fort Collins, Colorado (K. Jeon)

November 2-4 Symposium of the International Society for Cell Biology (K. Jeon and I. J. Lorch)

November 6-8 Annual Meeting of the American Society for Cell Biology, Detroit, Michigan (K. Jeon and I. J. Lorch)

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

K. W. Jeon participated in teaching Biology 125, Principles of Modern Biology in the Department of Biology.

ANNUAL REPORT FROM WORKING PARTY ON MODELS OF CENTRAL NERVOUS SYSTEM AND SENSORY COMMUNICATION

1. DEFINITION OF FIELD OF INTEREST:

Theory of information processing in the nervous system.

2. FINANCIAL SUPPORT:

NIH Grant NB 06682 to K.N. Leibovic and Robert A. Spangler

NASA Grant NGR 33-015-016.

3. FACULTY AND OTHER PARTICIPANTS:

K. N. Leibovic	Working Party Chairman, Associate Professor, School of Medicine (Biophysical Sciences)
Eric Balslev	Visiting Associate Professor, Faculty of Natural Science and Mathematics (Mathematics)
Elaine Hull	Associate Professor Faculty of Social Science and Administration (Psychology)
Robert A. Spangler	Assistant Professor, School of Medicine (Biophysical Sciences)
Student Participants:	V. S. Jayanthinathan, Biophysics
	A. Kaufman, Biophysics
	Richard Kendall, Biophysics
	Thomas Mathieson, Biophysics
	Nassir H. Sabah, Biophysics and Sir John Eccles' Laboratory
	Edward Shapiro, Biophysics

4 RESEARCH PROGRAM:

During the last year the following problems have been investigated:

I. Psychophysical Visual Thresholds:

The square root law as well as the Weber-Fechner law

can be deduced from a general expression relating the frequency of ganglion cell firing to quantum flux on the retina, quantum: spike ratio and mean interval between ganglion cell spikes. This work is an extension and modification of Barlow's work on the same subject (Barlow 1965). Combined with our work on cell responses and interactions in the retina, we are attempting to define the contributions of different cell types to the psychophysical threshold data.

II. Binocular Space Perception:

There is a considerable psychophysical literature on this topic (Ogle, 1962) and there is Luneberg's phenomenological theory (1947) with its later developments by Blank (Hardy et al, 1953). This theory is capable of integrating a number of experimental data, although some discrepancies do exist. More recent experimental work to test various psychophysical propositions has been carried out by Foley (1968, 1969), Gogel (1963) and Shipley and Williams (1968) among others. There is no theory, however, which provides a neural basis for binocular space perception. Some recent experiments of Barlow (Barlow,et al, 1967) have led us to propose such a model. Barlow has shown that specific neurons in the visual cortex of the cat receive inputs from specific pairs of retinal locations in the two eyes. Our theoretical considerations have led us to the view, however, that visual perception must be based on the activity of groups of cells - not of single cells. Hence, we postulate that the perception of a pattern, such as a circle or a straight line arises

from the activity of specific groups of neurons in the brain. But, if this is the case, then it should be possible to predict how the objective counterpart of a subjective pattern will change with a change in the point of fixation. For the same set of cortical neurons which signals, say a circle, must then be activated by the same retinal areas for different fixation points. We have carried out calculations for Hillebrand hyperbolae and for circles centered subjectively in the observor (approximated by Vieth-Müller circles) and have found good agreement with our theory. Moreover, the mapping of equivalent configurations in our theory can be shown to be equivalent to the iseikonic transformations used by Blank (Hardy et al, 1953) which are known to be in good agreement with a number of experimental data. However, calculations based on the assumption as stated, do not agree with the data on the subjective fronto-parallel planes. This indicates that the correspondence between geometric pattern and neural activity in a fixed set of cells can only hold for a restricted class of patterns. This class may have a special significance for a perceptual co-ordinate system; and the problems are presently under investigation.

Accounts of our work to date are in preparation (Leibovic et al, 1970; Balslev and Leibovic, 1970). This work on space perception supplements our previous work on size perception based on geometric probability (Leibovic, 1966; Leibovic, 1967). Some further extensions of the latter are also under review at present.

III. Single Cell Response:

We have investigated subthreshold oscillations in active membranes (Sabah and Leibovic 1969). This is of some importance in the interpretation of physiological recordings. In our paper, the classical cable equation, in which membrane conductance is considered constant, is modified by including the linearized effect of membrane potential on sodium and potassium ionic currents, as formulated in the Hodgkin-Huxley equations for the squid giant axon. The resulting partial differential equation is solved by numerical inversion of the Laplace transform of the voltage response to current and voltage inputs. The voltage response is computed for voltage step, current step and current pulse inputs, and the effect of temperature on the response to a current step input is also calculated.

The validity of the linearized approximation is examined by comparing the linearized response to a current step input with the solution of the nonlinear partial differential cable equation for various subthreshold current step inputs.

All the computed responses for the squid giant axon show oscillatory behavior and depart significantly from what is predicted on the basis of the classical cable equation. The linearization procedure, coupled with numerical inversion of the Laplace transform, proves to be a convenient approach which predicts at least qualitatively the subthreshold behavior of the non-linear system.

IV. General Principles:

Our understanding of single cell responses and interactions in small groups of cells is greatly enhanced through the perspective gained from a study of general principles of structure and function in the nervous system. We have considered several topics in this context: the interplay of randomness and design, the significance of the information encoded in single cells and groups of cells and the significance of different stages of information processing in the nervous system. Our results imply that the principles of communication in the nervous system must be quite different from those in man-made systems. A paper on this subject is under preparation.

References

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Barlow, H. B., C. Blakemore, V. D. Pettigres (1967) J. Physiol. 193:327

Foley, J. M. (1968) Percept. Psychophys. 3: 265

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Hardy, L. H., G. Rand, M. C. Rittler, A. A. Blank, P. Bolder, (1953) The Geometry of Binocular Space Perception, Knapp Memorial Laboratories, Columbia University, College of Physicians and Surgeons

Luneburg, R. I. (1947) Mathematic Analysis of Binocular Vision, Princeton University Press.

Ogle, K. N. (1962) H. Davson (ed.) "The Eye", Vol. 4, Academic Press.

Shipley, T. and D. Williams (1968) Vision Res. 8: 325.

5. PUBLICATIONS:

K. N. Leibovic, "Some Aspects of Visual Information Input and Transmission:, Ann. NY Acad. Sci., 156, (2) 1969

K. N. Leibovic, "Information Processing in the Nervous System", Science, 164, 457-460, 1969

K. N. Leibovic, "Some Problems of Information Processing and Models of the Visual Pathway", J. Theor. Biology, 22, 62-79, 1969

K. N. Leibovic, "Information Processing in the Nervous System", proceedings of a Symposium held at SUNY/B, October, 1968, Springer Verlag, N.Y. (in press)

K. N. Leibovic (ed.) "On Signal Transmission at Synapses, in Nerve Fibers and In Network Structures" with N. H. Sabah, Springer Verlag, N.Y. (in press)

N. H. Sabah and K. N. Leibovic, "Subthreshold Oscillatory Responses of the Hodgkin-Huxley Cable Model for the Squid Giant Axon", Biophys. J., 9 (10), 1206-1222, 1969

6. PAPERS AND SEMINARS PRESENTED: MEETINGS ATTENDED

K. N. Leibovic, paper on "Present Emphasis in Research on Information Processsing in the Nervous System" presented at Conference on Information and Control Process in Living Systems, Pacific Palisades, California, February, 1969.

N. H. Sabah and K. N. Leibovic, paper on "A Consideration of Nerve Signals" presented at 13th Biophysical Society Meeting, Los Angeles, California, February, 1969

E. Hull, paper on "The effects of septal and hippocampal lesions in active avoidance acquisition in the guinea pig" co-authored with Bradley Lown and Leonard Ireland, presented at the Eastern Psychological Association Meeting, April, 1969

K. N. Leibovic presented a seminar "On Functional Significance of the Convergence and Divergence of Fibers in the Nervous System", in the Biomathematics Lecture Series, University of California, San Francisco, California, May, 1969.

E. Balslev presented a seminar on "Mathematical Theory of Space Perception" in the Biomathematics Lecture Series, University of California, San Francisco, May, 1969

E. Balslev presented a seminar on "Binocular Space Perception" to the Division of Medical Physics, University of California, Berkeley, May-June, 1969

K. N. Leibovic presented a lecture course on "Theoretical aspects of Nervous System Function and Organization" to the Division of Medical Physics, University of California at Berkeley, May-June, 1969

E. Hull attended Rochester Conference on Physiology of Vision, Rochester, N.Y., June, 1969.

N. H. Sabah attended the Conference on Systems Analysis Approach to Neurophysiological Problems, Brainard Minnesota, June, 1969.

K. N. Leibovic presented a seminar "On the Information Contained in the Activity of Single Cells and Groups of Cells in the Nervous System", at the Theoretical Biology Summer Colloquium, Fort Collins, Colorado August, 1969

E. Balslev, T. Matheison and V. S. Jayanthinathan attended the Theoretical Biology Summer Colloquium, Fort Collins, Colorado, August, 1969.

K. N. Leibovic paper on "Convergence and Divergence of Fibers in the Nervous System" presented at 3rd International Biophysics Congress, Cambridge, Massachusetts, September, 1969

E. Balslev attended the 3rd International Biophysics Congress at Cambridge, Massachusetts, September, 1969

8. OTHER ACTIVITIES:

K. N. Leibovic was Visiting Professor at University of California at Berkeley, May-June, 1969

K. N. Leibovic was a faculty member at the Theoretical Biology Summer Colloquium, Fort Collins, Colorado, August, 1969.

ANNUAL REPORT FROM WORKING PARTY ON STATISTICAL MECHANICS IN BIOPHYSICAL SYSTEMS

1. DEFINITION OF FIELD OF INTEREST:

The field of interest of members of this working party may be broadly defined as the application of statistical mechanics, thermodynamics and irreversible thermodynamics to biological problems. Individual members' interests are broad and diversified, ranging from lipid film stability to the investigation of fundamental problems in statistical mechanics.

2. FINANCIAL SUPPORT:

In addition to support from Center funds, a grant from Life Insurance Medical Research Fund was utilized, #G-68-16.

NASA-NGR 33-015-016

Graduate School Grant #50-8694

3. FACULTY AND OTHER PARTICIPANTS:

V. S. Vaidhyanathan	Chairman, Associate Professor, School of Pharmacy (Pharmaceutics)
Peter Bright	Research Instructor, School of Medicine (Biophysical Sciences)
Shinpei Ohki	Assistant Professor, School of Pharmacy (Pharmaceutics)
M. S. Seshadri	Research Associate, Center for Theoretical Biology
Robert Spangler	Assistant Professor School of Medicine (Biophysical Sciences)

Fred Snell	Professor. School of Medicine (Biophysical Sciences)

Consultants:

Dr. Franco Conti	Consiglio Nazionale delle Richerche, Genova, Italy
Dr. Narendra Goel	University of Rochester, Rochester, N.Y.
Dr. Ruth S. Aranow	Research Institute for Advanced Study, Baltimore, Maryland

Student Participants

V. Jayanthinathan
Joseph Miao
V. Renugopalakrishnan
Robert Sayre
Mrs. K. W. Yuan Wu

4. RESEARCH PROGRAM:

It is difficult, if not impossible, to describe in the short space given, the research programs carried out by this group, except to state simply that all problems of interest in membrane and transport phenomena are being studied by individual members of the group. The programs detailed below are only representative and not exhaustive of the research being carried out by various members.

Research Report:

Our research endeavour has been directed during last year along the following four lines of investigation.

Two of the outstanding questions regarding physiological membranes yet to be answered satisfactorily theoretically are why the bilayer structure is almost universal and why the membranes are more or less of similar thickness (40 to 100 Å). Lipids obtained from biological sources have been utilized

to obtain thin film artificially which is stable in aqueous electolyte solutions. These resemble physiological membranes satisfactorily. We have been concerned with the theory of stability of such thin lipid films in aqueous media. The electrostatic energy of interactions of charged species of aqueous media across the lipid film which contributes to stability has been studied in detail in collaboration with Narendra Goel. These aspects which are of significance in physiological systems have been published (J. Theoret. Biol., 21, 331-347, 1968). Additional work to include noncoulombic energy of interactions is in progress.

The electrical conductance problem of ion transport across membranes has been our second line of approach. Initial results explaining the observed presence of a minimum in conductance as function of pH in sodium chloride system and its absence in calcium chloride system were presented in an invited talk during the symposium on Biophysical Aspects of Permeability (Israel Biophysical Society, Jerusalem, Israel, 1968). These results have since been published (J. Theoret. Biology, 23, 232-250 1969).

Our desire has been to formulate the conductance and related potential problems at the molecular level and with this objective we have attempted to generalize the theoretical technique of Onsager and Fuoss to be applicable for ion transport across membrane systems containing fixed charges. The potential of component mean force has been obtained so far and this aspect has been the subject of a manuscript

which is under consideration for publication.

Metabolic reactions have long been suspected to influence the flux of species across biological membranes and active transport. Blumenthal and Katchalsky (Biochimica et Biophysica Acta, 173, 357, 1969) have recently considered an interesting but simplified model for facilitated transport. They consider the effect of an association-dissociation reaction with a carrier on the flux of a nonelectrolyte across the membrane. Their approach has been generalized by us to include coupling of fluxes of different species and analyze the effects of permeant flows on complex formation reaction rate. This work has been accepted for publication. (Biochimica and Biophysica Acta.) Further work on this complicated problem is in progress in order to take into account the concentration dependence of mobilities in the membrane system.

The electrical characteristics near resting state of nerve membranes has been the subject of experimental investigation by Dr. Franco Conti of the Institute of Physics, University of Genoa, Italy. Visits were exchanged between Dr. Conti and Dr. Vaidhyanathan.

5. PUBLICATIONS:

V. S. Vaidhyanathan, Conductance Behavior of Electrolyte Transport Across Bimolecular Lipid Films, J. Theor. Biol., 23, 232 (1969)

6. PAPERS AND SEMINARS PRESENTED: MEETINGS ATTENDED:

V. S. Vaidhyanathan presented a discussion on "Structure of Membranes", New York Heart Association

V. S. Vaidhyanathan attended the following meetings:
Sanibel Island Conference on Quantum Biology, 1/69

Biophysical Society Meetings, Los Angeles, 2/69

Lecture at University of Genoa, Genoa, Italy 6/69

Lecture at St. Joseph's College, Trichinopoly, India, 4/69

Five lectures at Institute of Physics, University of Genoa, Italy 7/69

Talk presented on "The Uncertainty Principle in Membrane Structure" at Biochemistry Club meeting 12/69

Lecture presented at Institute of Mathematical Sciences, Madras, India, 12/69

7. CONTRIBUTION TO UNIVERSITY TEACHING:

V. S. Vaidhyanathan taught:

Thermodynamics of Irreversible Process, Biophysics, spring, 1969

Coordinated Seminars, fall, 1969, Biophysics Department

Selected topics in Pharmaceutics Department.

V. S. Vaidhyanathan elected one fellow one meeting,
Sanibel Island Conference on Quantum Field Theory, 1/7
Bioanalytical Geochemistry, Amherst, Dec.
Lecture at University of Genoa, Genoa, Italy 6/17
Lecture at St. Georgia College, Fredericopoly, V. 11
Five Lectures on Inertial Confinement Physics, Summer,
Cannon, Italy 7/20
Talk presented on "The Uncertainty Principle in Vanno
Seminars on Hydrocarbons, Clair Morning 10:00
Lecture presented at Institute of Technology, Jacora
Bowser, Dubin, 12/80

7. CONTRIBUTION TO UNIVERSITY PROGRAMS

V. S. Vaidhyanathan Dolphin

Thermodynamics of Irreversible Fronts, Pumphydion
Spring, 1982

Coordinated Seminars, Fall, 1982, L. Pedigrew

Related Topics in Thermoanalytical Determinant

WORKING PARTY REPORT ON SYMBOLIC RELATIONAL SYSTEMS

1. DEFINITION OF FIELD OF INTEREST

This working party is concerned with the philosophical foundations, formal representation, and applied studies of the biological aspects of Symbolic Relational Systems.

2. FINANCIAL SUPPORT

NASA Grant NGR 33-015-016

NIH Grant GM16603

3. FACULTY AND OTHER PARTICIPANTS:

Jon Ray Hamann	Working Party Chairman, Assistant Professor, Faculty of Natural Sciences and Math (Biophysical Sciences)
Luigi M. Bianchi	Assistant Professor, Faculty of Natural Sciences and Math (Biophysical Sciences)
Mary Danielli	Adjunct Lecturer, Program in American Studies
Mac Hammond	Professor, Faculty of Arts and Letters (English) Master, Cassirer College (E)
Martin Kriegel	A.N. Whitehead Fellow Program in American Studies
Erwin M. Segal	Associate Professor, Faculty of Social Science and Administration (Psychology)
Consultants:	Robert Beckwith, York University
	C. A. Hilgartner, Rochester, N.Y.
Student Participant:	Richard Danielli

4. RESEARCH PROGRAM:

A brief summary of the progress of this working party is presented below. It is divided into two carefully related categories including the philosophical foundations of biology (I Relationalism) and the development of relational theories (II Relational Systems Formalisms).

It should be noted that considerable effort has been spent during this year and will continue into the coming year, to critically (re-) define and integrate the various sub-group interests in this working party and to evaluate their relevance to the overall objectives of the Center for Theoretical Biology

I. Relationalism

J. R. Hamann and L. M. Bianchi have prepared a brief introductory review of Relationalism together with an annotated bibliography of some explicit and implicit literature on Relational Systems Formalisms, especially in the Natural Sciences.

Together with M. Kriegel, L. M. Bianchi and J. R. Hamann have initiated a Program in Natural Philosophy as a special study in Relationalism.

J. R. Hamann and L. M. Bianchi have developed a Relational Philosophical Psychology, in particular, the aspects of a Personal Relationalism have been outlined.

II. Relational Systems Formalisms

As a study on the bio-psychological foundations of inference, L. M. Bianchi and J. R. Hamann have formally

characterized the problem of conservatism in subjective probability estimation.

On the Natural Systems Sciences, physics, chemistry and biology, considerable work has been completed by this working party. In physics, in particular, three problems have been investigated. J. R. Hamann and L. M. Bianchi have elucidated the relations among prior probabilistic decisions, the path probability method, optimal entropy inference, and statistical mechanics. L. M. Bianchi and J. R. Hamann have initiated the construction of a general formalism for classical temporal relational systems. Finally, J. R. Hamann has developed a unified (relational) probabilistic foundation underlying both the equilibrium and nonequilibrium aspects of the phenomenological level of the theory of quantum fluids. The relevance of this work to the study of biological order and superconductivity in biosystems is now being explicated. In chemistry, R, Danielli has been involved in a study of the temporal organization of molecules and an algebraic analysis of the periodic table. In the study of biosystems explicitly, five problems have been investigated. L.M. Bianchi and J. R. Hamann have laid the relational basis for hierarchical theory of biosystems. L. M. Bianchi and J. R. Hamann have also applied the relational formalism to multicomponent biosystems, specifically demonstrating the interrelation between statistico-mechanical and stochastic theories or models. J. R. Hamann and L. M. Bianchi have given a hierarchical explication of the relational nature of irreversibility. L. M. Bianchi and J. R. Hamann have studied the

evolutionary origin of life in terms of considerations of necessary and (possibly) sufficient conditions as well as a model for their realization. Finally, J. R. Hamann and L. M. Bianchi in the study of symbolic relational systems, have developed a multilevel approach to the central nervous system.

In the Anthroposystems Sciences, psychological, anthropological and sociological studies have been performed. J. R. Hamann has investigated the biopsychological meaning of hierarchical control and continuability in a study of the foundations of psychosystems theories. M. Danielli has studied the geomantic function of the tombs in Imerina, Madagascar, and the relational nature of ritual. J. R. Hamann has analyzed the foundations of democratic decision-making as the first of a series of studies on socio-political systems.

In the Humanities, J. R. Hamann and L. M. Bianchi have developed a (relational) hierarchical theory of language. This work is being continued by E. Segal.

In the Arts, the pre-theoretical foundations of Art as a Symbolic Relational System have been analyzed by J.R. Hamann.

5. PUBLICATIONS:

J. R. Hamann and L. M. Bianchi, "A Note on the Relations among Prior Probabilitstic Decisions, the path Probability Method, Optimal Entropy Inference, and Statistical Mechanics", Progr. Theor. Phys. 42, 982 (1969)

6. PAPERS AND SEMINARS PRESENTED: MEETINGS ATTENDED

L.M. Bianchi and J. R. Hamann paper on "Relational Hierarchies in Biosystem Theories" presented at the Symposium on Mathematical Theories in the Life Sciences, Kingston, Ontario, June, 1969

L. M. Bianchi papers presented at the following meetings:
The Biophysical Society Annual Meeting, Los Angeles, March, 1969;
Symposium on Mathematical Theories in the Life Sciences, Kingston, Ontario, June, 1969
and attended
Conference on Formal Theories of information, Buffalo, N.Y., June, 1969;
Meeting of the Society for Natural Philosophy, Ann Arbor, Michigan, November, 1969

L. M. Bianchi, J.R. Hamann and R. Danielli participated in the Summer Colloquium in Theoretical Biology, Fort Collins, Colorado, August 1969.

7 CONTRIBUTIONS TO UNIVERSITY TEACHING:

As part of the contribution of members of this Working Party to University teaching, the following educational problems have generated a foundation for general relational synthesis . They have also developed specific methodology for relational teaching. and have organized a University-wide mechanism for independent study. J. R. Hamann and L. M. Bianchi have studied the evolution of meaning via symbol-to-symbol relations as an educational experiment. They have founded a Peripatetic College as a new and contrasting approach to higher education.

L. M. Bianchi - FS 119 "Experiential Approaches to Science.
- COE 405, "The Divided Man"

L.M. Bianchi and J.R. Hamann - NSM 470, "Natural Science and Mathematics

M. Danielli-Communications College (with J.F. Danielli), "Future of Man".

M. Danielli - Communications College, "The Mandala, Madagascar and Modern Times".

J. R. Hamann - FS 141, "Science: Order and Disorder"
- COE 101, "Symbolic Form - Linguistics"

Mac Hammond - COE 101 Symbolic Form - Linguistics.

E. M. Segal - COE 101, Symbolic Form-Linguistics.

8. MISCELLANEOUS ACTIVITIES:

M. Danielli, "The Quest", a poetic triologue (Mitre Press, London, 1969)

WORKING PARTY ON
SYSTEMS THEORY AND RELATIONAL BIOLOGY

1. DEFINITION OF FIELD OF INTEREST:

The major problems of the working party are:

1. To characterize the functional organization of biological systems, with particular reference to their regulatory and control aspects.

2. To relate the functional organization of biological systems to their structure.

3. To integrate the functional organization of biological systems at their several different levels of organization.

4. To develop, where necessary, the mathematical tools necessary for the investigation of the biological problems; these have included variational methods (for optimal structure and optimal controls), stability theory, theory of categories, theory of automata.

2. FINANCIAL SUPPORT:

At present, the program of this working party is supported entirely by the Center and by NGR 33-015-016. We have submitted one proposal on Relational Biology to NIH and another, on Morphogenesis in Biological Systems, is in the process of preparation.

3. FACULTY AND OTHER PARTICIPANTS:

Robert Rosen — Chairman,
Assistant Director, Center for Theoretical Biology,
Departments of Mathematics and Biophysics

George Blakley	Associate Professor Faculty of Natural Science and Mathematics (Mathematics)
James F. Danielli	Professor, School of Pharmacy (Center for Theoretical Biology)
Richard Gordon	Research Assistant, Center for Theoretical Biology
H. R. Martens	Associate Professor Faculty of Engineering and Applied Sciences (Electrical Engineering)
John Myhill	Professor Faculty of Natural Science and Mathematics (Mathematics)

Visiting Professor:

Otto Rössler	Visiting Fellow University of Tübingen, Germany

Consultants:

Nicholas Findler	Professor, Faculty of Engineering and Applied Sciences (Computer Science)
Narendra Goel	Assistant Professor, Department of Physics and Astronomy University of Rochester, N.Y.
K. Nicholas Leibovic	Associate Professor School of Medicine (Biophysical Sciences)
Martynas Ycas	Professor, Upstate Medical Center Syracuse, N.Y.

In addition, we hope to undertake effective collaboration with Dr. L. von Bertalanffy and Dr. C. H. Waddington when appropriate.

4. RESEARCH PROGRAM:

A. In addition to the ongoing work described in previous issues of the Annual Report, we have begun a study of self-organization and self-assembly as it manifests itself at a number of different biological (and physical) levels. There are numerous discussions of self-organization in the "cybernetic" literature, particularly with reference to learning and the organization of the central nervous system. This material is primarily of a philosophical nature. There are, however, three concrete areas in biology which exhibit behavior which may be called "self-organizing", and which are sufficiently well characterized so that a detailed study of each may be made, which may throw light on the general problem of self-organization. They are:

1. Spontaneous folding of polypeptide chains.
2. Spontaneous assembly of active virus from subunits.
3. "Sorting out" of mixed populations of embryonic cells.

Each of these situations shares the following properties: (1) they are locally motile, so that a variety of neighboring configuations can be explored; (2) there is at hand a measure of "energy" or "free energy", which determines the relative favorability of particular configurations. For a variety of reasons we have been specially concerned with sorting out, with a particular eye toward determining the role played by this process in natural morphogenesis. Our progress has been encouraging; we hope to combine this work with other morphogenetic mechanisms to get insight into the

dynamical aspects of the development process, one of the most important (and carefully controlled) of all biodynamical processes.

To explore the morphogenetic capabilities of self-assembling systems, we have studied a somewhat simplified two-dimensional model, which will be described in the next section. Our objectives have been: (a) to determine what configurations of cells actually minimize the surface free energy for a particular choice of adhesive interactions and motility rules, and (b) to determine whether histologically interesting configurations can be achieved and/or maintained with an appropriate choice of cell interactions and motility; and if so, to specify the limits within which such a choice is possible. For this latter purpose, both positive and negative results are of interest; if a histological structure can be achieved using only these minimal postulates of differential adhesiveness and motility, then it becomes plausible that only these postulated factors are operative in producing the structure. On the other hand, if such a structure cannot be produced and maintained, this will indicate that other morphogenetic factors must be involved; e.g. directional anisotropy of cell adhesions, cell interactions which require more than nearest neighbor type, elaboration of extra cellular matrices, differential cell multiplication and death, changes of cell properties in time, etc. In addition, we have found that the study of such a simplified model system is a great aid in clarifying and sharpening thinking in this field. In general, the

prototype for all dynamical discussions is in the familiar description of the dynamics of the system of Newtonian particles, and all discussions of dynamical activity of systems of whatever kind, are patterned on this model. It will be helpful to see how our study of self-assembly follows this pattern.

The discussion of dynamics resolves itself into two parts. First of all, to appropriately describe what we shall mean by an instantaneous state of the system of which we are interested, and second, to describe the manner in which the states change in time as a function of the forces or stresses applied to the system. In Newtonian mechanics, the instantaneous states are specified by giving three coordinates of position and three coordinates of momentum to each particle of the system. In mechanics, this information is suitable to enable us to compute any other attribute of the state in question, such as its energy, etc. Kinetic problems are attacked by writing down the so-called equations of motion of the system. These equations describe the rate of change of the state variables as functions of the impressed forces acting on the system. In order to obtain kinetic information it is necessary to integrate the equations of motion and to specify an initial state. Each possible initial state then determines a trajectory in the space of states, a curve which describes the evolution of the system in time. It should be noted that the equations of motion are purely local descriptions, which tell us how we can move a given

initial state to an infinitely neighboring state in an infinitesimal time interval, and that full trajectories are obtained by piecing together all these little local pieces.

We are mainly interested in the stability properties of such systems. The equations of motion contour the space of states into stable and unstable regions. The stable points or equilibrium points in the simplest case set at the bottom of more or less deep valleys or wells, while the unstable points are at the tops of hills or on the sides.

In general, if we start a system out in any initial state, the trajectory of the system in the phase space will approach the nearest available stable region and ultimately stop there at the bottom of the well. In many important cases, it is possible to follow the evolution of these system trajectories by means of a numerically valued function on the space of states which achieves its minimum value at the bottom of the wells I have described. In physics, such a function plays the role of a potential, or a free energy, and the existence of such a function considerably simplifies the study of the dynamics of the system which possesses one.

Self-assembly is a dynamical process and thus is amenable to the kind of analysis we have just described. As we have noted, it is necessary first to decide what shall constitute a description of the instantaneous state of a population of basic units and then to describe how such a system can change state as a response to the stresses or forces imposed on the system. The idealized populations we shall consider are

two-dimensional square arrays or tesselations. For simlicity, we suppose that there are only two types of units or cells, which we can call black, denoted by b, and white, denoted by w. Our population consists of a fixed number of black cells and white cells, and we suppose that this number does not change in time. A specification of the state of such an array consists merely in stating whether a black cell or a white cell occupies an available square in the tesselation. Hence, if we number the available squares serially, an instantaneous state will consist of a linear sequence of b's and w's, assigning a color to each available square.

We noted that the equations of motion tell us how to go from a given instantaneous state to a neighboring instantaneous state. In physics, the states are specified numerically, so that it is obvious what a neighboring state should be. In our cell system, however, we must specify what the neighboring states are. One way of doing this is as follows: if P_o denotes an initial pattern or state, we shall say that the pattern P is an immediate neighbor of P_o, if P can be obtained from P_o by exchanging any or all of the white squares with one of their nearest neighbor black squares. We must now specify the forces or stresses acting on the system and see how these determine its kinetics. We do this in terms of adhesive properties of our idealized cells. Let us note that there are five different kinds of edges that can occur in our system; a black cell may abut with

another black cell on any side, or with a white, or with the environment, which is the boundary of the tesselation. Likewise, a white cell may abut with another white cell, a black cell, or with the environment. These kinds of edges may be denoted by bb, ww, bw, bw, we.

Let us associate definite numerical values with each of these edges, which represent a kind of bond energy. Given a pattern or state P, we can count the number of edges of each type in the pattern, multiply it by the numerical value of each type and add up all the resulting numbers. This gives a number denoted by E(P), which is a measure of the total energy of the state or pattern in question.

The equations of motion of the system are given implicitly by specifying an initial state P_o and requiring the system to move sequentially from P_o to the neighboring state P_1 of smallest E-value, from P_1 to the neighboring state P_2 of smallest E-value, etc. Thus, E plays the role of a potential, and such a system will ultimately arrive at the nearest available state of minimum E-value.

Now we can ask a variety of questions of our metaphor, which depend on the stability properties of the underlying, system. For instance, we can derive necessary and sufficient conditions which assure the existence of an unique state P to which the system will tend, whatever the initial state. The space of states in this case will be so contoured as to consist of only one well, with a unique state P at the bottom,and all other states at the sides. If these conditions are not satisfied, then the space of states is contoured

into two or more wells, separated by unstable ridges.

What do such results mean for cell sorting? In the former case, no matter what the initial pattern or configuration, the end point is the same. Knowing that this is the case, we can determine the end point by choosing any convenient initial configuration. Hence, the information obtained from a randomized cell population is the same, in this case as from any other cell configuration; for instance, from the intact embryo. In this case, and only in this case, cell sorting experiments give full information about real morphogenesis.

In all other cases, the choice of initial state is decisive. It many happen that the randomized population tends to the same final state as the configuration in the intact embryo, but this must be proved. Moreover, it will be possible to find initial configurations which do not tend to this final state, and in our metaphorical system at least, such initial states can be specified in detail. And there will be states at the tops of intervening ridges, which can go either way. This type of picture is closely related to the "epigenetic landscape" of Waddington.

Moreover, we can supplement our model in various ways, to discuss in detail the morphogenetic effects of other processes on cell sorting. For instance, we can increase the number of types of cells. We can arrange the cells on three-dimensional tesselations, in order to discuss the morphogenesis of such structures as tubules. We can introduce the effect of differential cell multiplication and

differential cell death. We can make the adhesive strengths (which we assumed constant) functions of time.

We can ask what algorithm using these various mechanisms are required in order to generate actual histological structures. It is already clear from preliminary work that the same structures can be generated in a variety of different ways. Having insight into the ways in which it is possible to generate particular structures, we can in individual cases design experiments to indicate the actual mechanism of morphogenesis in real differentiating systems. Our work in this area is just beginning, but it is already clear that a wide variety of useful insights can be obtained by a systematic development of this type of approach.

R. Rosen

B. 1. It has been assumed that cell motility and selective adhesion are sufficient mechanisms to allow cells to sort into distinct and separate tissues. We programmed computer simulations of cell sorting in two and three dimensions, using a lattice model in which neighboring unlike cells were allowed to exchange places. It turned out that such motility rules did not give clean-cut sorting out of a random mixture of cells. Thus the real motility rules must be of a special kind, whose nature is yet to be discovered. We speculate that the more adherent cell type acts as a liquid network within the less adherent type. This network would undergo contractions due to surface tension, but the exact course of events would depend on the resisting viscosity

of the cells. This is currently being explored both by calculations and by experiments on model systems consisting of viscous immiscible liquids.

2. Filamentous blue-green algae have single cells called heterocysts more or less evenly spaced along the chain of vegetative cells. The vegetative cells grow and divide. Heterocysts do not. When the distance between two consecutive heterocysts approximately doubles, one of the vegetative cells somewhere in the middle turns into a heterocyst. The process has a large stochastic component, because the spread in distances between heterocysts has at least a threefold variation, rather than twofold, which a deterministic model would predict. Thus we are faced with two major questions: a) what characterizes the vegetative cell in an interval which is chosen to become heterocyst? and b) how does that cell inhibit its nearest neighbor from also becoming heterocysts?

These questions are best answered by direct observation, and we now have an inverted microscope and time-lapse cinemicrography equipment on order, and am setting up a small laboratory. In the meantime analytical and computer analyses of a few models of this system are now being studied.

3. In collaboration with Professor Lewis Wolpert of the Middlesex Hospital Medical School, London, models for the establishment of polarity in Hydra are being developed. We now have a model based on active transport of a morphogenetic substance which exhibits "regulation" in that the

concentration gradient adjusts itself to the size of the hydra.

4. In collaboration with Professor Antone Jacobson, University of Texas, Austin, we have been attempting to analyze the movements of cells during formation of the neural plate in newt embryos. The analysis leads to a new one-dimensional theory for the organization of vertebrate eggs.

5. The vertebrate skull is composed of a number of nearly fused plates, which start development separately and then run into one another. Similar simpler patterns are seen on the shells of turtles. In collaboration with Professor C. H. Waddington we have begun a study of the formation and growth of such plates.

6. When a picture is taken with an electron microscope, it records the top, bottom, and middle of the object all superimposed. If the object is rotated a few times and more pictures taken, it is reasonable to suppose that information is now available for reconstructing its three-dimensional density in space. We have devised an algorithm for accomplishing this from such flat pictures, and am currently testing its effectiveness. The algorithm hay have applications for efficient image storage and transmission.

R. Gordon

C. Two series of working sessions have been performed together with Dr. Rosen. The first served to discuss dynamical systems with a time-behavior that can be considered analogous to biological evolution. Since the main problem involved is the transition between different hierarchic

levels of description, the possible role of optimality principles in selecting the proper behavioral aspect of a complicated system has been discussed. The results have been tentatively applied to a particular dynamical system consisting in total positive, simultaneous ordinary, first-order differential equations with conditionally constant coefficients, and a working manuscript has been prepared.

In a second series of sessions, the biological hypothesis of maximal substantial growth led, as a tertium comparationis, to a discussion of the general dependence of maximal substantial growth on (a) physico-chemical, (b) relational, and (c) optimal-design constraints. The combined approach seems to bear immediate consequences on cell theory. Implications on a general theory of 'chemical biologies' are possible. The co-operative work has been condensed in so far, two papers (Rössler, O., and R. Rosen, "Kinetic theory of maximal growth I and II," to be submitted for publication).

O. Rössler

5. PUBLICATIONS:

a) Robert Rosen

Monograph: "Optimality Principles in Biology", London: Butterworth and Co., Ltd., U.S. by Plenum Press.

"Discrete and Continuous Representations of Metabolic Models". Appeared in Quantitative Biology of Metabolism Proc. of Helgoland 3rd. International Symposium, A. Locker, ed. Springer-Verlag, 24-32, 1968-1969.

b) Richard Gordon

"On Monte Carlo Algebra", J. Appl. Prob., in press

"Saltation and Self-chromatograph of Sand", Proc. Royal Soc., London, Section A, in press, R. Gordon, J. B. Carmichael, and F. W. Isackson.

6. PAPERS AND SEMINARDS PRESENTED: MEETINGS ATTENDED:

During 1969 Robert Rosen was a participant in the Visiting Lectureship Program of the Society for Industrial and Applied Mathematics, lecturing in the field of Biomathematics and Mathematical Biology. Lectures were given at the following institutions in this program:

1/69 Boston College
3/69 Bowling Green State College (2)
4/69 Stevens Institute of Technology
4/69 Adelphi University

The following seminars were given:
3/69 Plattsburgh (SUNY)
5/69 Duke University
10/69 Case-Western Reserve University

Papers and talks presented at meetings (invited):

2/69 Biophysical Society, Los Angeles
3/69 Biomathematics Symposium, Houston
6/69 Biomathematics Symposium, Salk Institute

The following meetings were attended:
Robert Rosen:
8/69 International Biophysics Congress, Boston
11/69 American Society for Cell Biology, Detroit

Richard Gordon:

12/69 Phylogenesis and Morphogenesis in the Algae, N.Y. Academy of Science, New York City

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

Contributions to University teaching fall under the heading of the development and teaching of courses in the Biomathematics Program, and also lectures presented in various survey courses offered by the Department of Biophysical Sciences. The course notes used in place of text material in the courses taught on Dynamical Systems in Biology have been turned into textbook manuscripts, to be published by John

Wiley (Interscience). This will be a two-volume series, the first volume already in the hands of the publisher and scheduled to appear within 6 months.

Also to be included in this heading are sponsorships of Ph D. candidates. R. Rosen is on the committees for seven Biophysics students, two Mathematics students and one Engineering student.

8. MISCELLANEOUS ACTIVITIES.

The following activities were engaged in during the past year:

Robert Rosen

1. Assistant Directorship of the Center for Theoretical Biology.

2. The editor of a multi-volume textbook on Mathematical Biology for Academic Press.

3. Reviewing and refereeing of Manuscripts and Books for the following Journals and presses:

Zentralblatt für Mathematik
Journal of Theoretical Biology
Bulletin of Mathematical Biophysics
Biophysical Journal
Science
Quarterly Reviews of Biology
Wiley (Interscience)
Academic Press

4. Member of Faculty for Summer Colloquium in Theoretical Biology, Fort Collins, Colorado 7 and 8/69

Richard Gordon:

1. Refereed for the Journal of Applied Physics.

2. Member of Working Party, Summer Colloquium in Theoretical Biology, Fort Collins, Colorado, 8/69

3. Chairman of Theoretical Biology luncheon meetings.

ANNUAL REPORT FROM WORKING PARTY ON THEORETICAL PHARMACOLOGY

1. DEFINITION OF FIELD OF INTEREST:

Theoretical studies on drug-structure and action with the objective being the elucidation of theoretical methods for drug design and development.

2. FINANCIAL SUPPORT:

NASA Grant NGR 33-015-016

UHF Grant G-F-68-UB

3. FACULTY AND OTHER PARTICIPANTS:

J. on Ray Hamann	Working Party Chairman, Faculty of Natural Science and Mathematics (Biophysical Sciences
Luigi M. Bianchi	Assistant Professor, Faculty of Natural Science and Mathematics (Biophysical Sciences)
Wally Giordano	Physician, University Health Service
Consultant:	John F. Olsen New York University and Staten Island Commerical College
Student Participants	Arthur Hedley Bruce Peterson

4. RESEARCH PROGRAM:

I. Formalism

To achieve the objective of this program in theoretical pharmacology, we are constructing a hierarchical theory of pharmacological systems including atomic, molecular and biocomponent levels which are correlated with an

observational physiological level. Each of these levels is further minimally characterized by deterministic and probabilistic "particle" sublevels together with a deterministic "thermomechanical" sublevel. A brief summary of the progress during 1969 in the formal development of the indicated levels is as follows:

A. Atomic Level.

Considerable effort was expended at the atomic level in formulating an adequate basis for the molecular level theorization. In particular, J. R. Hamann and L. M. Bianchi have formalized the relations among prior probabilistic decisions, the path probability methods, optimal entropy inference and statistical mechanics. They have also initiated a program in the characterization of classical temporal relational systems. J. R. Hamann, in order to eventually develop a theory of biological organization as it applies in drug receptor studies, has constructed a unified (relational) probabilistic foundation underlying both the equilibrium and nonequilibrium aspects of the phenomonological level of the theory of quantum fluids.

B. Molecular level

At the deterministic particle sublevel of the molecular level, J.F. Olsen has studied the electronic structure of carbon suboxide and m-phenylenedicabene and m-phenylenedinitrene. This work as well as other small-molecule quantum chemical (CNDO/2) calculations was intended to

further develop the potential of the methods for application to drugs.

At the probabilistic particle sublevel, J. R. Hamann and L. M. Bianchi, in conjunction with M. Pincus from Brooklyn Polytech are developing a numerical method for resolving the optimal entropy problem.

Studies at the thermomechanical sublevel have taken the form of the development of a theory of "microthermomechanics" by J. R. Hamann and W. Giordano. In particular this work has led to an explication of the concept of "electronegativity".

C. Biocomponent level

Work at the deterministic particle sublevel of the biocomponent level consisted of quantum chemical (XHMO) calculations by B. Peterson, A. Hedley and J. R. Hamann. These calculations have again been confined to the cholinergic system including acetylcholine, cholinamimetics, and cholinergic inhibitors and reactivators. The bulk of the work was confined to completion of the study of the pyridinium aldoxime reactivators.

J.R. Hamann and W. Giordano have begun a study of the probabilistic aspects of molecular decision theory at the probabilistic particle sublevel and the microthermomechanical aspects at the microthermomechanical sublevel.

II. Applications

On the basis of this hierarchical construction, the following specific areas of study constitute the principle concerns of this group.

First, the continued characterization of the cholinergic system was pursued by J. R. Hamann, B. Peterson, A. Hedley and J. F. Olsen, with the goal of developing a more adequate model of this particular drug-receptor interaction process. Secondly, an application to the studies of alcoholism and drug addiction was initiated with the formulation of a general theory of chemohabituation and an associated computer model by J.R. Hamann and W. Giordano.

5. PUBLICATIONS:

J. R. Hamann and L.M. Bianchi, "A Note on the Relations among Prior Probailistic Decisions, the Path Probability Method, Optimal Entropy Inference, and Statistical Mechanics" Progr., Theor. Phys., 42, 982 (1969)

J. F. Olsen and L. Burnell, "The Electronic Structure of Carbon Suboxide", J. Phys. Chem. 73, 2298 (1969)

J. F. Olsen, "m-phenyl-enedicarbene and m-phenylanedinctrine: Compounds having Quintent Groud States, Spectroscopy Letters 2(7) 217 (1969)

6. PAPERS AND SEMINARS PRESENTED: MEETINGS ATTENDED:

L.M. Bianchi and J.R. Hamann paper on "Relational Hierarchies in Biosystem Theories" presented at the Symposium on Mathematical Theories in the Life Sciences, Kingston Ontario, June, 1969.

L.M. Bianchi paper presented at the Biophysical Society Annual Meeting, Los Angeles, March, 1969.

L. M. Bianchi attended the Conference on Formal Theories of information, Buffalo, N.Y., June, 1969

L. M. Bianchi attended Meeting of the Society for Natural Philosophy, Ann Arbor, Michigan, November, 1969

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

L.M. Bianchi - FS 119 "Experiential Approaches to Science"
- COE 405 "The Divided Man"

L.M. Bianchi and J. R. Hamann -
NSM 470 "Natural Science and Mathematics"
NSM 101 "Symbolic Form - Linguistics"

J.R. Hamann - FS 141 "Science: Order and Disorder"
- COE 101 "Symbolic Form - Linguistics"

B. Peterson and A. Hedley - "Experimental Learning in Physics"
For the fall and spring semester we formed a group of about ten people interested in science. We obtained use of the physics laboratory and as an initial goal are learning to use the basic equipment. We plan for the course to evolve into a flexible laboratory allowing each student to follow his interests.

ANNUAL REPORT FROM WORKING PARTY ON QUANTUM BIOCHEMISTRY

1. DEFINITION OF FIELD OF INTEREST:

The general field of interest of this research effort is the application of quantum mechanical and related techniques to biologically important molecules (bio-molecules) and the interpretation and correlation of such calculations with regards to molecular stability and interactions. Such information will allow biological inferences to be made.

2. FINANCIAL SUPPORT:

Research activities of the group were supported mainly by the respective departments of the members. A particularly important role was played by the Department of Experimental Pathology of Roswell Park Memorial Institute. Further support was received from Roswell Park Memorial Institute through Graduate School training NIH Grant No. CA 5016-12.

Additional support was received from NIH Grant No. 213002 through SUNY Computer Center, in the form of free computer time. The Center for Theoretical Biology supported the work of this group through its facilities and supporting personnel, as well as through NASA Grant No. 33-015-016

3. FACULTY AND OTHER PARTICIPANTS:

Robert Rein	Chairman, Research Professor of Biophysics and Principal Cancer Research Scientist, Department of Experimental Pathology and Division of Graduate School, Roswell Park Memorial Institute
James P. Harlos	Cancer Research Scientist Department of Experimental Pathology Roswell Park Memorial Institute
Mordechai Kleiner	Cancer Research Scientist Department of Experimental Pathology Roswell Park Memorial Institute

Consultants:

Frank E. Harris	Professor of Physics University of Utah, Salt Lake City
Michael Pollak	Professor of Physics University of California, Riverside

Student Participants:

George Pack	Biophysics
James Rabinowitz	Physics
Marc Rendell	Summer fellow
V. Renugopalakrishnan	Biophysics
Robert Sayre	Biophysics

Computer Programmers:

Ehud Artzy
Dennis DeGweck
Joseph Lampl
Miss Hsin-yu Wang

4. RESEARCH PROGRAM:

The application of quantum theoretical methods to biological systems yields a rewarding amount of insight, on a molecular level about those systems. In view of this,

our research has a two-fold approach - the application of quantum mechanical calculations to biological systems and the development of new methods.

The latter approach is typified by our research concerning the evaluation of multicentered integrals. In order to develop a more sophisticated treatment of molecular energies or interactions for biological systems, one requires a rapid, accurate method for evaluating those integrals. Our investigations indicate that the use of single center expansions yields a formulation that fulfills those requirements.

The application of theoretical methods to biological systems is given by our studies on biological interactions. One of these studies is involved in the basic translation of the genetic code in protein synthesis. This study considers the primitive recognition process of an amino acid by its particular +-RNA. This we consider as a physical interaction between an amino acid and the nucleotide bases.

Another area of interest is the problem of thymine dimerization. This process involves the interaction of two thymine molecules, one of which is excited. The dimerization is experimentally observed in DNA as well as in solution. Our studies have been concerned with the calculation of the energies of two interacting thymines. We consider various geometrics as well as the cases where both molecules are in their ground states.

The problem of the tautomeric distribution of the

nucleotide bases is also being investigated. This problem is being examined as a function of intrinsic stability and also solvent stabilization. The intrinsic stabilities are being obtained by extensive calculations using both IEHT and CNDO/2 techniques. The solvent effects are obtained by a simple application of reaction field techniques.

Another area currently being investigated is the evaluation of antibody-hapten interactions using classical electrostatic reaction field techniques. Also, a preliminary study is being undertaken dealing with enzyme-substrate interaction where specific intermolecular interactions are being considered.

Research reports appended:

1. The Electronic Mechanism of Photodimerization of Thymine, R. Sayre, J. Harlos, R. Rein

2. Possible Interaction in the Primitive Translation Process, M. Rendell, J. Harlos, R. Rein

3. Solvent effects on the Stability of Tautomers in DNA Bases, M. Kleiner, J. Harlos, R. Rein

4. Theoretical Model for Hapten-Antibody Interaction, G. Pack, R. Rein.

5. Integral Approximation, J. Rabinowitz, R. Rein

5. PUBLICATIONS:

Pierre Claverie and Robert Rein, "Theory of Intermolecular Interactions: The Long Range Terms in the Dipole-dipole, Monopoles-dipole and Monopoles-Bond Polarizabilities Approximations", International Journal of Quantum Chemistry, Vol. III, 5, 537-551 (1969)

Robert Rein, Narendra S. Goel, Nobuo Fukuda, "Studies on the Calculation of Stacking Energies in DNA", Annals, N.Y. Academy Science, 153, 805 (1969)

J. Manassen and Robert Rein, "The Reactive Intermediates in Acetylene Polymerization. Results of Quantum Chemical Calculations on Change Delocalization and its Consequences", J. Polymer Sciences, in press.

Robert Rein, George Clarke, Frank E. Harris, "Iterative Extended Huckel Studies of Electronic Structure with Application to Heterocyclic Compounds", Proc. Israeli Acad. of Sciences, in press.

Robert Rein, Marc Rendell and J. P. Harlos, "Possible Interactions in the Primitive Translation Process", Proceedings Symposium on Quantum Biology, Springer Verlag, Berlin, in press.

Robert Sayre, J. P. Harlos and Robert Rein, "The Photodimerization of Thymine", ibid, in press.

Frank E. Harris, J. P. Harlos and Robert Rein, "Analytical Evolution of Multicenter Integrals", Journal American Chemical Society, in process of publication.

6. PAPERS AND SEMINARS PRESENTED: MEETINGS ATTENDED:

Robert Rein presented invited papers, "The Photodimerization of Thymine" by R. Sayre, J. P. Harlos, and R. Rein; and "Possible Interactions in the Primitive Translation Process" by R. Rein, M. Rendell and J. P. Harlos, at the Symposium on Quantum Biology, Seattle Washington, October 20-23, 1969.

R. Rein presented invited paper, "Interactions in the Amino Acid - RNA Recognition Process" at the Symposium on Biological Interaction, Brooklyn, N.Y., October, 1969.

R. Rein presented invited paper, "IEHT calculations of Heterocyclic Molecules" by R. Rein, F. E. Harris, and G. A. Charkes at Symposium on Quantum Aspects of Heterocyclic Molecules, Jerusalem, Spring, 1969.

Robert Rein presented the following seminars:

1. Weismann Institute of Science, Rehoboth, Israel

2. Soreg Research Center, Ybne, Israel

3. Argonne National Laboratory, Argonne, Illinois

J. P. Harlos presented a paper , "The Mechanism of the Thymine Dimerization Process" at the Third International Biophysics of the IUPAB, Boston, Massachusetts, August-September, 1969.

Robert Sayre presented a paper, "Theoretical Considerations on Pyrimidine Photodimerization", at the Northeast Photobiology Group, Ithaca, N.Y., May, 1969.

M. Pollak presented a paper, "The Energetics of the Thymine Photodimerization" by R. Rein, R. Sayre, J. Smith, J. P. Harlos and M. Pollak, at the 13th Annual Meeting of the Biophysical Society, San Francisco, California, February, 1969

7. CONTRIBUTION TO UNIVERSITY TEACHING:

R. Rein	Biophysics Research 696
R. Rein	Quantum Biophysics 548
R. Rein	Supervision of Dissertation Research
J. Rabinowitz	Physics 107

8. MISCELLANEOUS ACTIVITIES:

Robert Rein is member of Academic Committee of the Center for Theoretical Biology.

He presented a course of twenty lectures on selected topics in Quantum Biochemistry at Technion, Israeli Institute of Technology, Haifa, Israel.

He is also referee for Journal of Theoretical Biology, the Biophysical Journal and the Journal of American Chemical Society.

APPENDIX

The Electronic Mechanism of Photodimerization of Thymine

R. Sayre, J. Harlos, R. Rein

This report is a continuation of a project begun and reported initially in last year's Annual Report.

The studies reported below are published in detail in Sayre, Harlos and Rein, "Theoretical Study of Photodimerization of Thymine", in Proceedings of the Battelle Memorial Institute Symposium on Quantum Biology, in press.

The energies of interaction between ground state and excited state thymine molecules have been studied. Four terms have been included in the total energy of interaction: 1) a perturbation treatment involving the pi electron systems 2) the electrostatic interactions between both molecules, 3) the sigma dispersion interaction energy, and 4) the sigma polarization interaction energy. These terms have been calculated and compared for ground-ground state interactions and ground-excited state interactions.

Four idealized isomers representing the excited state thymine dimer were studied. Weak stabilization of the ground state thymine complexes was observed; however, a repulsive barrier was shown to be present which prevented possible thermal dimerization from occurring. Upon excitation of one of the monomers, attractive stabilizing interaction occurred. The results indicate that the cis

(head to head) isomer forms the most energetically stable excited state dimer and the cis (head to tail) the least. See Figures 1 and 2 below for a comparison of the total interactions between the cis (head to head) isomer in the ground state and in the excited state configuration.

A refinement of these studies indicates that for the cis (head to head) isomer a 20 degree rotation about the 5-6 double bond increases the stabilization in both the ground and excited states. These results tend to indicate that as the initial geometries more nearly approximate those of the final ground state dimer, the greater the stabilization. Such results would be consistent with a dimerization process that requires only little nuclear rearrangment. Such processes could originate through either a singlet or triplet state. These theoretical predictions agree with the experimental finding that the formation of this isomer may proceed through either singlet or triplet states.

Finally there is shown to be a barrier to simply twisting and compressing the stacked adjacent thymines in double stranded DNA to form the ground state dimer. These results indicate that some, perhaps more complicated reaction pathway is needed to explain the formation of the cis (head to head) dimer and to obtain the appropriate nuclear geometry for dimerization in DNA.

FIGURE 1

Total Ground State Interaction
Cis (head-to-head) Configuration

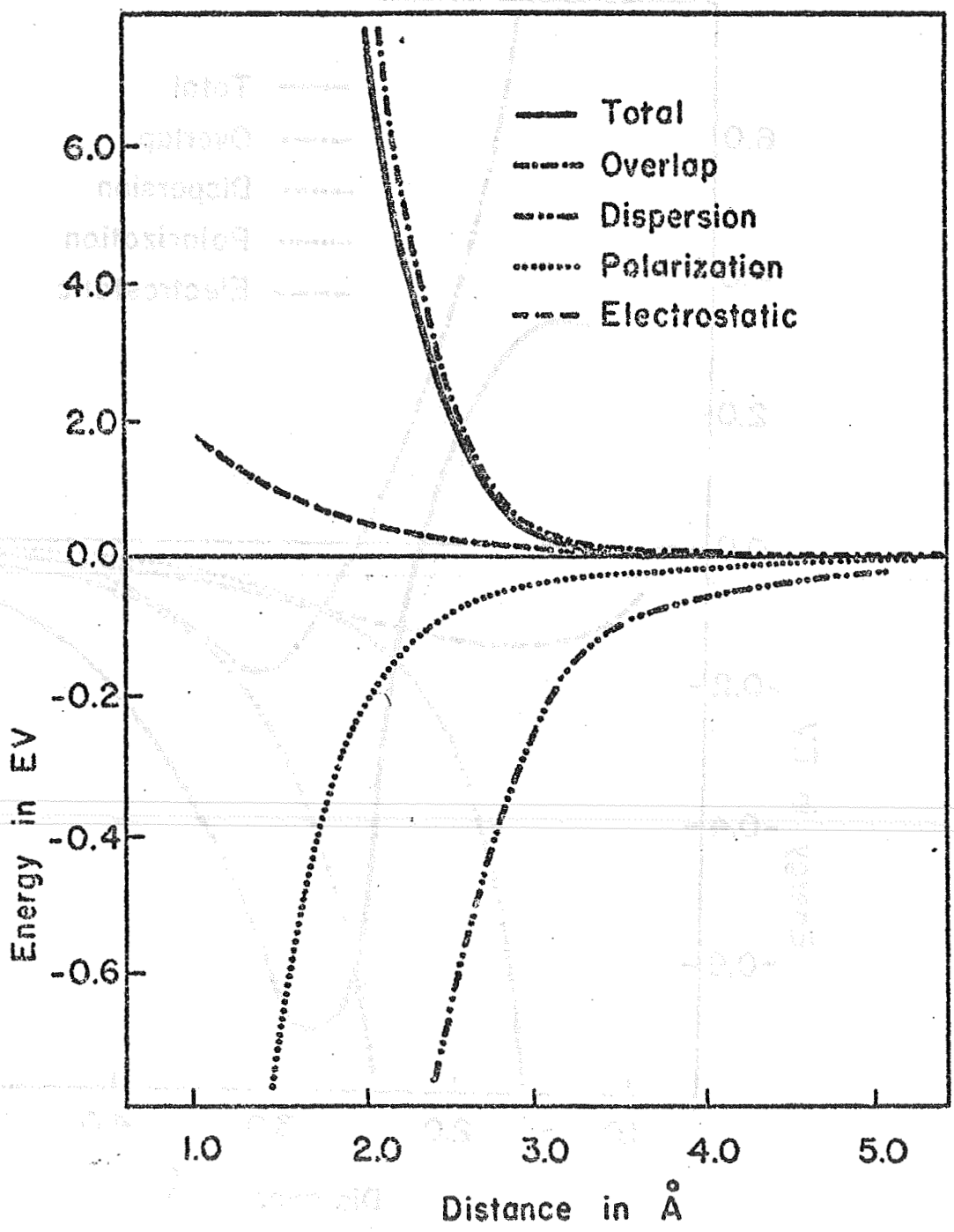
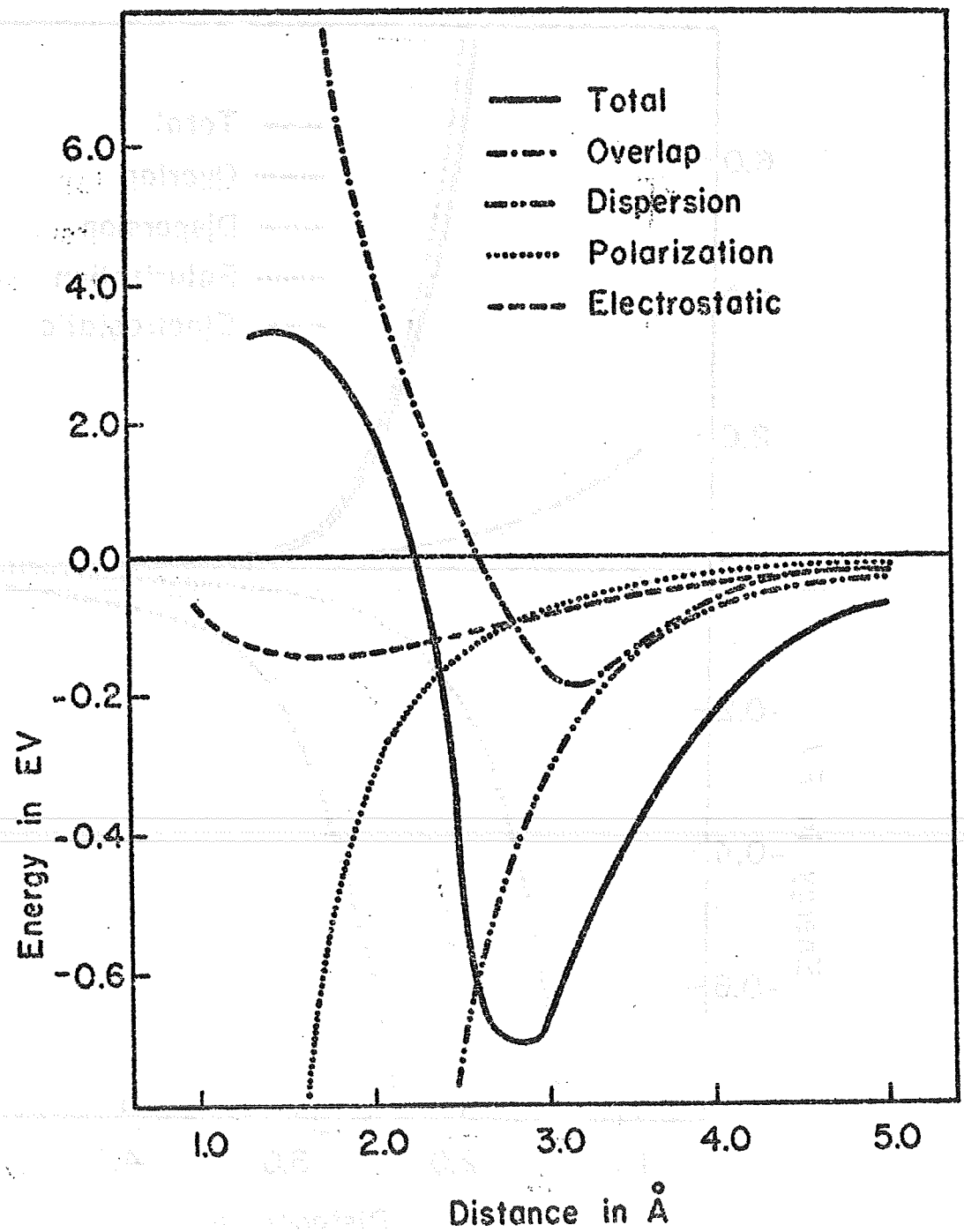


FIGURE 2

Total Excited State Interaction
Cis (head-to-head) Configuration



Possible Interaction in the Primitive Translation Process

M. Rendell, J. Harlos, R. Rein

This study is concerned with the processes involved in the recognition of an amino acid by a particular t-RNA. In the contemporary process the recognition requires not only the amino acid and its t-RNA, but also an enzyme and ATP. While the detailed involvement of each of the components is incompletely known, the currently popular view of this mechanism attributes both the recognition of the amino acid and the required t-RNA to the enzyme.

The requirements of such a mechanism, however, are rather stringent with regard to the evolution of the genetic code, its transciption and translation. These requirements include the development of a highly sophisticated enzyme capable of recognizing an amino acid and it's particular t-RNA. While it is possible that such a mechanism is utilized in contemporary protein synthesis, it is difficult to envision the spontaneous development of such an enzyme in the primitive protein synthesis process. It appears more realistic to postulate an existing recognition process.

This primitive process, first proposed by Orgel, involves only the amino acid and an RNA codon. The recognition process may then involve the physical forces, of a non(covalent)bonding nature, between the RNA, or part of the RNA, and the amino acid.

In order to ascertain the reasonableness of the hypothesis, we propose to examine the interactions between various amino acids and the RNA bases. In keeping with our earlier studies of biological interactions, we divided these forces into electrostatic, polarization and dispersion forces. The general method consists of scanning the configuration space of the amino acid and base(s) and calculating the electrostatic interactions. This provides a crude map of the interaction energy surface. At those points where an electrostatic interaction minimum has been located, the energies are refined by including the dispersion and polarization energies. Thus, we obtain the interaction energy of the most stable configuration.

In this preliminary study, we limited the calculation to a simple amino acid (glycine) interacting with the nucleotide bases one at a time. Furthermore, constraints were applied to the region scanned, limiting it to the plane containing the base. Also the calculations were performed in a rigid molecule approximation. The required charge distributions were obtained using The Interactive Extended Huckel Theory method.

The results of these calculations, however, are extremely interesting and suggestive. The electrostatic energy is the largest single contribution to the total interaction energy. The relative order of the interaction energies of glycine with the nucleotide bases is then, C>G>U>A. This order also reflects the ability of the

6-oxygen to direct the relative orientation and interaction energy by its net atom charge. The addition of the dispersion and polarization energies then results in the following order, C>G>A>U. It is of interest to note that the inclusion of the second order dispersion and polarization energies causes are reversal in the relative stabilities of the complexes utilizing adenine and uracil. Further more, the interaction with Cytosine is extremely stable, in fact some 13 Kcal more stable than Guanine, the next most stable complex. The total energies involved are C (-41.4), G (-28.5), A (27.2), U (22.1).

These results are extremely interesting and lend support to the proposed mechanism. The fact that such interactions have not been experimentally observed to date is not entirely unexplicable. The experimental situations used to examine those interactions have utilized protonic solvents capable of strong interactions with the nucleotide bases and amino acids themselves. The nature of the forces involved suggest that a low dielectric media might be more useful for the characterization of these complexes.

This study is now being extended to other amino acids and also to include neighboring nucleotide bases in RNA.

Solvent Effects on the Stability of Tautomers in DNA Bases

M. Kleiner, J. Harlos, R. Rein

Replication of nucleic acids is considered to occur by building up of a new chain on to an existing molecule. In this process adenine pairs with thymine, guanine with cytosine and vice versa.

Spontaneous mutation happens when a "mistake" is made in the DNA base sequence, if an incorrect base is incorporated into the forming chain. Watson and Crick (1) have suggested that this might occur when one of the molecules reacts in an alternative tautomer form. Knowledge of the intrinsic stabilizers of the relevant forms which is related to their equilibrium distribution is therefore pertinent for possible correlation with spontaneous mutation. Since it is experimentally observed that DNA exchanges rapidly its protons involved in hydrogen bonds, it is necessary to include explicitly the solvent media in any investigation of tautomeric stability.

We investigate the possible influence of solvent effects and how it modifies the intrinsic energy gaps, estimated by the IEHT (previously described) and Pople's CNDO/2 procedures. To estimate the medium effect, a reaction field technique is utilized. According to this method of calculation, the medium is represented by a continuous dielectric model, while the molecule is represented by a dipole inside the dielectric cavity. Since solvent stabilization is proportional to the square of.

the dipole moment, the medium favors a form that is highly polarized, This effect amounts to about 10 Kcal/mole for a dipole moment of ∿15D, in a cavity of 5 Å radius. In lactam $\rightleftarrows$lactim or (normal) amino $\rightleftarrows$(rare) amino tautomerism, the energy gap is at least 25 Kcal/mole for rather similar values of dipoles, and therefore the medium can't completely reverse the order of natural stability, but only (slightly) modify it, i.e. the solvent exerts a leveling effect on the normal and rare forms in tautomerism in the iminazole moiety. However, in purine and adenine, the intrinsically slightly preferred 9(H) forms are predicted to shift to the medium favored 7(H) forms, in dielectrics higher than 10. The present study of solvent effects in the ground state is extended to the first excited state.

References

1. J.D. Watson, F.H.C. Crick, Nature 171, 964 (1963)

2. R. Rein, Nobuo Fukuda, Htain Win, F. A. Clarke, F. Harris, J. Chemi. Phys. 45, 4743 (1966)

Theoretical Model for Antibody-Hapten Interaction.

G. Pack, R. Rein

The mechanism by which an antibody is produced and therefore the manner in which it acquires its specificity is as yet unknown. By studying the energetics of cross-reactions of an antibody with a group of chemically related haptens, some insight into the essentials of the specificity may be gained.

Pressman has measured the equilibrium constants for such a group, permitting a calculation of the free energy of interaction. By a consideration of the forces involved, subject to the constraints of structure and free energy, the physical reality may become more clear.

The forces relevant to the system considered (positively charged hapten, negative antibody site), are assumed to be the following. An electrostatic bond is caused by the coulombic attraction of the oppositely charged species. This can be calculated from Coulomb's Law, using point charge distributions from molecular orbital theory and an effective dielectric constant for the medium. Another force to be considered is the reaction field energy of the dipole created by these charges. A point dipole is used for the calculations. It is assumed to be polarizable, and to be contained in a spherical cavity whose dielectric constant differs from the bulk dielectric constant of the surroundings.

The solvation of the hapten after bond breaking is also considered. The first step of this process is the creation of a cavity in the aqueous phase. Since the intermolecular forces are position dependent, a change in free energy is associated with a rearrangement of the solvent molecules. The other solvation contribution to the free energy is the restoration of the charge which was removed from the hapten when the electrostatic bond was broken. This is calculated using the Born charging process for a uniform conducting sphere.

The effect of translational entropy is taken into account in the individual terms.

Integral Approximation

J. Rabinowitz, R. Rein

Any rigorous treatment of the electronic structure of molecules in a molecular orbital scheme depends on the evaluation of integrals of the type

$$\iint \psi_a(1)\ \psi_b(2)\ \frac{1}{r_{12}}\ \psi_c(2)\ \psi_c(2)\ d\tau_1 d\tau_2$$

(where the numbers 1 and 2 indicate the set of electronic coordinates the integration is carried out over and the letters a, b, c, d indicate the center of the spherical polar coordinate system ψ is described in.) For both physical and computational reasons we expect that large (certainly molecules of biological interest) molecules will be best treated when the ψ's are Slater orbitals i.e.

$$\Psi = N\rho^{(n-1)}\ e^{-\delta r} Y_{\ell m}(\theta,\phi)$$

where N is a normalization constant, δ is a determined parameter, $Y_{\ell m}$ is a spherical harmonic, and n, ℓ and m are the principle, Azemuthal and magnetic quantum numbers. The time required for the large number of these integrals necessary for even the smallest problems of biological interest would make a rigorous calculation impossible. Therefore a well understood mathematical approximation to these integrals is desirable.

We are treating these integrals by a scheme in which we note the integrals look like the integrals for the

the electrostatic energy of two charge distribution

$$\int \frac{\rho_{ab}^{(1)}\ \rho_{cd}^{(2)}}{r_{12}}\ d\tau_1 d\tau_2.$$

We also note that for Slater orbitals if a = b and c = d, the integrals are computationally simple and are in general a combination of a small number of overlap integrals. With this foresight the two center charge distributions are then expanded in a linear combination of one center charge distributions.

$$\rho_{ab}(1) = \sum_i C_i\ \rho_a{}^i\ (1) + \sum_i C_i\ \rho_b{}^i(1).$$

Now our integrals are just sums of integrals of the type which as previously noted, are simple. This expansion is then terminated after four terms, one term of each parity about each center. In previous work it was shown that an expansion of this type could be obtained by expanding S.O.'s about one center in terms of S.O.'s about the other center and that reasonable results could be obtained after the four term truncation. This leads to $\rho_a{}^i$ of the form

$$e^{-\delta i r}\ r^{(n_1+n_2-1)-1}\ Y_{\ell_1 m_1}\ Y_{\ell_2 m_2}$$

where

$$\delta_i = \delta_{i_1} + \delta_{i_2}.$$

We are also considering as ρ_a^i suitably chosen individual Slater orbitals. This is a special case ... not always different than the first choice. It is always computationally simpler.

After truncating the expansion we are free to select the C_i"s and also adjust the δ in any way. Indeed these δ's not forced to have any relationship to have any relationship to the δ's in the Hartree-Fock problem itself, and are varied to try to get the best possible integrals. The type of variation we use is to minimize the absolute square of the difference of the approximated and the approximating function. We use a search technique in the eight-dimensional (C, δ) space and project into the four dimensional manifold where the function is always minimum with respect to variations in the C's. It has been found that also constraining the lowest non-zero order, electrostatic multipole moment to be the same gives consistently better integrals and is computationally faster.

Our problems are versatile enough that we can change our choices of the ρ_a^i's to see which choice gives consistently better results both for ρ_a^i as a pair of S.O.'s and a single S.O. However,in a Hartree-Fock scheme this would be an added computational step and therefore a disadvantage. At present much work is being done to find the optimal choice of the ρ_a^i's for each possible ρ_{ab} that might be needed in a limited basic set calculation. It appears that using S.O. pairs give better

results than using individual S.O.'s. At present this is not strong enough evidence to reject the choice of individual S.O.'s as our approximating functions, since a scheme using them would be computationally more simple.

The existing programs are also being expanded to allow us to also constrain higher multipole moments to remain constant. This again will be more complicated but faster computationally and from preliminary calculations should give better results.

ANNUAL REPORT FROM WORKING PARTY ON MEMBRANES AND SURFACES

1. DEFINITION OF FIELD OF INTEREST:

Study of cell membranes and of the physics and chemistry of related systems.

2. FINANCIAL SUPPORT:

NASA Grants NSG 501 and NGR 33-015-016

3. FACULTY AND OTHER PARTICIPANTS:

James F. Danielli	Chairman, Professor, School of Pharmacy Director, Center for Theoretical Biology
Charles Akers	Roswell Park Memorial Institute
David A. Cadenhead	Associate Professor, School of Pharmacy (Biochemical Pharmacology)
Robert Good	Professor, Faculty of Engineering and Applied Sciences (Chemical Engineering)
Johannes Hoogeveen	Veterans Administration Hospital
Chan Jung	Veterans Administration Hospital
Harold Kimelberg	Roswell Park Memorial Institute
John Moran	Assistant Professor School of Medicine (Biochemistry)
Shinpei Ohki	Assistant Professor School of Pharmacy (Pharmaceutics)
D. G. Papahadjopoulos	Assistant Research Professor School of Medicine (Biochemistry)
Donald Parsons	Roswell Park Memorial Institute
Jagneswahr Saha	Roswell Park Memorial Institute
David J. Triggle	Professor School of Pharmacy (Biochemical Pharmacology)

Charles Wenner	Roswell Park Memorial Institute
Darold Wobschall	Assistant Professor School of Medicine (Biophysical Sciences)

Student participants:

Kenneth Jacobson
Joel Pursner
Edward Shapiro

4. RESEARCH PROGRAM:

This working party operated in the following sub-groups:

Synthetic Membranes	Convenor - James F. Danielli
Lipid Bilayers as Models of Cell Membranes	Convenor - Darold Wobschall
Monomolecular Films	Convenor - David Cadenhead
Receptor Structure, Function and Isolation	Convenor - David J. Triggle
Cell Membranes and Membrane Functions	Convenor - Charles Wenner

REPORT - Sub-group on LIPID BILAYERS AS MODELS OF CELL MEMBRANE

Convenor - Darold Wobschall

1. DEFINITION OF FIELD OF INTEREST:

This group is interested in the physico-chemical properties of lipid bilayer lipoprotein membranes as models of cell membranes with an emphasis on understanding the structural-function interrelationship.

2. FINCANCIAL SUPPORT:

Some support services were obtained via Center for Theoretical Biology and from NSG 501 and NGR 33-015-016. Individual grant support of experimental projects was obtained by members via their respective departments.

3. FACULTY AND OTHER PARTICIPANTS:

Johannes Hoogeveen	Veterans Administration Hospital
Kenneth Jacobson	Student (SUNY/B, Biophysics)
Chan Jung	Veterans Administration Hospital
Shinpei Ohki	Assistant Professor School of Pharmacy (Pharmaceutics)
D. G. Papahadjopoulos	Assistant Research Professor School of Medicine (Biochemistry)
Jagneswahr Saha	Roswell Park Memorial Institute
Edward Shapiro	Student (SUNY/B, Pharmaceutics)
Charles Wenner	Roswell Park Memorial Institute

4. RESEARCH PROGRAM:

Because this group was formed shortly before the end of the year, no cohesive program was planned or implemented. Most of the members of the group are primarily experimentalists and have participated in the Center for Theoretical Biology

discussions and meetings in order to better understand and interpret their own work. Several members of this group have cooperated in joint experimental projects in the past and have planned future joint efforts.

Studies of the stability of phospholipid membranes were made by S. Ohki. In order to elucidate the formation and the function of biological membranes (e.g. selective permeability, excitability and pinocytosis), it is relevant to study the molecular basis of stability and structure of artificial membranes.

Expressions of interlayer interaction for the lipid bilayer system were derived from the second order perturbation theory of intermolecular forces. As one of the factors of the stabilization energies of the lipid bilayers, the interlayer dispersion energy were estimated.

The molecular theory for dielectric polarizability as applied to the lipid bilayer model was then calculated and the thickness of lipid bilayers estimated. The possibility of the structural change of the lipid bilayer due to the change of environmental solutions was investigated in terms of the net charge of the polar groups. Finally the stability of a symmetrical lipid bilayer membrane was considered in terms of the net charge of polar groups and the degree of chelation of the polar groups with metal ions.

The results of this investigation will be published as a chapter in a book, "Physical Principles of Biological Membranes", F. M. Snell, ed., (Gorden and Breach, publishers).

5. PUBLICATIONS:

S. Ohki, "The Variation of the Direct Current Resistance of Lipid Bilayers", J. Coll. Inter. Sci. 30 413 (1969)

S. Ohki, "Properties of Lipid Bilayer Membranes; Determination of Membrane Thickness", J. Theor. Biol. 23, 158 (1969)

J. F. Danielli, A. Goldup and S. Ohki, "Review of Lipid Bilayers", in Recent Progress in Surface Sciences, Academic Press (in press)

7. CONTRIBUTIONS TO UNIVERSITY TEACHING:

The following gave University course in Biophysics and Biochemistry.

J. Hoogeveen	BPH 517
C. Jung	BPH 517/512
S. Ohki	BPH 517/589
D. Papahadjopoulos	BCH
C. Wenner	BCH
D. Wobschall	BPH 517/512/401/402/550
	ENG 470/453
	EAS 204

REPORT - Sub-group on MONOMOLECULAR FILMS

Convenor - David Cadenhead

1. DEFINITION OF FIELD OF INTEREST:

a. Characterization of monolayer properties (air-water interface) of various membrane lipid components and related molecules.

b. Studies of molecular interactions in mixed monomolecular films

c. Evaluation of film-substrate interactions

2. FINANCIAL SUPPORT:

Financial support during 1969 came from NASA NGR 33-015-016; State Grant in Aid 0603-02-050-68; and PHS National Heart Institute HE 12760-01

3. FACULTY AND OTHER PARTICIPANTS

Frank Tsien	Research Fellow, Chemistry
Chian Shan I	Graduate Student, Chemistry
Judith E. Csonka	Technician (terminated 1969)

4. RESEARCH PROGRAM:

a. Monolayer Characterization. Particular emphasis has been placed on ascertaining those molecular characteristics which establish the physical state of a film (gaseous, liquid-expanded, intermediate liquid-condensed, solid). Among the factors studied have been:the condensing effect of ether as opposed to ester alkane chain attachment to glycerol, chain length and branching and the behavior of rigid as opposed to flexible amphipathic molecules. Such studies have enabled us to specify that at (say) room temperature, only, 1,2-dipalmitoyl-3-lecithin and 1,2-dimyristoyl-3 cephalin

in their corresponding homologous series exhibit an isotherm possessing an intermediate region. Based on the failure of rigid amphipathic molecules to exhibit such a region an evaluation was made of the relative merits of the Langmuir and Kirkwood theories concerning the nature of this "phase". The increasing amount of evidence relating this phase in monolayers to liquid crystalline, bilayer and membrane lipid states justifies the effort made in this direction.

b. Molecular Interactions in Mixed Monolayers. While studies have been made primarily with systems using cholesterol as a condensing agent, non-cholesteric mixed films have also been studied. An evaluation of results based on mean molecular area and dipole plots has led us to two definite conclusions:

1. The postulation of "molecular complexes" at compositions corresponding to sharp inflections in molar plots is completely unjustified. Such inflections arise through phase changes in the state of the more expanded monolayer component.

2. In the systems studied by this group, a thermodynamic analysis reveals that the condensation process is exothermic and involves molecular interaction. "Space filling" as defined by Shah and Schulman may play a partial role. Present efforts are directed towards established improved experimental data and theoretical treatment, particularly with regard to gaseous films.

c. Film Substrate Interactions. Where interaction between the aliphatic chains of amphipathic molecules and aqueous substrates are possible, addition of various substrate additives produce enhanced interactions and expansion effects. Coupled with this, there appears to be a reduced ability of the polar groups to orient the substrate molecules.

When the film is condensed, only the polar group interaction is evident. Such studies have enabled us to evaluate the role of the substrate in establishing the state of a monolayer.

d. Theoretical Studies (Frank Tsien)

An attempt is being made to derive theoretical equations for long chain saturated acids in the region of low and intermediate spreading pressures (the gaseous and the liquid expanded states). The saturated acids are assumed to be rod-like. The attractive term thus derived will be dependent on the following quantitites: the number of carbon units in the chain, the degree of inclination of the rod-like acids with the air-water interface, and the dispersive interaction of the carbon-carbon units.

Auxilliary experimental data will be performed in these regions in supplement to the existing data. Intercorrelation between the experimental data and theory will shed light on all the above mentioned quantities. The different regions in the π-A curve of various saturated acids will give an account of the interdependence on the number of hydrocarbon units in the chains and their degree of inclination with the surface. Deuterated and protonated saturated acids will give a magnitude of the dispersive interaction of the carbon-carbon units and an indication on how far the theory will be valid.

e. Bacterial Lipids (Judith E. Csonka)

Initial investigations of the film properties of thermally resistant bacterial lipids clearly indicate the

feasibility of the study of such materials as insoluble monolayers at the air-water interface. Unfortunately, the unknown composition plus increasing film loss with increasing surface pressure prevent a precise definition of such systems at the molecular level. Provided a suitable separation of the various lipids can be carried out, an attempt will be made to relate the overall behavior with the surface properties. Particular attention will be paid to the saturated branched chain lipids. This work is being carried out in cooperation with Dr. W. Heinen of the Ames Research Center of N.A.S.A.

5. PUBLICATIONS:

D. A. Cadenhead, "Monomolecular Films at the Air-Water Interface: Some Practical Applications", Ind. and Eng. Chem. 61, 22 (1969)

D. A. Cadenhead, R. J. Demchak, "A New Representation of Condensation Effects in Mixed Monolayers. Part I. Films of Elaidic Acid and Cholesterol on Aqueous Glycerol Substrates", J. Colloid and Interface Sci. 30, 76 (1969)

D. A. Cadenhead and R. J. Demchak, "Observations and Implications of Glycerol-Mono-molecular Film Interactions", Biochem Biophys. Acta, 176, 849 (1969)

D. A. Cadenhead, "Monomolecular Films at Liquid-Air Interfaces" Chapter in Book, "Chemistry and Physics of Interfaces", Volume II, 1969, published by the American Chemical Society.

D. A. Cadenhead, Monolayers of Synthetic Phospholipids", Chapter in book, "Recent Progress in Surface Science", Vol. III, 1969.

D. A. Cadenhead, "Membrane Related States of Monomolecular Films" and "Monolayer-Substrate Interactions", J. Amer. Oil Chem., (1969) In press. (Notes on subjects)

D. A. Cadenhead, "Monomolecular Films", Hyomen (Surface) (in press.)

D. A. Cadenhead and Judith E. Csonka, "The Effects of Ethanol on Condensed and Expanded Monolayers at the Air-Water Interface", J. Colloid Interface Sci. in press.

6. PAPERS AND SEMINARS PRESENTED: MEETINGS ATTENDED:

D. A. Cadenhead invited member of discussion group, "International Membrane Workshop", American Oil Chemists Society, April, 1969.

D. A. Cadenhead presented a seminar, "Physical States of Membrane Lipids", Department of Chemistry, University of California, Santa Barbara, November, 1969

D. A. Cadenhead presented a seminar, "Cell Membrane Structure", Department of Zoology, University of California, Davis, 1969.

D. A. Cadenhead presented a seminar, "Monomolecular Films of Individual Membrane Components", Department of Chemistry, University of Northern Arizona, Flagstaff, November, 1969

D. A. Cadenhead presented a seminar "Some Applications of Monomolecular Film Studies", Ford Motor Company, Dearborn, Michigan, December, 1969.

7 CONTRIBUTIONS TO UNIVERSITY TEACHING:

D. A. Cadenhead	Chemistry 512 - for graduate students
D. A. Cadenhead	1969 Chairman of Education Committee of the American Chemical Society Division of Surface and Colloid Chemistry
Frank Tsien	Chemistry 101-102

REPORT - Sub-group on RECEPTOR STRUCTURE, FUNCTION AND ISOLATION

Convenor - D. J. Triggle

1. DEFINITION OF FIELD OF INTEREST:

The interactions of neurotransmitters (norepinephrine and acetylcholine) with their corresponding receptors and the relationship of this interaction to the subsequent physiological and biochemical responses: the regulatory properties of cell membranes: general considerations of the mechanisms by which small molecules affect the properties of macromolecules and macromolecular assemblages.

2. FINANCIAL SUPPORT:

NIH (GM 11603, HE 09336)

NASA (NGR 33-015-016)

United Health Foundation of Western New York

American Association of Colleges of Pharmacy (Undergraduate Research Award).

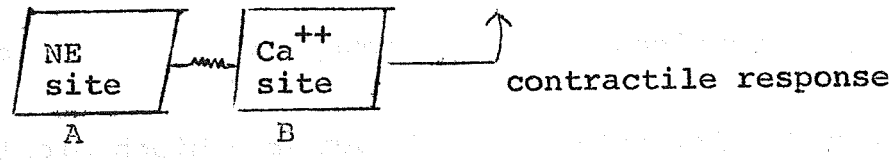
3. FACULTY AND OTHER PARTICIPANTS:

J.F. Moran	Assistant Professor, School of Medicine (Biochemistry)
V.C. Swamy	Assistant Professor, School of Pharmacy (Biochemical Pharmacology)
D. R. Garrison	Technician, Center for Theoretical Biology
Student Participants:	B. Avner - Biochemical Pharmacology
	R. Janis Biochemical Pharmacology
	K. Chang - Biochemical Pharmacology
	R.C. Deth - undergraduate

4. RESEARCH PROGRAM:

In continuation of work on the interaction of cholinergic ligands with the cholinergic receptor we have established the existence of a multiplicity of interacting binding sites at which activation or antagonism may be produced (Section 5 Ref.) These findings have important implications for the general interpretations of structure-activity data of ligands active in this system. Quite generally in this system we find that the recognition sites distinguish between polar and nonpolar ligand structures and that progressive increase in ligand nonpolarity causes progressive increase in antagonist activity.

In the adrenergic system we have devoted considerable effort to elucidating the nature of events initiated by the activator (norepinephrine) - receptor interaction. Our general approach is again through the use of irreversible antagonists. Our studies indicate that in the smooth muscle systems employed we must regard the adrenergic α-receptor as a "linked function" of an activator recognition site obligatorily coupled to a Ca^{++}- mobilization site,



and that activation of A automatically activates B and leads to response. Coupled with our previous studies on the quantitation of activator -α - receptor interactions (Mol. Pharmacol., 3, 15, 28 1967) it appears that the

activator-receptor interaction is determinant for the entire sequence of events leading to the adrenergic α-receptor response.

Over the past few years there has been an increasing awareness of the role that the cell membrane plays, not only as a permeability barrier, but as one site of a number of regulatory properties including neural transmission and conduction processes. We have also paid greater attention to the cell membrane and a number of joint meetings of the "receptor groups" and "membrane groups" have taken place which have been of some interest. Among the important topics that have been discussed are the role of lipids in lipid-protein interactions (see publications no. 9 and 10), the effect of Ca^{++} in lipid-bilayers and membranes and the problem of pheromone recognition. We intend to continue this close collaboration in the coming year and have jointly planned a two-day symposium (May 18, 19, 1970) on Structural and Functional Aspects of Cell Membranes. In the same month a symposium jointly sponsored by the Departments of Biochemistry and Biochemical Pharmacology, on Cholinergic Ligand Interactions will take place.

Future developments in the receptor area are difficult to predict: however, an unquestionably valuable approach at both the theoretical and experimental levels will continue to be the analogies with regulatory phenomena in enzyme systems.

5. PUBLICATIONS:

J.F. Moran, C.R. Triggle and D.J. Triggle, "Mechanism of Action of α-Halogenoethylamines at the Adrenergic α-Receptor, J. Pharm. Pharmacol., 21, 38 (1969)

D.R. Garrison, M. May, H.F. Ridley and D. J. Triggle, "Studies on the Cholinergic Receptor II", J. Med. Chem., 12, 130 (1969)

M. May, H. F. Ridley and D. J. Triggle, "Studies on the Cholinergic Receptor III", J. Med. Chem., 12, 320 (1969)

H. F. Ridley, S. S. Chatterjee, J. F. Moran and D. J. Triggle, "Studies on the Cholinergic Receptor IV", J. Med. Chem. 12, 931 (1969)

S. Vickers, P. Hebborn, J. F. Moran and D. J. Triggle, "Synthesis and Evaluation of Esters of N,N-bis-2-chloroethyl-p-aminophenol as potential antitumor agents" J. Med. Chem. 12, 491 (1969)

D. J. Triggle, H. F. Ridley and D. M. DeMaio, "3-Alkoxyestra-1,3,5(10) trien-17-β-ols", J. Med. Chem. 12, 345 (1969)

D. J. Triggle (Ed. A. Berger), "The Adrenergic Hormone" in Medicinal Chemistry, J. Wiley 1969)

J. F. Moran and D. J. Triggle (Ed. J. F. Danielli), "Fundamental Concepts in Drug-Receptor Interactions", Academic Press (1969)

D. J. Triggle, "Some Aspects of the Role of Lipids in Lipid-protein Interactions and cell membrane Structure and Function." Prog. Surface Science 3, (in press)

D. J. Triggle, "A Comment on the Generalized Role of Phospholipids in Cell Membranes", J. Theoret. Biol. (in press)

6. PAPERS AND SEMINARS PRESENTED: MEETINGS ATTENDED:

Seminars were presented by D. J. Triggle at the University of Minnesota, Ohio State University, University of Ottawa, University of Edmonton and San Francisco Medical Center dealing with aspects of the work described under Section 4.

D. J. Triggle attended the Symposium on Quantum Biology, Battelle Institute, Seattle, October, 1969

7. UNIVERSITY TEACHING

D.J.Triggle,V.C.Swamy	B.P. 405/406 undergraduate Pharmacology
D.J.Triggle and V.C.Swamy	B.P. 320 undergraduate Pharmacology
J.F.Moran, D.J.Triggle	BP/BC 630/630R, Graduate, "Molecular Basis of Cehmical Transmission Process.
J.F.Moran	Biochem. 446, General Biochemistry
J.F.Moran	Biochem. 503, Student Seminar

REPORT - Sub-group on CELL MEMBRANES AND MEMBRANE FUNCTION

Convenor - Charles Wenner

1. DEFINITION OF FIELD OF INTEREST:

Theoretical and experimental work relevant to the understanding of cell membranes.

2. FINANCIAL SUPPORT:

NIH, American Cancer Society support.

3. FACULTY AND OTHER PARTICIPANTS:

Charles Akers	Roswell Park Memorial Institute
Donald F. Parsons	Roswell Park Memorial Institute
Jagneswahr Saha	Roswell Park Memorial Institute

4. RESEARCH PROGRAM:

Our research program involves the study of the dynamic aspects of cation and organic solutes across natural membranes, and our emphasis is on mitochondrial membrane function and its relation to energy generation and utilization. Our goal is to understand the molecular events responsible for transport in biological systems, and as part of this study, we are attempting to learn the physico-chemical basis of ion translocation across model membrane and its relevance to natural membranes. Another aim is to establish what elements of previously proposed models of membrane structure are unifying for the demonstration of common membrane function and conversely to learn what are the necessary components which lead to specialized membrane function.

The Electron Optics Laboratory of the Roswell Park Memorial Institute, headed by Dr. D. F. Parsons, is engaged

in a program of development of the electron microscope for the purpose of obtaining more informative electron images of cell membranes. The development program involves NIH, NSF and the American Cancer Society support for the development of a 200 kV electron microscope for electron diffraction and imaging of cell membranes in the hydrated state, the development of a phase contrast microscope and small angle X-ray diffraction of cell membranes.

5. PUBLICATIONS:

C. K. Akers and D. F. Parsons, "X-ray Diffraction of Myelin Membrane. I: Optimal Conditions for Obtaining Unmodified Small Angle Diffraction Data from Frog Sciatic Nerve", Biophys. J., in press (1969)

C. K. Akers and D. F. Parsons, "X-ray Diffraction of Myelin Membrane. II: Determination of the Phase Angles of the Frog Sciatic Nerve by Heavy Atom Labeling and Calculation of the Electron Density Distribution of the Membrane", Biophys. J., in press (1969)

C. E. Park and C. E. Wenner, "Mitochondrial Lipids of Ehrlich lettre ascites tumor cells", Oncology, in press.

J. Saha, D. Papahadjopoulos and C. E. Wenner, "Studies on Model Membranes: I. Effects of Ca^{++} and antibiotics on permeability of cardiolipin liquid-crystalline vesicles", Biochim. et Biophysica Acta, in press.

C. E. Wenner and J. Hackney, "Mitochondrial energy flux and ion-induced ATPase activity and Light Scattering Changes Mediated by Gramicidin", Biochemistry, 8:930, 1969

R. C. Moretz, C. K. Akers and D. F. Parsons, "Use of Small Angle X-ray Diffraction to investigate Disordering of Membranes during Preparation for Electron Microscopy. I: Osmium Tetroxide and Potassium Permanganate. Biochim. Biophys. Acta, 193: 1-11 (1969)

R. C. Moretz, C. K. Akers and D. F. Parsons, "Use of Small Angle X-Ray Diffraction to Investigate Disordering of Membranes during Preparation for Electron Microscopy. II: Aldehydes. Biochim. Biophys. Acta, 193: 12-21 (1969)

R. C. Moretz, G. Hausner, H. M. Johnson and D. F. Parsons, "Design of a Wet Specimen Chamber for Investigation of Hydrated Specimens in the Electron Microscope," Biophys. J. 9: A-194 (1969)

D. F. Parsons, "Electron Imaging of Biological Materials in the Intact State", Biophys. J., 9: A-195 (1969)

D. F. Parsons, "X-ray Diffraction of Membrane Structure Changes Occurring During E.M. Specimen Preparation", (Abstract) Proc. Electron Microscope Society of America (1969)

D. F. Parsons, and C. K. Akers, "Neutron Diffraction of Cell Membranes (Myelin)", Sci. 165: 1016 (1969)

D. F. Parsons and C. K. Akers (Abstract) "Neutron Diffraction of Cell Membranes (Myelin)", J. Cell Biol., (1969)

R. C. Moretz and D. F. Parsons, "Modification of the Electron Microscope for Investigation of Fully Hydrated Biological Specimens", Proc. Electron Microscope Soc. of America (Abstract) (1969)

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REPORT - Sub group on SYNTHETIC MEMBRANES

Convenor - J. F. Danielli

1. DEFINITION OF FIELD OF INTEREST:

The design of a bimolecular polymer membrane for use in purification of water.

2. FINANCIAL SUPPORT:

None

3. FACULTY AND OTHER PARTICIPANTS

H.T. Cullinan, jr.	Associate Professor, Faculty of Engineering and Applied Sciences, (Chemical Engineering)
R. J. Good	Professor, Faculty of Engineering and Applied Sciences, (Chemical Engineering)
J. A. Howell	Assistant Professor Faculty of Engineering and Applied Sciences, (Chemical Engineering)
K.F. O'Driscoll	Professor, Faculty of Engineering and Applied Sciences, (Chemical Engineering)
S. Ohki	Assistant Professor, School of Pharmacy, (Pharmaceutics)
D.J. Triggle	Professor, School of Pharmacy (Biochemical Pharmacology)
S. Weller	Professor, Faculty of Engineering and Applied Sciences, (Chemical Engineering)

4. RESEARCH PROGRAM

The faculty listed above have drawn up a draft grant application, part of which is given below. The implementation

of this proposal is now being discussed with the Office of Saline Water.

1. Title: DESIGN OF A BIMOLECULAR POLYMER MEMBRANE

2. Scientific Objective:

Studies on cell membranes have shown that they can provide the basis for very efficient ion transport. The continuous unit of structure in cell membranes is a bimolecular lipid leaflet. Such leaflets are too fragile to be of value for industrial purification of water. Our objective is to prepare bimolecular polymer membranes, similar in basic structure to cell membranes, and dependent for physical stability on the same physical principles that are responsible for the structure of cell membranes. It is expected that replacement of lipid molecules by appropriate polymers will provide mechanical properties appropriate to industrial situations.

3. Relevance to Saline Water Conversion:

Biomolecular polymer membranes, provided with appropriate carrier molecules, will provide a mechanism for removal of salt from water which is expected to be an order of magnitude more efficient than existing membranes.

4. Scientific Justification:

If a bimolecular polymer membrane of the type envisaged here can be synthesised it will provide a new basic type of membrane for industrial use. This membrane in itself will be relatively impermeable, but can be given a wide variety of specific transport properties by secondary modifications,

the nature of which is outlined below. One such modification can be used for the removal of salt from water.

The background from which this project arises is as follows: If a membrane is to be selectively permeable, it must be first highly impermeable to most diffusing species, and provide a special structural feature which facilitates permeation of a small number of molecular species. Cell plasma membranes are a remarkable example of such selective membranes, with all the necessary features built into a membrane usually less that 100 Å thick. Let us consider what may be learnt from such membranes, first with respect to a general impermeability and then with respect to selective permeabilities.

The impermeability of cell membranes is due to what, operationally, appears to behave as a continuous hydrocarbon phase about 40 Å thick. This is constructed mostly of lipids, usually having hydrocarbon chains about 18 carbons long. The major factor determining the rate at which hydrogen bonding molecules penetrate a thin hydrocarbon membrane is the rate at which the hydrogen bonds between solute and water can be broken at the hydrocarbon-water interface (Danielli, 1941). Since the rate-determining step is usually at the membrane-water interface, an increase in thickness of the membrane, even by a factor of a hundred fold or more, will not in most cases further diminish the permeability of the membrane, i.e. will not reduce the simple diffusion flux across it below the value found for a membrane of molecular thickness.

The basic unit of structure at the continuous lipid phase is a bimolecular leaflet, as in fig. 1A. A striking peculiarity of cell membranes, and of phospholipids in general is that under most experimental conditions the lipid moiety is only two molecules thick. Even when large amounts of non-polar material are added to such membranes, they usually do not increase in thickness, remaining bimolecular. The reason for this is that, if such a membrane does transiently incorporate hydrocarbon and become thicker than bimolecular, the increase in thickness results in the formation of a randomly oriented phase between the two oriented surface monolayers (fig. 1B). At the interface between the random and the oriented molecules there is a discontinuity of intermolecular forces, and consequently a surface free energy $\gamma_{o/r}$, approximately 10 ergs./cm^2. Since this free energy $\gamma_{o/r}$ disappears if the membrane becomes bimolecular, the stable configuration is bimolecular, and in fact the bimolecular membrane is a natural unit of structure (Danielli 1966, 1967, 1968; Ohki 1967). See fig. 1C.

An important point which must now be made is that, if in the proposed synthetic membranes reliance is to be placed, not on simple diffusion, but on special built in transport mechanisms, it will be advantageous to retain the bimolecular thickness. This will be done provided the polymers have hydrocarbon chains arranged in the polymer molecule in such a way that an oriented hydrocarbon chain phase is formed when the polymer molecules are assembled into a bilayer.

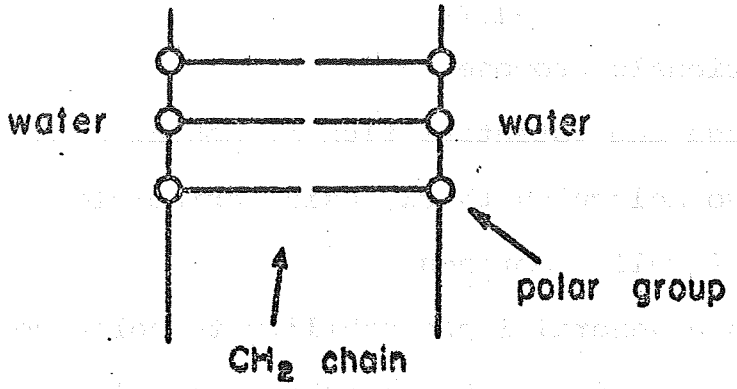

Fig. IA

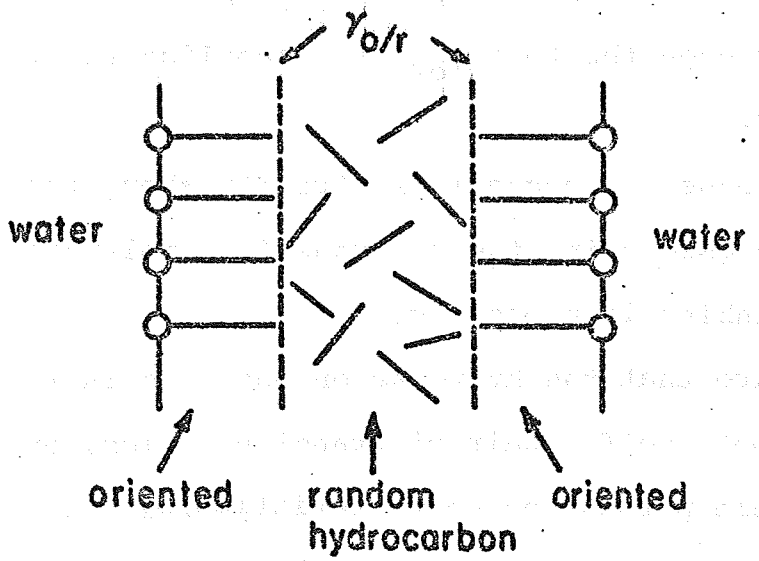

Fig. IB

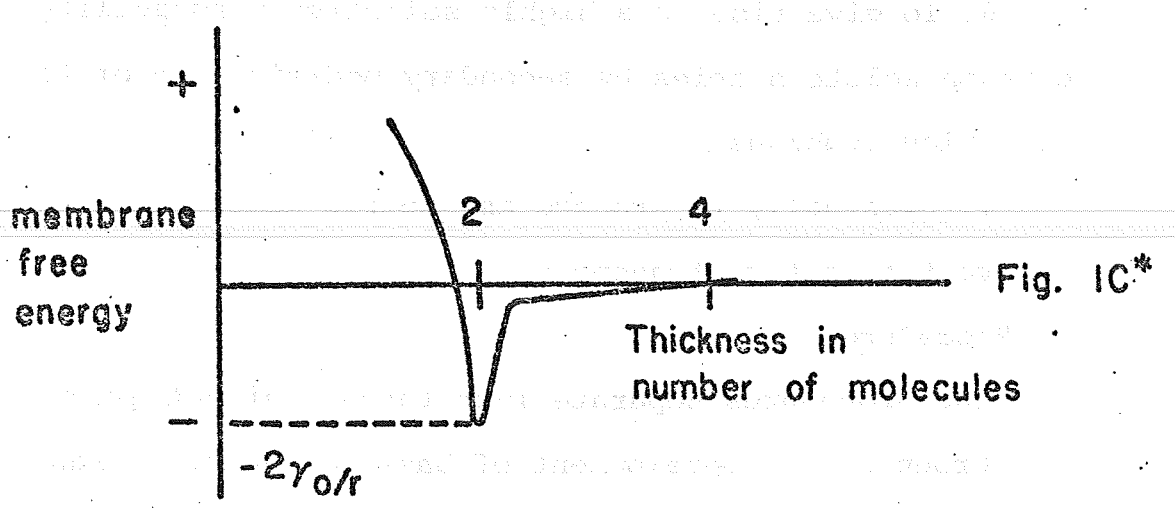

Fig. IC*

* Note: The reason for the rapid rise in membrane free energy as the thickness falls below bimolecular is given in Danielli (1966: 1968).

Thus the rationale proposed here is;

1. To increase the potential flux by making a membrane approximately two molecules thick, using principles learnt from the study of cell membranes.

2. To obtain a general impermeability to polar solutes by formation of a continuous hydrocarbon phase in the membrane.

3. To rely upon the term $\gamma_{o/r}$ to stabilise the thickness at bimolecular.

4. To increase the mechanical strength above that found in bilayers by assembling the membrane from polymers, with later cross-linking if necessary.

5. To ensure that the hydrocarbon phase is in the liquid state (to promote self-repair of transient holes, and ensure desirable permeation characteristics) by adjusting the chain length of the hydrocarbon chains.

6. To give rise to a highly selective permeability to certain solute species by secondary modification of the assembled membrane.

7. Eventually to produce asymmetric membranes with asymmetry relevant to active transport.

5. Procedure:

The procedures separate into three distinct groups: -

Group I. Development of basic polymer membrane

Group II. Secondary modifications to secure selective high flux.

Group III. Secondary modifications to produce relevant asymmetry.

Work can be done on I and II in parallel, but probably III should be deferred until progress has been made with I.

I. Development of a basic membrane. The basic steps are

1. build space-filling models and select polymers for synthesis with suitable geometry.

2. synthesise simplest suitable polymers

3. study membrane formation and permeability properties

4. study system properties, especially design of support material and hydrodynamics

5. build pilot scale system.

II. Secondary Modifications for Selective High Flux.

Our present thinking is that this will best be done by developing cage-like molecules, to provide either for ion fluxes, or water flux. The basic steps are:

1. build models of cages and select relevant types to give selective fluxes for eg. water, Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-.

2. synthesise cages

3. calculate increase in flux expected with specific cages.

4. check out cages behaviour on simple lipid membranes

5. check out cages on polymer membranes

6. study cage behaviour, transport properties, and stability problems in pilot or pre-pilot assemblies.

III. Development of Asymmetric Membranes

We shall not attempt to work out a procedure until progress has been made with I.

References:

Ohki, S. N. Fukuda (1967): J. Theoret. Biol. 15:362.

Danielli, J. F. (1966): J. Theoret. Biol. 12:439.
(1967): Sympt. Int. Soc. Cell Biol.
(1968): in "Molecular Association in Biology" Edit. B. Pullman (Academic Press, NY)

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WORKING PARTY REPORT

CANCER CHEMOTHERAPY

Chairman A. Mittelman

No report has been submitted by this working party.

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WORKING PARTY REPORT

BEHAVIORAL STUDIES

Chairman: J. F. Danielli

The development of this program, desirable though it is, has been postponed for lack of funds.

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Individual Report - STRUCTURE AND FUNCTION OF MACROMOLECULES

M. Derechin and E. Barnard

1. DEFINITION OF FIELD OF INTEREST:

The relationship between structure and function of macromolecules with special reference to self-associating systems. Ultracentrifugation.

2. FINANCIAL SUPPORT:

Support was received from graduate school funds and institutional research funds, as well as from the Center for Theoretical Biology.

3. FACULTY AND OTHER PARTICIPANTS:

M. Derechin	Assistant Professor, School of Medicine (Biochemistry) School of Pharmacy, (Biochemical Pharmacology)
Eric Barnard	Professor, School of Medicine (Biochemistry)

4. RESEARCH PROGRAM:

The main areas of experimental research during 1969 were a) the quarternary structure of hexakinase by means of sedimentation equilibrium b) studies on chymotrypsinogen and chymotrypsin from the turltle and c) studies on hematin.

Research into the theory of self-associating systems was done and results of this work have been published. A theoretical treatment was developed which allows the calculation of equilibrium constants of ideal and non-ideal self-associating systems. The theory is being further developed at present in order to define methods for their computation. The theory is being experimentally applied

using lysozyme as a model.

Modifications of the analytical ultracentrifuge for sedimentation equilibrium studies have been developed and published.

E. A. Barnard. A model of chymotrypsin was built at the Center for Theoretical Biology from published co-ordinates for use in research and teaching. It is used to examine the interactions in the active center of the enzyme.

5. PUBLICATIONS:

Derechin, M. "Modification of the Model E Analytical Ultracentrifuge for Sedimentation Equilibrium Study", Analyt. Biochem. 28, 385 (1969)

Derechin, M., "Self-Association Systems, II. Multinomial Theory for Non-Ideal Systems." Biochem. 8, 921 (1969)

Derechin, M. "Self-Associating Systems, III. Multinomial Theory for Ideal Systems Using the Z-average Molecular Weight", Biochem. 8, 929 (1969)

Derechin M., W. Moekel and E. A. Barnard, "Sedimentation Equilibrium Studies of Some Turtle Chmotrypsins", B.B.A. 191, 379 (1969)

Barnard, E. A. "Ribonuclease", Ann. Rev. Biochem., Vol 38. 677 (1969)

V CONTRIBUTIONS TO THE UNIVERSITY TEACHING PROGRAM

Courses participated in by Center members:

Member	Department and Course #
K. W. Jeon	Biology 125
V. S. Vaidhyanathan	Biophysics - spring
	Coordinated Seminars - Biology
	Selected topics - Pharmaceutics
L. M. Bianchi	FS 119
	COE 405
Bianchi and Hamann	NSM 470
M. Danielli - J.F. Danielli	Future of Man
M. Danielli	Communications College - The Mandala, Madagascar and Modern Times
J.R. Hamann	FS 141
	COE 101
Mac Hammond	COE 101
E. M. Segal	COE 101
Robert Rosen	Courses in Biomathematics
Robert Rein	Biophysics 696
	Supervision of Dissertation Res.
	Physics 107
J. Hoogeveen	BPH 517
C. Jung	BPH 517/512
S. Ohki	BPH 517/589
D. Papahadjopoulos	BCH
C. Wenner	BCH
D. Wobschall	BPH 517/512/401/402/550
	Eng 470/453
	EAS 204
D. A. Cadenhead	Chemistry 512
Frank Tsien	Chemistry 101-102
D. J. Triggle, V.C. Swamy	BP 405/406
	BP 320
J. F. Moran, D.J. Triggle	BP/BC 630/630R
J. F. Moran	Biochem. 446
	Biochem 503
M. May	Pharmacology 501
	Pharmacology 503
K. N. Leibovic	Biophysics 656
	Biophysics 540

SEMINARS PRESENTED - CENTER FOR THEORETICAL BIOLOGY

K. W. Jeon - Co-ordinator

We have succeeded in maintaining our regular schedule of fortnightly seminars during the past year, except for the summer months. In spite of the purported role of seminars in bringing together the Center members as well as others on the ground of common interest in an intellectually exciting atmosphere, it has not been easy always to attract a sizable audience from the Center for each seminar. This problem of numbers attending is apparently not unique to the Center seminars. On the whole, however, our seminars during the past year have been well received and quite fruitful, smaller numbers seeming to generate stimulating discussions.

The seminars held at the Center and the abstracts as they appeared on the notices are as follows:

January 6 — Dr. Arthur T. Winfree
Princeton University, Princeton, N.J.

THE TEMPORAL MORPHOLOGY OF A BIOLOGICAL CLOCK

This seminar was co-sponsored by the Department of Biophysical Sciences.

January 16 — Dr. P. D. Papahadjopoulos
Biochemistry Department, SUNY/B

PHOSPHOLIPID LIQUID CRYSTALS AS MODEL MEMBRANES

Dispersion of phospholipids in water by ultrasonication produces unilamellar closed vesicles. These structures incorporate small molecules and ions in the interior aqueous compartment and exhibit characteristic permeability properties.

February 6 — Dr. Joseph G. Hoffman
Physics Department, SUNY/B

THE BIOPHYSICAL SIGNIFICANCE OF FLUORESCENCE IN WATER

Fluorescence in water suggests mechanisms for aggregating energy. A model of water clusters will be described to explain the observed radiations. The conversion of thermal to near infrared energy may be a source or free energy in living systems.

February 13 — Dr. V. S. Vaidhyanathan
Center for Theoretical Biology, SUNY/B

REPORT ON THE INTERNATIONAL SYMPOSIUM ON ATOMIC, MOLECULAR AND SOLID-STATE THEORY AND QUANTUM BIOLOGY

February 20 — Dr. Peter Hebborn
Biochemical Pharmacology, SUNY/B
and
Dr. Pierre Band
Principal Clinical Investigator, Roswell Park Memorial Institute

A TUMOR-SPECIFIC ALKYLATING CARBAMATE: PHARMACOLOGIC AND CLINICAL ACTIVITIES

A marked structure-activity relationship is seen with a series of carbamate esters of aromatic nitrogen mustards in tumor-bearing rodents. Data from pharmacologic and clinical studies will be summarized and theoretical implications of this study will be discussed.

February 27 — Dr. Lejaren Hiller
Slee Professor of Composition,
Music Department, SUNY/B

SOME PROGRAMMING TECHNIQUES FOR MUSIC COMPOSITION

The speaker has been developing a computer language for music composition. Excerpts from these compositions will be used during the talk.

March 6 — Dr. Philip Rosen
Department of Physics and Astronomy
University of Massachusetts

A KRONIG-PENNEY MODEL OF SALTS OF DNA

A one-dimensional Kronig-Penney model for a salt like Na DNA is given. The helical periodicity is treated in a manner suggested by Tinoco and Woody. Using data on the semiconductor band gap the ten bands filled by 20 π electrons are obtained.

May 18
Friday — A. E. Shields
Registrar, University of Sussex, England
and
Harry Hoff
United Kingdom Atomic Energy Authority
Consultant to the Central Electric Board
London, England

TOTAL INVOLVEMENT OF STAFF AND STUDENTS IN RUNNING A UNIVERSITY
Co-sponsored by Faculty of Natural Science and Mathematics

May 22 — Dr. Narendra Goel
Department of Physics and Astronomy
University of Rochester, N.Y.

GENETIC CODE AND CODON FREQUENCIES IN DNA

A model, based on the genetic code, for calculation of the frequencies of 64 triplets (codons) of nucleotides in DNA will be presented. The implications of these calculations on the range of the frequencies of nucleotides in the naturally occurring DNA molecules, on numerical taxonomy and evolution of life will be discussed.

June 5 — Dr. Richard A. Elliott
Department of Physics and Astronomy
University of Rochester, N.Y.

THE EFFECT OF LATTICE VIBRATIONS ON TRAP-LIMITED EXCITON LIFETIMES

The problem of exciton migration and trapping on a linear polymer is treated as a random walk on a one-dimensional lattice. The average number of steps required for a walker to be trapped is calculated when the probability of stepping to adjacent lattice sites is not symmetric, and is found to be less than that calculated for a symmetric walk. An asymmetric stepping probability is shown to result from the thermal vibrations of the lattice. The magnitude of this effect on the exciton lifetime is estimated and found to be significant.

September 5 Friday — Dr. Alex Bangham
Senior Principal Scientific Officer
Agricultural Research Council
Institute of Animal Physiology
Babraham, Cambridge, England

IONS IN MY LIFE

Co-sponsored with Department of Experimental Biology, Roswell Park Memorial Institute

September 25 — Dr. Warren G. Bennis
Vice President for Academic Development
SUNY/B

THE TEMPORARY SOCIETY

The effects of "the temporary society" on human relations, love and life.

October 9 — Dr. Franco B. Conti
Laboratorio di Cibernetica e Biofisica
Consiglio Nazionale delle Ricerche
Camogli (Genova) Italy

NERVE MEMBRANE ELECTRICAL CHARACTERISTICS NEAR THE RESTING STATE

Oscillations in the axonal membrane potential are invariably observed in response to stimulations with steps of current of any amplitude. The frequency of the oscillations is a characteristic property of the excitable membrane, which is independent of the extracellular ionic composition and depends strongly on temperature and on the steady electric field existing within the membrane.

October 30 — Dr. Norman L. Gershfeld
Research Chemist, NIH, NIAMD-LPB
Bethesda, Maryland

STEROID HORMONE-MONOLAYER INTERACTIONS

General properties of the steroid hormone - lipid monolayer interactions are discussed. An alternative to the concept of the binding specificity of the "target-site" is presented which accounts for the ubiquitous action of steroids.

November 6, — Dr. Jànos Ladik
Visiting Professor, CCNY, New York

QUANTUM MECHANICAL ASPECTS OF DNA"

The methods of the approximation of the electronic structure of DNA constituents and of the DNA macromolecule will be presented, together with interpretation of different physical properties of DNA, and possible biological consequences.

November 11, Tuesday

Dr. E. C. Pollard
Evan Pugh Professor of Biophysics
Pennslyvania State University
University Park, Pennsylvania

THEORY OF ACTION OF IONIZING RADIATION ON CELLS

November 13

Dr. Stuart Kauffman
University of Chicago, Illinois

METABOLIC STABILITY AND EPIGENESIS

A Model of the Genotype Phenotype mapping: Implications for Carcinogenesis Steroid Research.

Randomly constructed genetic control circuitry models, cell types, as stable oscillatory modes of behavior. A common feature of mutational epigenetic carcinogenesis may be disruption of flow pathway among cell types. Steroids and other hormones could be used as probes to explore those pathways.

Interfaculty Seminar - SYSTEMS IN THE SCIENCES

Ludwig von Bertalanffy
Faculty Professor

The working group of the Seminar has met weekly during the winter term, and has in particular discussed models and mathematical approaches in the systems fields. Presentations included:

L. von Bertalanffy - Survey of developments, in the various sciences, necessitating a systems approach.

R. Rosen - Dynamical system theory; mathematical formulations of system-theoretical ideas.

G. T. Herman - Theory of Automata and related topics, with discussion of computability, simulation, automata-theoretical models for cellular systems, etc.

W. F. Buckley(visiting lecturer) - Modern systems theory and sociology, considering a socio-cultural model as both adaptive and creating, and including conflict, deviance, power, coercion, etc.

L. von Bertalanffy - Open systems, including the apparent contrast of "dissipation" in physical,and "evolution" in living nature; kinetic and thermodynamic consideration of open systems, biological consequences.

D. S. Riggs - Steady-state behavior in multiple feedback loops, formulation of causal relationships; feedback (negative and positive); limitations of analysis in multiloop, nonlinear feedback systems, and approach by steady-state analysis; chemical control of breathing as example of such analysis, with explanation and prediction of actual

results.

Attention may also be called to some recent books containing contributions by L. von Bertalanffy on system problems:

Beyond Reductionism. Edited by A. Koestler and J. R. Smythies. London: Hutchinson, 1969

General Systems Theory and Psychiatry. Edited by W. Gray, N. Rizzo and F. Duhl; Little, Brown: Boston 1969

Biologische Modelle. Annual Meeting 1967 of Deutsche Akademie der Naturforscher Leopoldina. Leipzig: J.A. Barth, published 1969.