NEUROPHARMACOLOGY

TRANSACTIONS OF THE FIFTH CONFERENCE

MAY 27, 28 and 29, 1959

CONTENTS

Editor

HAROLD A. ABRAMSON, M.D.

Biological Laboratory, Cold Spring Harbor, and
State Hospital, Central Islip, New York

THE JOSIAH MACY, JR. FOUNDATION

PRICE: $6.00

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May 27, 28, and 29, 1959, Princeton, N. J.

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Sponsored by the
JOSIAH MACY, JR. FOUNDATION
New York, N. Y.

Library of Congress Catalog Card Number: 55-9013
Price: $6.00

The opinions expressed and any conclusions drawn are those of the participants of the conference and are not to be understood as necessarily having the endorsement of, or representing the viewpoint of, the Josiah Macy, Jr. Foundation.

Printed in the United States of America
By Madison Printing Company, Inc., Madison, New Jersey

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Fifth Conference on Neuropharmacology

THE JOSIAH MACY, JR. FOUNDATION CONFERENCE PROGRAM

DURING THE PAST fifteen years the Josiah Macy, Jr. Foundation has organized more than twenty conference groups, each group meeting for at least two days annually over a period of five or more years. Each meeting is limited to twenty-five participants (members and guests), selected to represent a multidiscipline approach to some urgent problem in the field of medicine and health. The goal of this conference program is the promotion of communication, the exchange of ideas, and the stimulation of creativity among the participants. The purpose of the publication of the Transactions of the meetings is to share, as far as possible, the conference process with a larger audience than could participate personally in the discussions.

These conferences provide an opportunity for informal give and take among the participants. To further this purpose, the number of presentations planned for each day is generally restricted to one or two. The member, or guest, selected to give such a presentation is requested not to "read a paper" but, rather, to highlight, in an informal manner, some of the more interesting aspects of his or her research, with the expectation that there will be frequent interruptions by participants in the form of questions, criticism, or comment. Such interruptions during the course of a presentation are encouraged and form an essential part of the "group interchange."

The conference program has always been viewed by the Foundation as an experiment in communication in which there is room for improvement and need for frequent reappraisal. Sufficient experience has already been gained to justify the conclusion that this type of conference is an effective way of improving understanding among scientists in medicine and allied disciplines, of broadening perspectives, of changing attitudes and of overcoming prejudices. The further conclusion has been reached, as a result of this experiment, that a major obstruction to understanding among scientists lies in the resistance of human attitudes to change, rather than in difficulties of technical comprehension. Less extensive experience with non-scientists has indicated that the effectiveness of this type of conference is not limited to groups of scientists, but will function in any group meeting where more effective communica-

tion is the primary goal. It is also clear that the same conference technique, with minor changes, is readily adapted to small international conferences.

The style of publication of the Transactions has aroused considerable interest and some criticism. The criticism has been directed primarily to editorial permissiveness which has allowed in the final text, in some instances, too many questions, remarks, or comments which, although perhaps useful during a heated discussion, seem out of context and interrupt the sequence of thought. A few have objected to the principle of publishing in this style and would prefer a depersonalized summary without interruptions.

The Foundation staff and the Scientific Editors of these volumes welcome criticism and hope to profit thereby in increasing the usefulness of the Transactions to scientists in this country and abroad.

FRANK FREMONT-SMITH, M.D.
Medical Director

AMINE METABOLISM AND ITS PHARMACOLOGICAL IMPLICATIONS

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I SHOULD LIKE to begin by reviewing the chemical processes involved in the formation and metabolism of the amines. I would like to consider all the amines at one time, for a change, because in the past it seems to me that we have had several schools of humoral agents. There has been the school of catecholamines, the school of serotonin, the group interested in acetylcholine, the group interested in GABA, and so on. Each one has its own adherents or disciples, and each acts somewhat as though neurochemistry revolved entirely around that particular substance. I think attempts to explain neurochemistry even on the basis of all, not to mention one, of them are rather difficult. It seems to me, also, that attempting to use one of the amines to explain mechanisms, might be like the blind man feeling the elephant, and trying to describe the whole by the part he is holding.

Table I indicates some of the amines that we have concerned ourselves with in the past, and some that we may have to concern ourselves with in the future. I will discuss the evidence for the latter as we go along. I think the important thing to point out is that everything we shall discuss, whether it be choline, acetylcholine, norepinephrine, GABA, or histamine is derived from dietary amino acids.

Figure 1 shows that all of the amines involve decarboxylation of an amino acid, whether it is a dietary amino acid or an oxidized form of amino acid, plus certain additional metabolic steps.

I would like to start the discussion by pointing out the similarities in the metabolism of amines, and then discuss those points which either have been attacked or utilized by physiological engineers or pharmacologists to influence the function of animals or human beings, and this might include therapy as well. Perhaps, from our discussion, we can

TABLE I

Dietary Amino Acid	Amine
Tyrosine	Dopamine, Norepinephrine, Epinephrine, Tyramine
Tryptophan	Serotonin, Tryptamine
Histidine	Histamine
Serine	Choline, Acetylcholine
Glutamic Acid	GABA, (OH-GABA), Carnitine
Phenylalanine	o-Tyramine, m-Tyramine

find out which points are vulnerable to such attack; which points are the poorer risks and which are the better ones, and what evidence there is that certain drugs which are supposed to act in a given manner are indeed acting in that way *in vivo* and in patients.

Before speaking about the enzymology of the amines, I would like to mention something about their occurrence. Most of these substances can be determined by chemical or by biological procedures, and it is known that they do not occur indiscriminately in all organ tissues. Acetylcholine is present in certain nervous tissues, serotonin is found in very defined areas, and epinephrine and dopamine are found in very specific areas. It is now evident that γ-amino-butyric acid is highly localized in the central nervous system. The mere localization of these substances, therefore, is an indication of where the substance is used, and it also indicates that something more than a mere oddity or some whim of nature must have produced them. As we find more of these substances and study them more carefully, we may get some further idea from such chemical localizations as to their possible functions.

The next step concerns some of the enzymes involved. The first enzyme I would like to discuss is one that involves oxidation of an amino acid to an oxidized form. A number of amines that we study are formed by the decarboxylation of a primary dietary amino acid. These

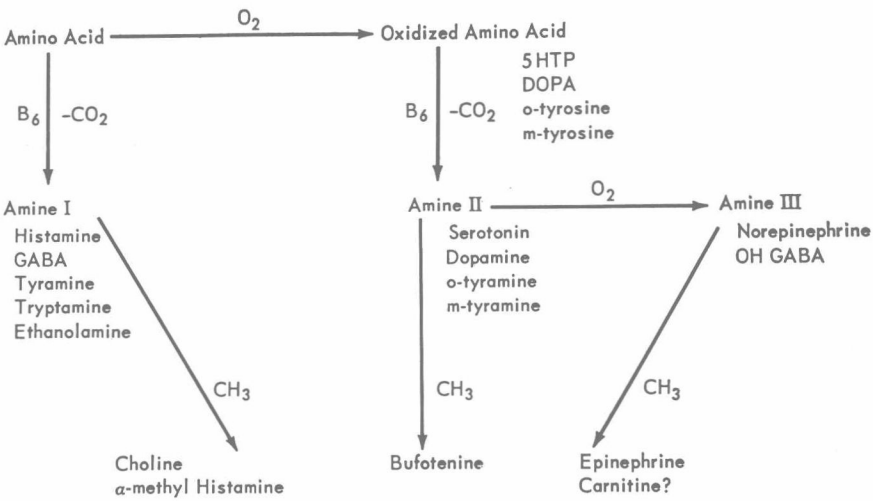

FIGURE 1.

include histamine, GABA, tyramine, tryptamine, and ethanolamine. Then, there are some very important substances, two of which we know particularly, 5-hydroxytryptophan and DOPA, which are formed by oxidation of tyrosine and tryptophan, respectively; these are new non-dietary amino acids. Here the amines are formed by subsequent decarboxylation, so that a primary hydroxylation is involved.

Figure 2 shows hydroxylation in the case of tryptophan. Up until now, we have been able to demonstrate this only in bacteria and in the toad, where an hydroxylation of tryptophan in the 5 position occurs. The nature of the enzyme has not yet been determined because it has not been possible to purify it from any of its sources.

I have recently received a letter from Dr. Jack Cooper* in Professor Welch's laboratory at Yale, indicating that he has been able to partially purify this enzyme from intestinal mucosa, which is about the richest source of serotonin. Dr. Cooper states that the enzyme appears to be flavoprotein in nature. We may be on the verge of getting some information about this important step in serotonin synthesis.

In the case of tyrosine, leading to 3, 4-dihydroxyphenylalanine, the first step leading towards norepinephrine, we know very little about the enzyme, except that it does not seem to be the same as the enzyme that forms DOPA, leading towards melanin. Tyrosinase, which we do know about, does not appear to be present in the adrenal medulla or in the

*Jack R. Cooper, Department of Pharmacology, Yale University: Personal communication.