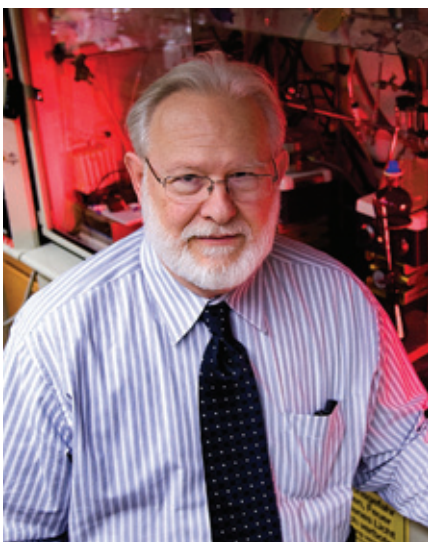


Serotonin, and the Past and Future of LSD

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SEROTONIN (5-HYDROXYTRYPTAMINE; 5-HT) IS AN ancient neurotransmitter, biochemically derived in living organisms from the common amino acid known as tryptophan. Receptors for serotonin can be found all along the evolutionary tree, from single-celled organisms to humans. It has been speculated that the earliest serotonin receptor may have appeared around 750 million years ago. All but one of the serotonin receptors are members of what are called Family A type G protein coupled receptors (GPCRs). When something works in evolution, nature tends to keep it, so it is no surprise that serotonin plays roles in a variety of physiological processes in both nervous tissue (e.g. the brain) as well as in numerous other bodily functions. We recognize today that serotonin is involved in a number of behaviors, including perception, appetite, sex, sleep, and cognition, among many others.

Although it is known that the serotonin system is crucial for these actions, none of them are well understood even today, and because of the complexity of the brain it will be a long time before the exact mechanisms of control and modulation by serotonin there are really understood. In contrast to what much of the general public might believe, most of the serotonin in the body (about 90%) is found in the intestinal tract, with very little in the brain. Serotonin also accumulates in blood platelets, a fact that proved to be quite fortuitous for its isolation, as described below.

The discovery of serotonin began with extracts of enterochromaffin cells from the gastrointestinal tract. After a meal, these cells were known to secrete a substance that caused contraction of the intestines, promoting digestion. Vittorio Erspamer, a scientist working in the late 1930s in Rome, Italy, had discovered that acetone extracts of these cells could cause contraction of the smooth muscle from the rat uterus. In those early days a lot of pharmacology was done using tissues from laboratory animals; scientists had very little understanding of mammalian physiology and tried all kinds of experiments in attempts to understand what caused muscles to contract or relax. Erspamer named this substance enteramine, because it had been isolated from the enteric nervous system, the name for the nervous tissue in the gut. He also carried out simple chemi-

cal tests and determined that enteramine contained an indole, a known type of chemical nucleus consisting of two rings fused together. He and his research group published a number of experimental studies on enteramine.

Meanwhile, Irvine Page's laboratory at the Cleveland Clinic had been studying substances that could cause contraction of blood vessels, searching for some natural factor that might be responsible for causing high blood pressure (hypertension). Page's group had discovered that

when blood coagulates, a substance is produced that causes blood vessels to contract. Maurice Rapport, an organic chemist in Page's laboratory, along with Arda Green, a biochemist, were able to isolate this contracting

factor from two tons of coagulated beef blood that they had obtained from a local slaughterhouse. After allowing the blood to coagulate, it could be centrifuged to sediment out the coagulated cells, producing 900 liters of serum that was enriched in the contracting factor. Of course, they didn't do the preparation all at once, but rather did it in bucketsful over a period of time. Just imagine those two scientists trudging from the slaughterhouse to the laboratory carrying buckets of blood, day after day, and how many buckets it took to total two tons of blood! They were then able to isolate the pure factor from the serum,

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followed by a variety of chemical tests that culminated, in 1948, in the determination of the chemical structure known today as 5-hydroxytryptamine. The substance was named serotonin, because it had been derived from serum (ser) and caused blood vessel constriction, that is, increased blood vessel tone (tonin). The structure proposed by Rapport was confirmed in 1951 when Hamlin and Fischer, two chemists working at the Abbott Laboratories, prepared the first synthetic serotonin.

In 1952, it was determined that enteramine was identical to the serotonin that had just been identified by Rapport, Green, and Page. After synthetic serotonin was made available for scientific investigation it became the subject of intense

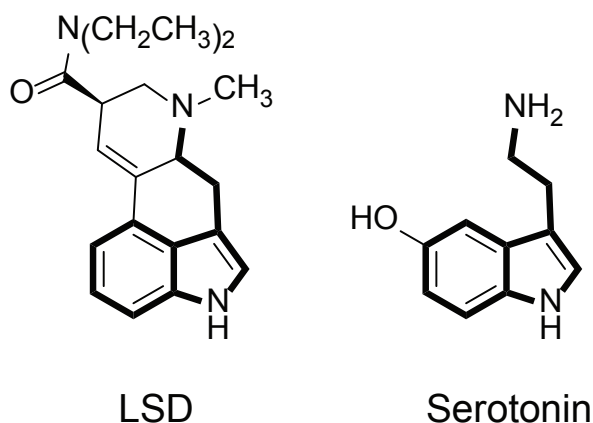
investigation by the scientific community. Whereas there was only one scientific publication on enteramine in 1950, and of course none on serotonin, by the end of 1955 serotonin had been the subject of 222 publications. Irvine Page was even featured on the cover of the October 31, 1955 *TIME Magazine!*

Although it was known that serotonin constricted smooth muscle in the intestines, as well as blood vessels, no one thought that serotonin had any role in brain function. But that notion was soon to change. Betty Twarog, a Harvard Ph.D. candidate, obtained a sample of serotonin from Abbott Labs and discovered

that it contracted the byssus retractor muscle of the edible mussel. She then developed a very sensitive bioassay for serotonin using the isolated heart of the hard shell clam *Venus mercenaria* (“quahogs”). She went to the Cleveland Clinic to work in Irvine Page’s laboratory, and began to assay various mammalian tissues for their serotonin content. Her proposal to test brain tissue for serotonin met with great skepticism from Page, but she readily detected serotonin in the brains of dogs, rats, and rabbits, publishing the surprising results of her work in 1953.

We now go back just a few years to Basel, Switzerland. It was there, in the Sandoz Laboratories in 1943, that Albert Hofmann had discovered the remarkable properties of what we now know as LSD. The first systematic clinical investigation of LSD was carried out in Zurich in 1947, and additional clinical reports on the effects of LSD began to appear in 1949. Initially, LSD was thought to produce a model psychosis and to be a potential aid in psychotherapy. Thirty scientific publications had appeared about LSD by the end of 1953.

In 1954, only one year after Twarog and Page reported finding serotonin in the brain, Woolley and Shaw recognized the structural relationship between LSD and serotonin and proposed that the mental effects of LSD might be caused by its interference with the actions of serotonin in the brain. Their hypothesis appears to be the first formal recognition that perhaps brain chemistry had something to do with behavior, and particularly with mental illness. That was what one might call an “ah-ha moment!” Suddenly, the role of brain chemistry became of more than academic interest. The chemical structure of LSD was known, and is shown below, alongside that of serotonin. The bonds that correspond in the two structures have been thickened to emphasize the similarity between them.



To put things in context, up until that time, mainstream psychiatry had no idea that behavior might arise from neurochemical events in the brain. Rather, if parents had a schizophrenic child, the mother might be blamed for not being nurturing enough, or for doing something wrong in the parenting of the child. Mothers of autistic children were sometimes referred to as “refrigerator” mothers, reflecting the belief that they had caused the autism by not having sufficient contact with the

child. Parents all across the world, and particularly women, who bore the brunt of childrearing, shouldered the guilt for a child with mental illness, including schizophrenia, believing that they had somehow failed as parents. It seems difficult to imagine such thinking today, but that was the reality of mainstream psychiatric theory back then.

The idea that disturbances in brain chemistry might be important to behavior was profound, and began to revolutionize thinking about the brain, and neuroscience in general, and we can see how LSD was the catalyst for that revolution. [Editor’s note: See Nicholas Cozzi’s article “*Psychedelic Breakthroughs in Neuroscience*” in this issue.] If neuroscience can be said to have a beginning, one could argue that it occurred in 1954, with the idea that the action of LSD might be related to its effects on the brain serotonin system. And if we look at the published scientific literature, we see a steadily increasing number of studies on the role of serotonin in the brain, which continues to the present day. In year 2012 alone, there were 3,859 scientific papers published that contained the key word “serotonin.” Drugs that affect the serotonin system such as fluoxetine (Prozac) and other SSRI type antidepressants, or the triptan class of drugs used to treat migraines, were certainly developed more quickly because of the discovery of LSD. The newest generation of drugs to treat schizophrenia also binds to one class of serotonin receptor. Would these medications have been developed without the discovery of LSD? Perhaps, but not nearly as soon as they were.

Where does that put us today? Unfortunately, when LSD became wildly popular among young people in the 1960s, the inevitable outcome of the resulting media frenzy was the passage of restrictive laws, both internationally through United Nations treaties, as well as at the national level. In the United States, we saw the passage of the Controlled Substances Act of 1970 (CSA). This law essentially ended not only clinical research on LSD, but basic research as well. LSD was placed into the most restrictive category of drugs, and required scientists to obtain a special license to work with it. Obtaining the license was an onerous process, requiring a secure storage facility and detailed record-keeping, even if the investigator was working only with tiny amounts of LSD. The few clinical applications that were submitted to the FDA were simply put on a shelf to languish and were never approved. The conventional wisdom quickly became “if you want to kill your scientific career, work on psychedelics.” Here was a novel substance that created intense interest among scientists and clinicians, and then suddenly it was anathema to work on it. As summarized by Grinspoon and Bakalar in their 1979 book, *Psychedelic Drugs Reconsidered*, between the 1950s and mid-1960s more than 1,000 clinical papers were published describing 40,000 patients, several dozen books, and six international conferences on LSD-assisted psychotherapy. All that came to a sudden stop.

There are few, if any, other events in science that can parallel what happened to LSD. Why and how it happened has been the subject of many books and essays, but no one can completely explain it, probably because there were so many different

factors in play. After the passage of the CSA in 1970, the first clinical protocols with *any* hallucinogen that made it through the Food and Drug Administration (FDA) review process were the studies of DMT carried out by Dr. Rick Strassman when he was at the University of New Mexico, Albuquerque. That was in the early 1990s, more than 20 years after the passage of the CSA.

Now that the media furor over psychedelics has had a chance to die down, renewed interest is developing in studies with LSD. Certainly, the promise and potential of LSD are still there. Sadly, no formal studies are underway in the United States, although one study has been completed in Switzerland (see below). But there have been several clinical studies with psilocybin, the use of which (instead of LSD) can be at least partially attributed to a continuing degree of social stigma attached to research with LSD. One also must keep in mind that the attitudes of the agencies responsible for enforcing the drug laws have not substantially changed; for them LSD is still a very dangerous drug with no redeeming virtues. Similarly, media echoes of the dangers of LSD from the 1960s still resonate in the minds of many members of Congress and federal regulatory officials, so changing the laws is unlikely to happen in the foreseeable future.

Nonetheless, given the opportunity, what studies of LSD might immediately be of greatest interest? The most well documented use for LSD was in the treatment of terminal cancer patients, where it could lead not only to a reduction in pain, but also improved mood and decreased fear of death. MAPS funded a randomized, active placebo-controlled double-blind dose-response, phase 2 pilot study of LSD-assisted psychotherapy in 12 subjects with anxiety related to advanced-stage illness. The study was recently completed in Switzerland under the direction of Dr. Peter Gasser, although the results have not as yet been published. [Editor's note: See Peter Gasser's article in this issue.]

The second area where we now know that LSD was effective was in the treatment of alcoholism. Although this latter indication was not appreciated for many years, a 2012 meta-analysis by Krebs and Johannsen of published studies using LSD treatment for alcoholism found it to be at least as effective as any current therapy. There also are fairly remarkable case and anecdotal reports of dramatic recovery from illnesses that do not ordinarily respond to conventional therapies. For example, there is a published report of an individual who suffered from debilitating obsessive-compulsive disorder (OCD) who recovered completely from the illness following monthly treatments with LSD. LSD also was reputed to enhance creativity, but no properly designed study has ever been carried out to test that idea in a definitive way. As another idea, Albert Hofmann believed that low doses of LSD ("microdoses") could enhance cognitive function. Would low doses of LSD be useful in treating Alzheimer's disease? We simply don't know. Would low doses of

LSD enhance working memory as we all grow older? No one knows. And some recent evidence suggests that psychedelics might be a novel treatment for depression that might eliminate the need for chronic antidepressants. We also must not forget the extensive studies by Dr. Stan Grof, who used high doses of LSD to treat psychotic patients, with many of them reported to become symptom-free. Although in today's climate it might be very difficult to get a protocol approved to treat mentally ill persons with high doses of LSD, if it was possible actually to cure certain psychiatric disorders with LSD, what a huge advance that would be!

Perhaps one of the most tantalizing potential uses for LSD would be in the study of consciousness.

Now that advanced brain imaging techniques are available, it would be fascinating to see the changes in brain activity that occur following LSD administration. LSD can produce such a range of behavioral effects and altered moods, perhaps it could be an important tool to help map out correlations between feelings, moods, and changes in brain activity.

The sad fact remains, however, that because regulatory agencies still consider LSD to be such a dangerous drug, it will be a long time before many of the possible uses of LSD can be investigated. There are no government agencies that are interested in funding studies of LSD (or any psychedelic) where the goal is to identify a positive benefit of the treatment. And as we all know, once laws are put into place it is very difficult to get them taken back off the books. LSD is a Schedule I controlled substance not only in the United States, but in most major countries, and is included in UN treaties. To move it into a less restrictive schedule so that it could be more available for research is not something that will come soon, or easily, if at all. Things do occasionally change, however, and perhaps we will witness events that ultimately allow new research to take place in the near future. 🌀

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