A BIOCHEMICAL AND PHARMACOLOGICAL SUGGESTION ABOUT CERTAIN MENTAL DISORDERS

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Recent findings in this laboratory[1, 2] and elsewhere[3, 4] have permitted an understanding of some aspects of mental diseases in relation to the hormone-like compound, serotonin. Furthermore, these findings lead directly to a suggestion for a logical treatment of diseases known as "schizophrenia." The experimental observations have been made solely on laboratory animals, but they have reached a point where clinical trials in human psychiatric patients are required to test the validity of the conclusions. Being only biochemists, we are unable to do these experiments on patients and can only hope that this paper will stimulate those who are professionally qualified to undertake in man what we cannot pursue further in laboratory animals.

This discussion is going to revolve about serotonin,[5] or enteramine, if Erspamer's terminology is followed.[6] Serotonin is one of the latest hormone-like substances to be discovered. Chemically it has been shown to have the structure given in Figure 1.[7] Being a simple molecule, it has been synthetically produced without great difficulty[8, 9] and is thus readily available. It was discovered because it is the vasoconstrictor long known to form in the serum when blood clots. Erspamer's work[6] with it, done independently of that of Rapport, *et al.*,[5] on the vasoconstrictor material, was based on the abundant occurrence of this new compound in the enterochromaffinic cells of the gastric and intestinal mucosa. Serotonin has now been isolated from several different organs, including the brain, of a wide variety of animal forms.[10–12] There can be no doubt of its wide-spread occurrence in living things. Furthermore, a variety of pharmacological properties in isolated organs and tissues has been demonstrated, in addition to the vasoconstrictor effect.[6, 13] The pharmacological properties which have been described thus far are attributable in large part to the ability of serotonin to cause various smooth muscles to contract; but there are indications that it has other effects which may become more clearly defined as time for study of them goes by.

Aside from the occurrence and importance of serotonin, a second general idea is prerequisite to this discussion. It is now well known that several classes of drugs are related chemically to individual hormones and other essential metabolites.[14, 15] In fact, a major part of the pharmacological effects of these drugs is attributed to a specific interference with the biological functioning of these metabolites to which the drugs are related structurally. That is, the drugs are antimetabolites.

Our thinking and experimentation about certain mental disorders has been in the following vein. Several synthetic compounds have been produced which are very closely related in structure to serotonin. These were shown to antagonize, in a competitive fashion, the contractions of artery walls caused by serotonin.[16, 17] Also, the fact that the ergot alkaloids are structurally related to serotonin was appreciated, and it was demonstrated that several of these actually did antagonize

the action of serotonin on artery walls.[1, 2] A derivative of the ergot alkaloids, namely, lysergic acid diethylamide (cf. Fig. 1), was then shown by Gaddum, *et al.*,[3] to act as an antimetabolite of serotonin on smooth muscles. It is well known that this amide calls forth in man mental disturbances resembling those of schizophrenia.[18] From these experiences we therefore conceived the idea that the mental disturbances caused by lysergic acid diethylamide were to be attributed to an interference with the action of serotonin in the brain. The failure of ergotamine or of ergotoxin to produce similar mental aberrations was postulated to be due to the failure of these more complex derivatives of lysergic acid to penetrate into the brain. Gaddum also was cognizant of the mental effects of lysergic acid diethylamide and of the occurrence of serotonin in the brain. We have surmised that he has been thinking, just as we have, about the relationship of serotonin to the mental disturbances induced by the drug.

Even before the study of the ergot alkaloids as antimetabolites of serotonin, another type of alkaloid, viz., yohimbine, was recognized to be structurally similar to serotonin and was actually demonstrated to function as an antimetabolite of it in the artery-wall test.[1, 2] Then two members of yet a third class of alkaloid—the harmala alkaloids—were seen to be structural analogues of serotonin and were actually shown to antagonize its action on artery walls.[2]

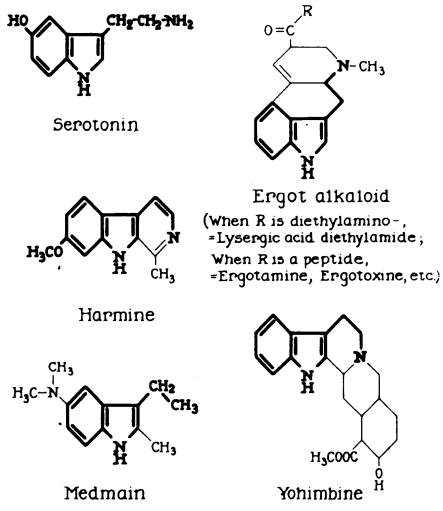

FIG. 1.

Although the chemical structures of the ergot alkaloids, yohimbine, and the harmala alkaloids are not very similar, all three classes of drugs have in common a resemblance to serotonin (Fig. 1). In each case the hormone has been modified in a different way in order to arrive at the particular class of alkaloid. Furthermore, they have all been shown to function as antagonists to the hormone.

The important point for the present discussion is that they all have something else in common. This is the ability of at least some members of each group to cause mental disturbances. If one does no more than read a textbook of pharmacology, one is struck by this fact.[19] Witness the production of schizophrenia with simple amides of lysergic acid, the hallucinations and euphoria called forth by some of the harmala alkaloids, and the mental disturbances attributed to the use of yohimbine. Perhaps even the aboriginal use of crude yohimbine as an aphrodisiac is further small evidence.

Bearing in mind the mental disturbances caused by alkaloids known to be antagonists of serotonin, let us examine other types of compounds which are not alkaloids but merely synthetic serotonin antagonists. What do we find? The highly active synthetic antimetabolite of serotonin, medmain (cf. Fig. 1),[20] when injected into mice, calls forth convulsions much resembling those of human epilepsy. Hydrazino-phthalazine, which is said by Taylor, Page, and Corcoran[4] to antagonize some

of the biological effects of serotonin, has been found to produce in man mental aberrations somewhat similar to those of schizophrenia.[21]

The thesis of this paper is that these pharmacological findings indicate that serotonin has an important role to play in mental processes and that the suppression of its action results in a mental disorder. In other words, it is the lack of serotonin which is the cause of the disorder. If now a deficiency of serotonin in the central nervous system were to result from metabolic rather than from pharmacologically induced disturbances, these same mental aberrations would be expected to become manifest. Perhaps such a deficiency is responsible for the natural occurrence of the diseases.

Of course, this may be the wrong inference from the pharmacological findings. It must be recognized that the classes of alkaloids and synthetic drugs we have been discussing are the very ones which, at one time or another, have been used for the reduction of high blood pressure. The mental disturbances may be no more than the reflection of diminished blood flow which they may cause in the brain. To this objection there is as yet no adequate answer, and it may be that it is the true explanation.

If the hypothesis about serotonin deficiency is accepted, then the obvious thing to do is to treat patients having appropriate mental disorders with serotonin. It is here that one must be a clinician rather than a biochemist; for how is one to induce, or even more to diagnose, schizophrenia in laboratory animals?

One may ask whether the administration of serotonin to humans is a safe procedure. More information is certainly needed on this point, but the few reports in the literature, where it has been done, as well as the toxicological studies in animals indicate no great risk.[22-24]

If serotonin is to be given to selected mental patients, it will probably have to be injected intramuscularly or subcutaneously. What assurance is there that it will find its way to the brain, even though it were to escape destruction by amine oxidase and possibly other enzymes in the periphery? The answer is that we have no assurance that it will reach the central nervous system or persist there. Most experience in experimental animals would, in fact, indicate that serotonin is rapidly destroyed, especially when given by the intravenous route. We have made estimations (by chemical assay) of the amount of serotonin found in the brain of a mouse 10 minutes after the intraperitoneal injection of 5 mg. of it, and have found less than 0.01 mg. Nevertheless, because mice are not necessarily the same as men in this respect, the clinical trial of serotonin in mental disorders may still be worth while.

If destruction or failure to penetrate the central nervous system should render abortive attempts to treat schizophrenia with intramuscular serotonin, then the idea should not be abandoned until the biochemists have made one more effort. This is so to alter the structure of the hormone that it will remain long-acting in the body and will penetrate into the brain from the peripheral circulation. This may not be an impossible task. There are already several indications that such desirable properties can be built into metabolites such as serotonin.

In summary, the suggestions we wish to make are the following: (1) serotonin probably plays a role in maintaining normal mental processes; (2) metabolically induced deficiency of serotonin may contribute to the production of some mental

disorders; (3) serotonin or a long-acting derivative of it may prove capable of alleviating disorders similar to schizophrenia.

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DYNAMIC PROGRAMMING AND A NEW FORMALISM IN THE CALCULUS OF VARIATIONS

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1. *Introduction.*—In a series of papers,[1-11] we have treated a number of mathematical problems arising from multistage decision processes. Problems of this type occur in the theory of probability;[1, 4, 5, 9] in mathematical economics;[1, 2, 6, 7, 8, 11] in control processes;[2, 8] in learning processes;[4, 9] and in many other fields as well.

In this paper we wish to show that the functional-equation technique introduced in the above works may be used to provide a new approach to some classical problems in the calculus of variations. In addition to furnishing a new analytic weapon, we feel that the method has great potentialities as a computational tool. As we have pointed out previously,[1, 3, 4] this approach seems ideally suited to the handling of variational problems involving stochastic processes. This point will be further enlarged upon in some forthcoming publications.

To illustrate the approach in its simplest setting, we shall consider first the problem of maximizing $\int_0^t F(x, z)\, du$, subject to the constraint $dx/du = G(x, z)$, $x(0) =$