Dis.nerv.Syst. 21, Monogr.Suppl. 87-96 (1960).

LSD 734/BOL/(PSI)

# Serotonin in Mental Disorders

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To state the case briefly, one should say that during the past few years evidence has been accumulated which indicates that the hormone serotonin has a function in maintaining normal mental processes, and that interference with its action in the brain leads to mental disorders and neurological dysfunction. This concept was first enunciated by Woolley and Shaw early in 1954.[16,17] It was based on their studies of antimetabolites of serotonin, the first of which was published in 1952.[13] Since that time a variety of observations have lent support to the original idea.

Because the idea that serotonin might be concerned in mental processes arose from studies of antimetabolites of it, let us first refresh our memories about what an antimetabolite is, and how it functions. In any living thing there are a number of chemical compounds which are specifically essential for various vital processes. These are called essential metabolites, or, more simply, just metabolites. Examples are vitamins such as thiamine, ascorbic acid, etc., and hormones such as thyroxine, testosterone, serotonin, adrenalin etc. Each of these metabolites serves as a specific substrate for a special metabolic reaction. The substrate fits the enzyme of such a reaction just as a key fits its lock, and the turning of the lock opens the door of some special living process. We may picture serotonin as one of these keys which fits a lock called the serotonin receptor. When the two interact we see the result as a pharmacological effect. With serotonin this is usually the contraction of a smooth muscle. This contraction is the most studied aspect of serotonin's action.

An antimetabolite of serotonin is a chemical compound which is shaped to resemble this hormone. Because of this structural resemblance, the antimetabolite can be thrust into the serotonin receptor, i.e., the special lock, just as the hormone itself can be. However, because the antimetabolite differs in some detail from the real metabolite, the lock cannot be turned by it. It therefore occupies the space, and excludes the normal entry of serotonin. The result is the creation of a specific deficiency of this hormone. We see this effect of the antimetabolite in an animal (or in one of its isolated tissues) by a failure to respond to administered serotonin. Such an animal still responds normally to other metabolites just as locks are not blocked by keys unrelated to the proper ones.

This crude mechanical analogy permits us to visualize what an antimetabolite is, and how it functions. An antimetabolite of serotonin is thus a structural analog of it, and one which is able to exclude the hormone itself from its receptor thereby creating a deficiency of it. It is important to note the two parts of this definition. An antimetabolite is not merely a structural analog of a metabolite. It must be both a structural analog and a biological antagonist. The structure of serotonin is shown in Figure 1. The first two antimetabolites of it, which were synthesized in 1952, are also shown there.

Woolley and Shaw had started the search for antimetabolites of serotonin in the winter of 1951-2 in the hope of thereby discovering a drug useful in the treatment of essential hypertension.[13] Some synthetic compounds, including those shown in the first slide, were produced and found to act on smooth muscles as antagonists to the contracting action of serotonin. Before this work had proceeded very far it was realized that various naturally occurring drugs in addition to these new synthetic compounds, were also structural analogs of this newly

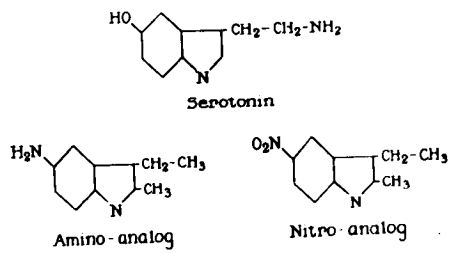


*Fig. 1.* Structure of serotonin with the amino and nitro analogs.

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discovered hormone. It was then quite easy to show that these drugs actually did function as competitive antagonists of serotonin on smooth muscles. This made it seem quite probable that part at least of their pharmacological action was due to this antiserotonin property. The drugs were actually naturally occurring antimetabolites of serotonin.[7,15]

There were three principal classes of such drugs. These were the harmala alkaloids of which harmine (Fig. 2) is an example, yohimbine, and its more recently discovered congener, viz. reserpine (Fig. 3), and the ergot alkaloids such as ergotamine and lysergic acid diethylamide, or LSD (Fig. 4). These slides have been arranged in this order so that the gradually increasing molecular complexity can be seen. The structural resemblance of harmine to serotonin is plain, but is not so plain with yohimbine and LSD. However, having seen the close analogy with harmine you can observe that yohimbine is just a more complicated compound of the same sort. Reserpine may then be regarded as a somewhat more complicated derivative of yohimbine. There thus exists an extended series of compounds (several of which have not been mentioned here) of graded complexity but with the common points of structural resemblance to serotonin and of pharmacological antagonism to it. The ergot alkaloids form a somewhat different group, because in them the resemblance to serotonin is different. The side chain of the hormone has been fused to the benzene ring rather than to the indole ring, as in harmine. In our studies of 1952-3 these substances were shown to act as competitive and reversible antagonists of serotonin when tested on segments of carotid artery or rat uterus. A few data to illustrate this point for LSD are shown in Figure 5, and for harmine as tested on the rat uterus, in Figure 6. Much more extensive data on these and related compounds can be found in our original papers and in subsequent publications from the laboratories of Dr. Gaddum[5] and of others.

Several of these naturally occurring antimetabolites of serotonin were known to cause psychiatric disorders in men and to cause behavioral changes in animals. Thus, LSD especially had been found to be outstanding in this respect because of the minute doses of it which would call forth a psychiatric state in man resembling schizophrenia.[9,10] In fact, LSD was not the first ergot alkaloid found to disturb the mind. It is well to remember that a prominent feature of ergotism in man was the mental or psychiatric changes which were reviewed long ago by Barger,[1] and to recall that since there is no LSD in natural ergot, the other ergot alkaloids must be capable of causing these effects if the dose is large enough. A distinguishing feature about LSD is the smallness of the dose required. The other types of alkaloids, now seen to be related to sero-

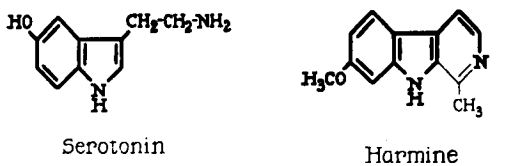



*Fig. 2.* Harmine structure.

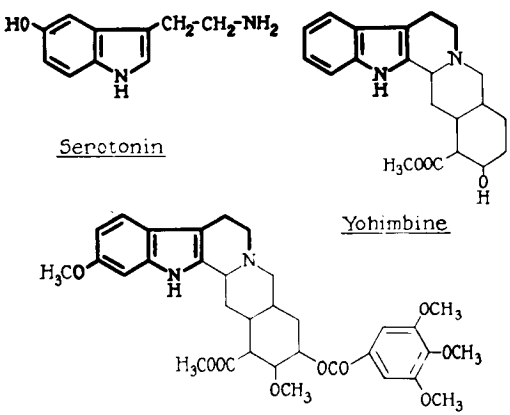



*Fig. 3.* Serotonin, yohimbine, and reserpine structures.

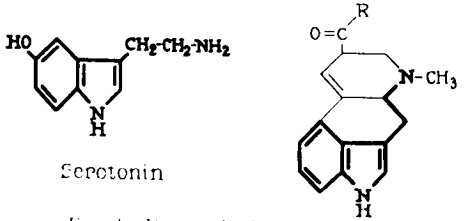



*Fig. 4.* Ergot alkaloid structures.
When R is diethylamino: Lysergic acid diethylamide;
When R is a peptide: Ergotamine, Ergotoxine, etc.

tonin likewise have a long history relative to psychiatry. Thus harmine has long been known to cause a type of deranged behaviour in dogs and other animals. The aboriginal use of crude yohimbine as an aphrodisiac may be taken as evidence that this compound as well affects the mind.

These psychiatric effects of compounds which we had just found to be antimetabolites of serotonin were engaging our attention when we were fortunate to find that some of the new synthetic antimetabolites of serotonin were capable of causing behavioural changes in animals. The nitroindole shown in Figure 1 had been the first promising antiserotonin suitable for trials in hypertension.[11] When it was studied for toxicity in mice prior to human trial, I had noticed that a few of these animals which had eaten large amounts of it for a long time showed a change in character. They became savage, and would run toward me and bite my hand when I fed them. This was an ill defined change, and was not seen in all the mice, and was consequently of questionable significance. When this same compound was given to Dr. R. Wilkins for clinical test, however, the significance of the mouse result was plain. This antimetabolite of serotonin caused profound mental depression in humans.

At about this same time, a new antiserotonin was synthesized and found to cause convulsive fits in mice. This was medmain, the structure of which is shown in Figure 7. This was a potent antiserotonin when tested on smooth muscles[8] but when it was given to mice in rather large doses it caused convulsive fits which were impressively reminiscent of epileptic seizures in man.

Since that time, we have made other close structural analogs of serotonin which have called forth in dogs irrational behavior. Other laboratories, also, in their search for antiserotonins, have had similar experiences. Thus, a few analogs of serotonin, which have shown no striking toxicity in laboratory animals have been given clinical trial in the treatment of hypertension, but have had to be abandoned because of psychiatric side effects. It was not until we had fully appreciated the danger of causing undesirable effects on the mind, and had found a way of avoiding these effects, that it was possible to produce a compound which showed clinical promise in hypertension. Such a compound has now been produced.[19] We may view the finding of mental disorders caused by certain antiserotonins as a byproduct of these efforts against hypertension.

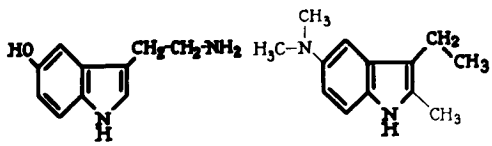
The reason why serotonin got into psychiatry, then, was because of pharmacological studies with smooth muscles. Several of the analogs of serotonin, which acted as antimetabolites of it, caused psychiatric changes in men and behavioral changes in animals. This correlation was first made in 1954[16,17] and it was argued that since the effect of the antimetabolites on muscle was to cause a deficiency of serotonin, the mental

*Serotonin vs. Lysergic Acid Diethyl Amide (LSD) in the Contraction of Carotid Artery Rings*

| Serotonin | LSD | Decrease in diameter of ring |
|---|---|---|
| gamma/cc | gamma/cc | per cent |
| 0 | 0 | 0 |
| 0.2 | 0 | 31 |
| 0.2 | 0.03 | 23 |
| 0.2 | 0.1 | 15 |
| 0.2 | 0.3 | 12 |
| 0.2 | 1.0 | 6 |
| 0 | 10.0 | - 3 |

*Fig. 5.* LSD on artery rings.

*Fig. 6.* Harmine on rat uterus. S=Serotonin; W=Wash; H=Harmine.




Serotonin Medmain

*Fig. 7.* Medmain structure.

effects of the same compounds might be the manifestation of a similar serotonin deficiency somewhere in the brain.

Although this idea of deficiency of serotonin is plausible, there is another view of the data which must be taken into account. This is that the analogs of serotonin which affect the mind do so because they act like serotonin rather than antagonistically to it. This alternative was considered in the original paper[17] and it has grown a little in stature since. To return to the lock and key analogy one would say that some of the serotonin relatives fit well enough into the serotonin receptor of the brain that they can take the place of the hormone and carry out some of its functions. One might also picture them as acting to inhibit the enzyme (amine-oxidase) in the brain which normally destroys excess serotonin. Inhibition of this enzyme would lead to the piling up of excess serotonin. Because this hormone is a substrate for this enzyme, a structural analog might be expected to inhibit it. Two modes of action, both leading to an excess of serotonin in the brain might thus be pictured, and are alternatives to the idea that a deficiency of cerebral serotonin is the cause of the psychiatric disorder. To distinguish with certainty between these two alternatives is very difficult. The need to do so is great because it is vital to the understanding of the disease and to rational attempts to control it via the serotonin route.

Although LSD has been shown by many workers in a variety of pharmacological tests to be a potent and a specific antagonist of serotonin, it can also be shown to act like serotonin. Marrazzi and Hart were the first to find evidence of this which they did by studies with the optic cortex of cats. We also found that LSD stimulates the heart of the clam Venus mercenaria in a serotonin-like manner. Welsh has made similar observations. Getting closer to home phylogenetically and examining dogs, we have also observed that just as serotonin caused rises and falls in the arterial blood pressure, so also LSD caused these same effects. In fact, on a weight basis, LSD was about three times as powerful as serotonin in both of these tests. Furthermore, the rise in blood pressure of the dog which was caused by LSD was prevented by a specific antimetabolite of serotonin (Figure 8). This was additional evidence that the action was serotonin-like. The antimetabolite used in this experiment was the one recently found to be active in human hypertension without causing mental disorders.[19] Its structure is shown in Figure 9. Clearly then, LSD has some serotonin-like actions.

Not only does LSD have serotonin-like as well as antiserotonin properties; serotonin itself will act as an antiserotonin, and will do so quite specifically. Gaddum showed that an excess of the hormone would render the rat uterus insensitive to the amounts which ordinarily would cause it to contract.[1] Shaw

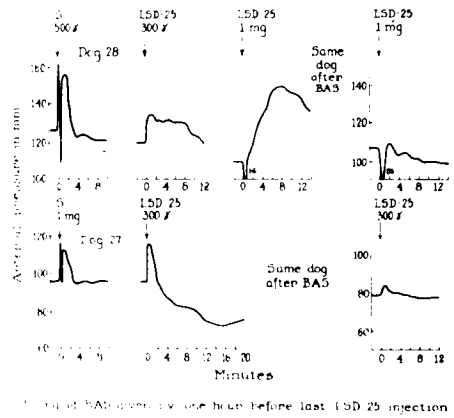
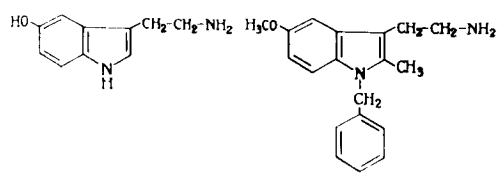



*Fig. 8.* LSD and BAS on dogs' blood pressure.




Serotonin 1 Benzyl 2,5 dimethyl-serotonin
Benzyl analog of serotonin (BAS)

*Fig. 9.* BAS structure.

and Woolley[9] have shown this same sort of antiserotonin action in living dogs in the blood pressure test. This type of effect is readily understood in terms of the lock and key model. The serotonin receptor is simply blocked by several molecules of the hormone all attached to the site at which one molecule must combine if the hormone is to exert its usual effect. This point should not be mystifying because it is the well-known phenomenon of inhibition of an enzyme by an excess of its substrate.

We must now ask ourselves whether all of the other analogs of serotonin which have been found to affect the mind and the central nervous system likewise have a serotonin-like action. If they do, then the idea of serotonin excess rather than deficiency as the causative factor must be given prominence. When harmine was tested on isolated rat uterus for serotonin-like action none was found. (Shaw and Woolley, unpublished data.) Similarly, when harmine was tested for pressor action in dogs, none was found. However, in the blood pressure test, subsequent challenge with serotonin revealed an enhancement of its action in the case of the dog, and an antagonism in the case of the rat uterus. Similarly, the nitroindole shown in Figure 1 was only an antagonist of serotonin in the dog, but Welsh[11] found it to act like serotonin on the heart of the clam. Medmain was found by Shaw and Woolley to be only an antiserotonin on sheep arteries, but to have some serotonin-like action on isolated rat uterus.[8] All of this indicates clearly that whether one finds antiserotonin or serotonin-like effects very often depends on the tissue or species chosen for study. It is useless to attempt to decide the matter by finding an hallucinogenic compound which acts only as an antiserotonin on all tissues. The risk is always great that although on 10 test objects a compound will act only as an antagonist, on the eleventh it may show some serotonin-like effect. Several substances have been found to act like serotonin and to be at the same time and on the same tissue antagonists of it. The effect which is seen depends on the concentration applied. Serotonin itself as described above is a case in point. Whether an excess or a deficiency is the causative factor is not easy to resolve. Especially is this true when attempts are made to infer from isolated muscles which of the opposing actions is being exerted on human brain.

You will ask why this question of too much or too little serotonin has not been solved simply by injection of this hormone. The reason is that in animals, peripheral injection leads to no increase in the brain content. In other words, peripherally administered serotonin passes into the brain only in amounts too small to measure. Direct injection into the brain has been tested in animals, but is not something which one can do in human beings. The chief impression gained from animals given intracerebral serotonin is lethargic behavior, a drowsiness and unwillingness to move normally (catatonia). If the dose is increased to gigantic amounts (1-5 mg. per kg.) this lethargic state may give place to violent convulsions, resembling those provoked by medmain. The natural precursor of serotonin, viz. 5-hydroxytryptophane, has been shown by Udenfriend and his collaborators to pass the blood-brain barrier, and to increase serotonin content of the brain. Peripheral injection of this precursor in huge amounts does lead to convulsions in some species and we have seen it cause marked central effects in dogs and mice. Some of its effects on man will be mentioned later.

To summarize these points then, it should be said that simple direct injection of serotonin has failed to show what sort of effect, if any, it has on the brain. The reason for failure seems to be that serotonin does not reach the brain. We now have as a result of Udenfriend's work the natural precursor of serotonin. This has the great advantage that it does penetrate into the brain and increases the serotonin content of that organ. Animals with increased cerebral serotonin do show behavioral changes as evidence that their brains are affected by the hormone.

As a result of the foregoing findings, we can picture an animal as being divided into two compartments with respect to serotonin. One of these is the nervous system. There it has been shown that serotonin is produced and the evidence suggests that it plays a role there. The other compartment is the remainder of the animal where serotonin is

also produced and exerts an effect. However, serotonin from the periphery appears to penetrate into the central nervous system only with difficulty, if at all. It must be remembered, however, that this is a working hypothesis. It is based on the experimental finding that injection of serotonin into the periphery in large amounts (compared to that already there) brings about no measurable change in the serotonin content of the brain. On the contrary, when the precursor of the hormone is injected peripherally, it does penetrate into the brain and is converted to serotonin there. A measurable increase of cerebral serotonin is achieved.

Let us return now to the antiserotonins because the evidence derived from human beings has been obtained mostly through the use of these antagonists. Some of these analogs of serotonin, as we have seen earlier, cause psychiatric effects in men. The fact that these analogs are antagonists to serotonin (and sometimes serotonin-like) has been demonstrated thus far only on isolated smooth muscles or in animals in which one measures a peripheral effect such as change in blood pressure. We want to know whether there is any justification for transferral of such results to arguments about action in the brain. Indeed we will want to know if serotonin has any demonstrable action at all on the brain. We have been troubled by these questions and have made the following experiments in an effort to study them. Through the cooperation of Drs. M. Murray and H. Benitez of Columbia University it has been possible to find a visible effect of serotonin on a special kind of brain cell cultured *in vitro*. Furthermore, it has been possible to show that a few of the antimetabolites of serotonin will overcome this action on the brain cells just as they antagonize serotonin in smooth muscles.

In the brain there are special cells, the oligodendroglia, which have a pulsating movement. This contraction and expansion of these cells reminded us of the characteristics of smooth muscles on which serotonin acts. It seemed possible that these structures would be caused to contract with serotonin. Both human and rat oligodendroglia were examined in tissue culture, and it was found that serotonin did in fact cause them to contract strongly. Dr. Murray has made a time-lapse movie which shows the normal pulsation and the effect of serotonin.

This effect of serotonin seemed to be specific for oligodendroglia, because astrocytes were not caused to contract. The appearance of human oligodendroglia during pulsation can be seen from Figure 10. This slide shows a group of these cells. You will note that some were in a state of contraction, while others were relaxed when this picture was taken. Consequently it is necessary to follow the actions of individual cells in order to see the phenomenon. For this purpose, certain cells in the photographs have been marked. Thus cell number 1, in the three exposures shown on Figure 10, can be seen relaxed, then in the process of contraction, and finally contracted. The fuzziness of outline in the middle picture resulted because during the exposure of the film the outlines of the cell had been changing.

The action of serotonin is shown in Figure 11. A fully developed contraction can be seen as it appeared 30 minutes after application of the serotonin (5 gamma per cc.). At this time the effect was at its greatest.

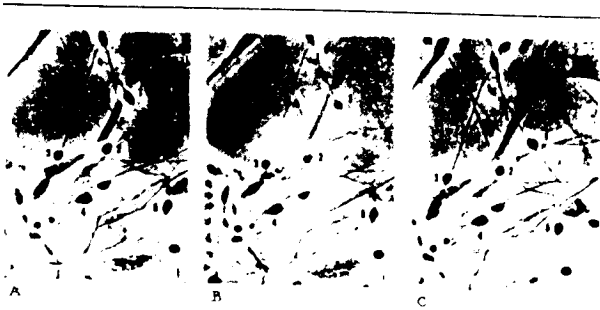



*Fig. 10.* Normal oligodendroglia during contraction.

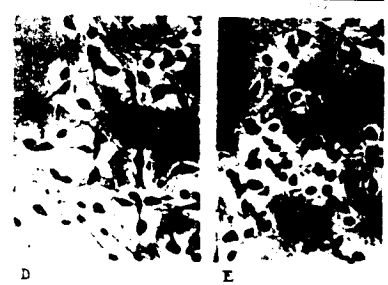



*Fig. 11.* Oligodendroglia contracted with serotonin.

The cells remained in this contracted state for about an hour, when they then slowly resumed normal pulsations.

The contractile effect of serotonin on human oligodendroglia was overcome by synthetic antimetabolites of serotonin such as medmain and 1-methylmedmain. Application of these compounds in low concentration to the contracted cells caused the resumption of normal pulsation. The antimetabolites caused no discernible effect at this same concentration when applied to normally pulsating cells in the absence of serotonin. However, at considerably higher concentrations they were toxic. The closeness of correspondence between the results obtained on smooth muscles (rat uterus) and those on the brain cells was striking indeed. Especially was this true with respect to one curious difference between medmain and 1-methylmedmain. These two antimetabolites of serotonin are very closely related in chemical structure, and they have equal potency as antiserotonins both when tested on rat uterus as well as when tested on human oligodendroglia. However, at higher concentrations, medmain, but not 1-methylmedmain, had a serotonin-like action on uterus. It was of much interest to see that the same was true on the oligodendroglia. What was even more interesting was that medmain, but not 1-methylmedmain, caused the convulsive fits in mice. We had earlier associated this convulsant action of medmain with its serotonin-like effect, and had regarded it as a serotonin-like compound which, in contrast to serotonin itself, was able to penetrate into the brain readily. The ability to demonstrate all of these findings again in brain cell cultures just as they had been found to exist in smooth muscle preparations, encouraged us to believe that the results on smooth muscles have a bearing on the reactions of brain to these compounds. A summary of the findings with the oligodenroglia is shown on Figure 12.

The action of LSD also was studied in human oligodendroglia. The results were more complex than with the two medmains. The first effect seen with LSD was a relaxation and vacuolization of the brain cells. This was then followed by a strong, serotonin-like contraction. Under suitable conditions of concentration one could prevent the initial flaccidity by administration of serotonin. In this respect then, an antagonism was demonstrated. The subsequent contraction was not antagonized by serotonin, in fact, it was augmented by it. In this system then, LSD showed both pro- and anti-serotonin actions just as is the case in the test using blood pressure responses of dogs.

These studies with oligodendroglia are only beginning, and much remains to be

*Serotonin and Analogs: Effects on Oligodendroglia*

| *Compound* | *Concentration per ml. (gamma)* | *Results* |
|---|---|---|
| Serotonin | 2 | Ineffective (normal pulsation) |
| Serotonin | 5 | Prolonged contraction for 60-90 minutes |
| Medmain | 100 | (Toxic) Contraction starting after 3 hours |
| Medmain | 200 | Immediate contraction (toxic) |
| Serotonin + medmain simultaneously | 5 + 50 | Normal pulsation |
| Serotonin + medmain after 33 minutes | 5 + 50 | Releases serotonin-contracted cells |
| 1-Methyl-medmain | 5 | Ineffective (normal pulsation) |
| 1-Methyl-medmain | 50 | Ineffective (normal pulsation) |
| 1-Methyl-medmain | 200 | (Toxic) |
| Serotonin + 1-methyl-medmain simultaneously | 5 + 50 | Normal pulsation |
| Serotonin + 1-methyl-medmain after 30 minutes | 5 + 50 | Releases serotonin-contracted cells |
| LSD | 5 | Relaxation —> contraction —> pulsation |
| LSD | 100 | Above course prolonged (toxic borderline) |
| Serotonin + LSD simultaneously | 5 + 50 | Increases contraction induced by serotonin |
| Serotonin + LSD after 33 minutes | 5 + 50 | Increases contraction induced by serotonin |
| Serotonin + LSD after 52 minutes | 5 + 5 | Increases contraction induced by serotonin |
| Serotonin + LSD after 35 minutes | 2 + 20 | Normal pulsation |
| Control (balanced saline) | | Normal pulsation |

*Fig. 12.* Summary of oligodendroglia results.

done. They seem to show that one can find a visible action of serotonin on a particular part of the brain, and they may provide a means of testing which is more relevant than are assays with smooth muscles. The reader is referred to the original paper for sequential photographs which illustrate the effects which have just been summarized.

The demonstrable action of serotonin on oligodendroglia provides us with a clue about one of the possible ways in which interference with serotonin in the brain may lead to hallucinations and convulsions. This is probably not the only function of this hormone in the brain and much more will need to be done to prove the following idea. Nevertheless, it may have some value since it seems to account for many of the phenomena which have thus far been seen. Because the brain is poorly vascularized in comparison to organs such as kidney, it has seemed that some means is necessary to insure adequate circulation of extravascular fluids in order that oxygen, glucose, and other requisites reach the cells rapidly enough. The pulsations of the oligodendroglia, and their anatomical situation in the brain, suggest that these cells are little stirring devices which circulate the extravascular fluid. If they were to be stopped, either by a tetanic contraction or by flaccidity, then this circulation would be impeded. It is well known that convulsions are a common result of anoxia of the brain. Conceivably, a deficiency of oxygen in the cell bodies could arise from stoppage of these stirring devices. It is not so well known, but most terrifying anxiety can be evoked in a nevertheless true, that hallucinations and normal man just before he loses consciousness in hypoglycemia. I myself have experienced this effect called forth by injection of insulin. Anoxia and hypoglycemia of the brain are thus known to elicit the effects which we wish to connect with serotonin. Interference with the stirring action of the oligodendroglia conceivably could bring about a deficiency of glucose in the cell bodies. However, it must be stated again that there may be other more direct actions of serotonin on neural functions. The action on oligodendroglia is possibly one of many. It is, however, one which we should not neglect.

Let us now return to the question of how the psychiatric effects of analogs of serotonin are to be interpreted in relation to mental disorders. If the analogs act like serotonin the inference for schizophrenia is that the symptoms may arise from too much serotonin, whereas if they act primarily as antagonists of serotonin the mental disturbance is probably to be interpreted as the result of too little serotonin. During the last few years considerable new evidence has been obtained which indicates that the excitement and mania can be the result of too much cerebral serotonin and that depression can result from too little. The evidence thus far presented may be summarized as follows:

(1) In experiments with normal men and normal laboratory animals given analogs of serotonin, the findings in general are that those compounds which cause hallucinations and other clear indications of excitement can be shown readily to have a serotonin-like action in several pharmacological assay systems. Those which cause depression and tranquilization usually behave as antagonists of serotonin. Of course, the lines are not cleanly drawn, for, as mentioned earlier, an analog which usually behaves as an antagonist can be found to show serotonin-like action if one searches long enough for a suitable test system. Nevertheless, the generalization just given seems to be true, and the numbers of new compounds which support such a view continue to increase. Thus, LSD, bufotenine (or N, N-dimethylserotonin), psilocybine (the phosphate ester of a bufotenine isomer), and medmain are all relatives of serotonin in which the ability to incite mental changes such as hallucinations, profound excitement, and personality changes are very prominent, and these are the compounds which act like serotonin pharmacologically. They differ from serotonin itself in that they can reach the brain when given peripherally. Compounds like 2-bromoLSD (BOL), 1-methylmedmain reserpine and many others, even though they also reach the brain, behave in most pharmacological tests as antagonists of serotonin, and only with some difficulty can one demonstrate a serotonin-like action. Since the antagonism of an antimetabolite is the result of deficiency of the related metabolite, these findings suggest that serotonin excess

in the brain is connected with excitement, and deficiency with depression. The deficiency can be readily seen with a depressant such as reserpine since analysis of brain and other tissues of reserpinized animals shows that their serotonin content is reduced. The same is true for some synthetic analogs of serotonin.

(2) In patients suffering from mental disorders, changes induced in brain serotonin lead to changes in their condition. These changes are compatible with the idea expressed above. Thus, a large number of patients with simple depressions have been treated with inhibitors of monoamineoxidase such as Marsilid (iproniazid) with the result that they have become better. These inhibitors retard the destruction of serotonin in the brain and other tissues and thereby increase the amount of this hormone. However, when schizophrenics are so treated they either do not change, or they become worse. This would be in keeping with the idea that their condition is associated with excess of serotonin rather than deficiency. The interpretation, nevertheless, is not clear because these inhibitors of monoamineoxidase increase not only serotonin but also other neurologically active amines such as norepinephrine and epinephrine. We must therefore say that depressions are benefited by increases in cerebro amines such as serotonin and the epinephrines. Schizophrenics are usually made worse.

A second way to increase brain serotonin is to give the precursor of the hormone, 5-hydroxytryptophane. In collaboration with Dr. Therman this has been done in carefully selected schizophrenics. They have usually become worse. In the same way bufotenine has been used on these patients. This is a derivative of serotonin which still retains its hormonal action, but which, unlike serotonin itself, can penetrate into nerves. Patients so treated have become worse during the administration, and then returned to their original state when the administration ceased. Patients with simple depression have not yet been tested with these compounds.

(3) Compounds have been found which are not analogs or antimetabolites of serotonin, but which are, nevertheless, antagonists of its action. Such compounds are less likely to possess serotoninlike effects than are the structural analogs mentioned earlier. Some of these compounds have tranquilized and benefited schizophrenic patients. One such is chlorpromazine, which is a powerful antagonist of serotonin on smooth muscles. Another which has not been tested by so many investigators is nicotinamide in massive doses. This substance which Hoffer found very useful for the treatment of the disease we have found to act as an antagonist of serotonin. These findings would be compatible with the idea of schizophrenia being the result of too much rather than of a deficiency of cerebral serotonin. Here again one must be cautious. Chlorpromazine is not only an antagonist of serotonin but also of the epinephrines and of histamine. The role of these hormones in the disease may be important.

(4) Measurement of the serotonin content of tissue and fluids has been rather indecisive. Most investigators have contented themselves with determinations on urine, but since the changes we are looking for are probably in the brain, and not necessarily in the body as a whole, the urine is probably not the tissue to examine. The extreme difficulty of getting from schizophrenic patients fresh samples of the tissues one wants to use for analysis (i.e. central nervous system) has been the reason why more has not been done. I speak from experience on this point. A few patients (less than 100) have been compared to normal people for serotonin content of their cerebrospinal fluids. The indications are that schizophrenics have more than normals but the differences have not been extraordinary and may disappear when sufficient numbers are examined. At the present, however, the meager findings are compatible with the idea of an excess of serotonin rather than a deficiency. In some non-schizophrenic patients with neurological and marked mental disorders we have found very large amounts of serotonin in the spinal fluid.

The accumulation of such evidence has tended to form the idea that an excess of serotonin in the brain may call forth the symptoms of excitement and that depression may be the result of serotonin deficiency there. The alternation of excitement and

depression which is frequently a feature of mental disease may suggest that something has gone wrong with the control mechanism which maintains a steady state for the serotonin content in normal individuals.

One must recognize that all that we have is evidence which does not yet constitute proof of the relationship of serotonin to mental diseases. Much of this evidence is highly suggestive and probably carries us further in the understanding of this disease than we have been before. Not the least point to be gained from the serotonin hypothesis is the clear possibility of being able to construct a therapeutic agent which will be effective in controlling some of these conditions.

Many objections to the serotonin hypothesis have been raised. Close examination of many of these will show that they have no sound basis and that the objections have been raised without a complete understanding of the facts. For example, Cerletti and Rothlin[3] described an antimetabolite of serotonin, viz. 2-bromoLSD or BOL, which did not cause hallucinations in normal people. Since they thus had an antagonist of serotonin which did not bring about the excitement phase caused by LSD they concluded that the actions of LSD were not the result of its relationship to serotonin. They apparently failed to notice that BOL caused severe mental depression in normal people just as certain other analogs of serotonin such as that shown in Figure 1 had been found to do.[18] The lack of induction of hallucinations by BOL therefore constitutes no valid refutation of the serotonin hypothesis.

The serotonin hypothesis does not insist that the only way to induce psychiatric disturbances is to tamper with the functioning of serotonin in the brain. Thus, the finding that changing the functioning of acetylcholine or of norepinephrine by various drugs, will lead to psychotic episodes, in no way invalidates the serotonin hypothesis. What these findings show is that these other hormones of the nervous system are important as well as serotonin. There are phamacological experiments which suggest a very close interrelationship of not only serotonin and acetylcholine[19] and the epinephrines, but also of histamine.

To summarize, I feel that sufficient evidence has been found to suggest that serotonin plays a role in the brain, and that pharmacological interference with this function there may influence mental and neurological processes. There is no proof that these relatives of serotonin do not affect other processes aside from those concerned with serotonin, and these other processes may be of great importance. However, the use of analogs of serotonin has brought to light so many phenomena related to mental function as to suggest a participation of this hormone in normal mental processes.

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