UCLA FORUM IN MEDICAL SCIENCES number 5

VOLUME III

BRAIN AND BEHAVIOR

THE BRAIN AND GONADAL FUNCTION

EDITORS

ROGER A. GORSKI and RICHARD E. WHALEN

1966

UCLA FORUM IN MEDICAL SCIENCES

NUMBER 3

BRAIN AND BEHAVIOR

VOLUME III

Proceedings of the Third Conference, 1963

THE BRAIN AND GONADAL FUNCTION

Sponsored by the Brain Research Institute, University of California Los Angeles,
in collaboration with the American Institute of Biological Sciences
and with the support of the Human Ecology Fund

EDITORS

ROGER A. GORSKI and RICHARD E. WHALEN

UNIVERSITY OF CALIFORNIA PRESS

BERKELEY AND LOS ANGELES

1966

EDITORIAL NOTE

The present volume contains the proceedings of the third in a series of conferences on Brain and Behavior, supported by grants made to Dr. H. W. Magoun of the Brain Research Institute of the University of California Los Angeles. The American Institute of Biological Sciences acted as co-sponsor and also published the proceedings of the first two conferences of this series, *Brain and Behavior, Vol. I: Analysis of the External Environment and Information Handling by the Nervous System* (1961), and *Brain and Behavior, Vol. II: The Internal Environment and Alimentary Behavior* (1962), both edited by Dr. M. A. B. Brazier.

An additional series published by the UCLA Forum in Medical Sciences is on Brain Function, of which the first two volumes appeared in 1963 and 1964. The third conference in that series (*Brain Function III: Speech, Language and Communication*) was held November 1963 and is currently in press.

CITATION FORM

Gorski, R. A., and Whalen, R. E. (Eds.), *Brain and Behavior, Vol. III: The Brain and Gonadal Function.* UCLA Forum Med. Sci. No. 3, Univ. of California Press, Los Angeles, 1966.

University of California Press
Berkeley and Los Angeles, California

Cambridge University Press
London, England

Library of Congress Catalog Card Number: 65-27542
Printed in the United States of America

UCLA FORUM IN MEDICAL SCIENCES

UNIVERSITY OF CALIFORNIA LOS ANGELES

BRAIN AND BEHAVIOR

VOLUME III

BRAIN AND GONADAL FUNCTION

PARTICIPANTS IN THE CONFERENCE

H. W. MAGOUN, *Co-Chairman*
Brain Research Institute, University of California Los Angeles
Los Angeles, California

F. FREMONT-SMITH, *Co-Chairman*°
American Institute of Biological Sciences
New York, New York

R. A. GORSKI, *Editor*
Department of Anatomy, University of California Los Angeles
Los Angeles, California

R. E. WHALEN, *Editor*†
Department of Psychology, University of California Los Angeles
Los Angeles, California

V. G. BARANOV‡
Pavlov Institute of Physiology
Leningrad, USSR

M. A. B. BRAZIER
Brain Research Institute, University of California Los Angeles
Los Angeles, California

V. N. CHERNIGOVSKY‡
Pavlov Institute of Physiology
Leningrad, USSR

A. E. FISHER
Department of Psychology, University of Pittsburgh
Pittsburgh, Pennsylvania

R. GALAMBOS
Department of Psychology, Yale University
New Haven, Connecticut

W. F. GANONG
Department of Physiology, University of California Medical Center
San Francisco, California

° Present address: Interdisciplinary Communications Program
New York Academy of Sciences
New York, New York

† Present address: Department of Psychobiology, University of California, Irvine
Irvine, California

‡ Not present

J. D. Green*
Brain Research Institute, University of California Los Angeles
Los Angeles, California

R. O. Greep
Harvard School of Dental Medicine
Boston, Massachusetts

R. Guillemin†
Laboratoire de Morphologie Expérimentale et Endocrinologie
Collège de France
Paris, France

S. Kanematsu
Department of Animal Husbandry, School of Agriculture
Kyushu University
Hakazaki, Fukuoka-Shi, Japan

C. D. Leake
Department of Pharmacology, University of California Medical Center
San Francisco, California

C. Leese
Department of Physiology, The George Washington University
Washington, D. C.

J. Lilly
Communication Research Institute
Miami, Florida

R. D. Lisk
Department of Biology, Princeton University
Princeton, New Jersey

R. B. Livingston‡
Division of Research Facilities and Resources
National Institutes of Health
Bethesda, Maryland

P. D. MacLean
Section on Limbic Integration and Behavior
National Institute of Mental Health
Bethesda, Maryland

* Deceased
† Present address: Baylor University College of Medicine
Texas Medical Center
Houston, Texas
‡ Present address: Department of Neurosciences, School of Medicine
University of California, San Diego
La Jolla, California

L. Martini
Istituto di Farmacologia e di Terapia, Università degli Studi
Milan, Italy

S. M. McCann*
Department of Physiology, University of Pennsylvania
Philadelphia, Pennsylvania

R. P. Michael
Institute of Psychiatry, The Maudsley Hospital
London, England

K. H. Pribram
Department of Psychiatry, Stanford University
Palo Alto, California

D. P. Purpura
Department of Neurological Surgery
College of Physicians and Surgeons, Columbia University
New York, New York

S. Reichlin
Department of Internal Medicine, The University of Rochester
Rochester, New York

O. E. Reynolds†
Office of Space Sciences, National Aeronautics and Space Administration
Washington, D. C.

C. H. Sawyer
Brain Research Institute, University of California Los Angeles
Los Angeles, California

S. Taleisnik
Instituto de Investigación Médica Mercedes y Martín Ferreyra
Córdoba, Argentina

H.-L. Teuber†
Department of Psychology, Massachusetts Institute of Technology
Cambridge, Massachusetts

W. F. Windle†‡
National Institute of Neurological Diseases and Blindness
National Institutes of Health
Bethesda, Maryland

* Present address: Department of Physiology
University of Texas Southwestern Medical School
Dallas, Texas

† Not present

‡ Present address: The Institute of Physical Medicine and Rehabilitation
New York University Medical Center
New York, New York

HERBERT McLEAN EVANS

It is appropriate that the members of the UCLA Conference on Brain and Gonadal Function think of Herbert Evans as a person and a scientist to whom its deliberations should be dedicated.

Herbert Evans is a vigorous Californian. He was born in Modesto, California in 1882. His father was a distinguished California physician, and an early graduate from the University of California Medical School, which had been established in San Francisco in 1864 by that extraordinary surgeon of the gold-rush days, Hubert A. Toland (1809-1900). Herbert Evans went to the University of California in Berkeley and received his Bachelor's Degree there in 1904. He then sought training in scientific medicine at the Johns Hopkins Medical School, from which he received an M.D. degree in 1908.

It was at Johns Hopkins that Evans became enthusiastically dedicated to a research career in biomedical fields. He was greatly stimulated by his distinguished German-trained professor of anatomy, Franklin Paine Mall (1862-1917), a master microscopist with an early interest in the pathology of human embryos. Evans learned from Mall the importance of care in microscopic details, and it was Mall who encouraged his passionate curiosity about biomedical processes.

At Baltimore, Evans was also strongly influenced by America's great pathologist, William Henry Welch (1850-1934), who so early insisted on the significance of adaptive processes in living material, and who distinguished himself as a microbiologist and humanist. At Johns Hopkins Evans also came under the stimulating humanistic influence of William Osler (1849-1919), who was at once such an outstanding pathologist, internist, humanist, historian, bibliophile, and all-around scholar. It may have been Osler's influence which led subsequently to Evans' enthusiasm for the history of science and of medicine.

During his studies at the Johns Hopkins Medical School Herbert Evans was appointed Assistant in Anatomy and rose rapidly to become Associate Professor. In 1915 he was made Professor of Anatomy at the University of California Medical School, with a laboratory in Berkeley. This position he held until 1953, when he became Emeritus Professor. Meanwhile, in 1930, he had been made Herzstein Professor of Biology and Director of the Institute of Experimental Biology, which had been established in a new laboratory building on the Berkeley campus for his increasingly active research group. This position he also held until 1953, when he became Emeritus Director.

As a young man, Herbert Evans had been a Research Associate at the Carnegie Institute in Washington from 1913 to 1915, and had also studied

abroad. It was during these years that he became interested in vital staining with benzidine dyes. He developed the well-known "Evans Blue" which has been so successfully used for the estimation of blood volume.

Evans' early interest in biological growth and his enthusiasm for the study of the processes of embryology led him in the 1920's to a systematic search of the interrelations of various vitamins and sterility. This study resulted in a series of significant reports on the nutritional importance of the vitamin B complex on sterility and on the integrity of the nervous system. These studies also resulted in the discovery of vitamin E which, after long investigation, was identified as a tocopherol. Herbert Evans' research skill enlisted the enthusiastic interest of an impressive number of pupils who later became well established in laboratories of their own in other parts of the country.

As early as 1922, in association with J. A. Long, Evans made a detailed study of the estrous cycle in rats, and investigated the many associated phenomena in this cycle. Skillful methods for hypophysectomy showed the involvement of the then mysterious anterior pituitary gland. The techniques so developed played a considerable role in many of the studies discussed at this conference. The studies of Evans and his associates led directly to an examination of the hormone content of the anterior pituitary in mammals, particularly as related to the gonads. Sex differences were detected in the hormone content of the anterior pituitary of rats, and the studies were extended to include the estrous cycle of dogs. This subject is also a topic of interest in this conference.

Events in ovogenesis and in the normal follicular cycle in adult mammals were soon systematically investigated by Evans and his colleagues. This work included the interactions between the uterus and ovary on the time of ovulation in primates. Some indications developed during the 30's of the possible significance of central neural factors in connection with the hormonal activity of the anterior pituitary. Again, this is a matter of prime concern in this conference.

The growth- and gonad-stimulating hormones of the anterior pituitary were well recognized early in the 1930's, and a detailed and impressive monograph on this subject was published in 1933 (1). By the end of the 1940's, Herbert Evans and his colleagues had separated the interstitial cell-stimulating and the follicle-stimulating fractions of the anterior pituitary gonadotropic complex. Subsequently, they investigated the adrenocorticotropic hormone and the thyrotropic hormones of the anterior pituitary. The important studies of his group of collaborators on the gonadotropic and growth hormones of the anterior pituitary became world famed.

Throughout this period, Evans urged his colleagues and students to take a broad humanistic approach in connection with their scientific interests. He organized a monthly dinner meeting at the Faculty Club in Berkeley devoted to seminar discussions on the history of science, which resulted in

many significant contributions in this field. Evans also supported early efforts to give medical students an opportunity to learn something of the history of medicine, and still continues to give seminar discussions in San Francisco on the history of anatomy.

Outstanding have been Herbert Evans' collections of the classics in the history of medicine and of science. He has made many, and he has distributed them wisely, so that they have enhanced the broad cultural interests of many important medical and scientific institutions in our country, ranging from the Institute for Advanced Study at Princeton to the great medical libraries on the West Coast. His artistic interest has been revealed on many occasions. During scientific trips to Latin America, particularly to visit his friend, the famed physiologist Bernard Houssay in Buenos Aires, Herbert Evans became interested in Spanish colonial church architecture, and his collection of illustrations of these remarkable buildings could well form the basis for an important monograph. His home is filled with works of art, many of them reflecting the sensitive interest he has maintained in ecclesiastical iconography.

Many honors have come to Herbert Evans from all over the world. He has received honorary degrees from universities in many countries, has given named lectures at many institutions, and has received a variety of medals and other awards. And with it all, Herbert Evans remains a modest, generous, inquisitive and exceedingly intelligent gentleman. A conversation with him is a stimulating experience. His wit and his broad knowledge make him a favorite among those who know him, and his informal remarks are always pointed and helpful. His formal presentations are meticulous and accurate in every detail. His stimulus has meant much to many of the participants in the UCLA Conference on Brain and Gonadal Function.

C. D. Leake
University of California School of Medicine
San Francisco

REFERENCE

1. Evans, H. M., Meyer, K., and Simpson, M. E., *The Growth and Gonad-Stimulating Hormones of the Anterior Pituitary.* Memoirs, Univ. of California, Vol. 11. Univ. of California Press, Berkeley, 1933.

CONTENTS

INTRODUCTION

H. W. MAGOUN
Chairman

Possibly because I have not attended other endocrine conferences recently, though I do not think solely for this reason, the advances disclosed in the proceedings of this conference seem to me to be of remarkable importance.

To refer to some specific examples, one of the most striking conceptual presentations is the proposal that the median eminence serves as a kind of hypothalamically-innervated neurohypophysis which produces the releasing factors or transmitter substances that guide pituitary secretion, so that the pituitary becomes, in turn, a kind of target endocrine organ. Of related significance has been the identification of these transmitter substances, the nature of which has been under study by many investigators over a period of more than a decade.

Moving from the endocrine field, in which there are many other contributions, into the hypothalamic region overlying the median eminence, it has been fascinating to learn of the ambivalent or uncommitted nature of its embryonic matrix and of the role of developing endocrine substances and other factors in determining its subsequent sexual polarization in maturity.

Of additional major significance has been the differentiation in the hypothalamic region of two distinct mechanisms, one of which deals with the regulation of endocrine activities concerned with ovulation and reproductive tract function, while the second, which is both spatially separate and functionally discrete, serves mating and other reproductive behavior. Unquestionably, there must be close operational relationships between these two mechanisms but they can, nevertheless, be differentially blocked. It has been of the greatest interest to learn of the application of these findings to the development of effective oral contraception, with its broad social implications for population control. Of particular ingenuity is the use being made of the biphasic action of the progestational steroids, to take advantage of their negative phase so as to block or reduce the excitability of the hypothalamic gonadotropic mechanism while leaving unimpaired and, possibly, even enhancing the excitability of the second mechanism serving mating behavior. As a result, all of the drives toward mating are preserved or increased, without the consequences of ovulation and potential conception.

The action of these antifertility agents thus appears to resemble that of the progestational steroids normally elaborated by the ovary during gestation, which, conveyed to the brain, prevent ovulation throughout the period of pregnancy. There is a paradoxical element in the circumstance that, by such "pharmacological" means, the human female is now able to simulate an aspect of pregnancy in order to prevent conception.

Stemming also from this work are findings relating to the direct endocrine potentiation of behavior. Dual and reciprocal influences have seemingly been identified; certain of them appear facilitatory, while others reduce excitability. The former initiate the exploratory and consummatory phases of sexual activity, while the latter are responsible for succeeding satiety. These contributions seem to be opening the basic processes serving innate behavior to substantive investigation.

Additionally, throughout the presentations, there have been repeated references to the more general organizational aspects of homeostatic regulation of neuroendocrine processes, with involvement of inverse feedbacks simulating automational models of contemporary technology and engineering systems. I would have found it difficult to have anticipated a succession of such fine presentations and the proceedings of this conference would seem to me to form something of a landmark in the neuroendocrine field.

NEUROENDOCRINE ASPECTS OF REPRODUCTIVE PHYSIOLOGY*

SEYMOUR REICHLIN
The University of Rochester
Rochester, N.Y.

I hope to provoke discussion because there are endocrinologists here who are not very good neurologists, and there are probably some neurologists here who are not very good endocrinologists; perhaps there are some here who are neither. My aim is to develop a theme of pituitary-gonadal regulation which can lead us into the brain and allow the neurologists to use some of their neurological insight to illuminate the problems that the endocrinologists face.

Three general areas have been chosen for discussion. The first is the general kind of evidence which links endocrine function to brain function. The second is the current status of the portal vessel-chemotransmitter hypothesis. And the third is the newer knowledge of neurosecretory mechanisms and how they may conceivably serve as a model for regulation of anterior pituitary function by the brain.

This is a particularly good time for a conference on the brain and gonadal function because, to use the words of Dr. Sawyer, neuroendocrinology in a sense has come of age. Just about twenty-five years ago, the Association for Research in Nervous and Mental Disease held a conference (29) which was a landmark in the study of the hypothalamus. The first paper was a reprint of Fröhlich's 1901 case report of adiposogenital dystrophy (28), from which he gained credit for having pointed out the association of disease of the diencephalon with disturbance of pituitary function. The same symposium included the Scharrers' report (78) that the supraoptic nuclei contained antidiuretic hormone, an analysis of the function of the supraoptic-hypophysial system, a discussion of anterior pituitary control by Uotila (86), and a great deal of material by Bard on the regulation of sexual behavior (5). We see, therefore, that by 1940 many of the problems of the current neuroendocrine concern had been well laid out.

* Studies carried out in the author's laboratory were supported in part by USPHS Grant No. NB 04051.

These problems include the relationship between the brain and gonads, the relationship between gonads and sexual behavior, the notion of neurosecretion, and the relationship between visceral function and regulation of pituitary function. The work in the intervening time has featured major contributions from many investigators, including a number of participants in this conference. I understand that the Association for Research in Nervous and Mental Disease is planning another symposium on neuroendocrinology, and this will round out the circle.

Sexual function has a place in any discussion of neuroendocrinology because the interrelations of gonadal and brain function are the most obvious of the pituitary influences and have been known for the longest time. Frank Beach (9) quotes Aristotle: "the ovaries of sows are excised with the view of quenching their sexual appetites". The effects of castration in the male were also known to antiquity.

Knowledge that the brain affects gonadal function is much more recent, but it was known as long ago as 200 years that some sexual phenomena were related to the environment. For example, we may cite the classic work of Haighton, whom Dr. Green (37) calls the father of neuroendocrinology: he showed very clearly that the corpus luteum did not appear in the ovary of the rabbit except after copulation, a notion implying that an external stimulus could trigger an internal sexual event.

One of the reasons why the neuroendocrinology of sexual function includes so many striking phenomena unlike those involving all the other systems of endocrine control is that it is the one in which internal secretory rhythm must be correlated behaviorally, so as to allow the successful union of sperm and egg. There must be a behavioral counterpart to the internal gametogenic activity. It can be said, in fact, that there are probably no sexual physiological phenomena that do not involve a close correlation of neural and endocrine events.

First, let me talk about timing of the onset of puberty. There are obvious and quite good reasons why puberty is delayed until adulthood, but until recently there was no clear idea about the factors which were concerned in regulating the onset of puberty. At one time this was thought to be a mysterious property of the pituitary gland itself which, at a certain age, became mature and produced gonadotropin. The role of the brain in this phenomenon has since become increasingly apparent, beginning with the classic pituitary transplantation experiments of Harris & Jacobsohn (44). In this elegant study, pituitaries from newborn rats were transplanted under the median eminence of adult females which had just delivered and been hypophysectomized. Such animals were then observed for a period of time, and it was possible to show, in some cases as early as ten days after transplantation of the fetal pituitary to the maternal median eminence, that cyclical sexual activity had begun. Ordinarily it takes forty days, at least, for a newborn female rat to come into mature sexual cycling.

Fremont-Smith: Why do you compare the hypophysectomized mother with a newborn?

Reichlin: When the fetal pituitary is in the fetus, it takes forty days to become a cyclical organ; if transplanted into a mature animal it will do so in ten days. One inference from this work is that the property of maturity of cycling resides in the host brain, or in relation to the host, rather than in relation to the transplanted pituitary.

Several other interesting points are to be made from this experiment. One is that it does not make any difference whether a male or female pituitary is transplanted into the mother. Harris & Jacobsohn (44) made the very nice point, which Dr. Greep had originally observed (40), that the sexual differentiation of the pituitary lay in the special relationship it had with a particular brain, in this case a fully developed female brain (the brain of a female that had had adult sexual experience, i.e., had mated, conceived and brought forth young) rather than the sexual nature of the animal from which the pituitary was transplanted.

The work of Barraclough & Gorski (7) indicates that, if the female brain is exposed to male hormone at a critical time in its development, it does not develop as a female brain; it becomes a male brain. The androgen-treated female brain will not support cyclical sexual activity or female sexual behavior.

Fremont-Smith: Therefore, a female brain does not always mean a brain in a female. It is one exposed to female hormone.

Reichlin: Yes. As far as one can tell now, it is a female brain that has differentiated its function in the presence of a particular hormonal environment at a critical stage in its development.

Ganong: In the presence of female hormones or in the absence of androgens?

Reichlin: I do not know.

Gorski: I would say that it depends on the absence of either male or female hormones at least with respect to the regulation of gonadotropin release, but the regulation of sexual behavior may be an entirely different story.

Greep: Fetal ovaries have been put into adult animals. The ovary itself will develop very speedily.

Guillemin: The question of the sensitivity of the young ovaries to gonadotropins would also enter the picture. There is evidence that the immature ovary, even when transplanted, is not as responsive as the adult ovary to gonadotropin.

Reichlin: This is a very important point and covers something that has come out of work done by participants in this conference, and by Harris & Levine (45). The brain guides the direction of sexual development in the pituitary and, also, of sexual behavior. It is possible to show that if one gives an androgen to a female mouse or rat at a critical stage (in these two ani-