

THE BECKLEY FOUNDATION GLOBAL DRUG POLICY SEMINAR 2005

HOUSE OF LORDS, PALACE OF WESTMINSTER, LONDON
MONDAY, 21 NOVEMBER 2005

THE SCIENTIFIC AND THERAPEUTIC POTENTIAL OF PSYCHEDELICS
Prof. David Nichols
Purdue University

Good afternoon. I am delighted to have the opportunity to speak to you about some of my own research, and for the invitation from Amanda and the Beckley Foundation to be here today.

Although I know you are all familiar with many drugs of abuse such as cocaine, heroin, methamphetamine, and cannabis, I suspect that the substances that I am going to talk about are less familiar to you. I plan to tell you something about them, and why they are a very distinct and unique category of drug that is very different from the dangerous substances that are of concern for most of you.

In my talk I will cover three areas: What are hallucinogens, what do they do, and what are they good for?

To begin with, we should consider the definition of hallucinogen, and I shall use the terms hallucinogen and psychedelic interchangeably in this talk. Although hallucinogen is the more accepted scientific term, psychedelic has been and remains the choice in the popular culture. The definition that I particularly like was one presented by Jaffe in the reference known as Goodman and Gilman, in the eighth edition. There we read, "*...the feature that distinguishes psychedelic agents from other classes of drugs is their capacity reliably to induce or compel states of altered perception, thought, and feeling that are not (or cannot be) experienced otherwise except in dreams or at times of religious exaltation*" Now, you will recognize that as a particularly unusual name for a class of pharmacological substance. But I will show you how it is really very appropriate with what we know about these drugs.

We tend to think of psychedelics as arising suddenly with the hippy culture of the sixties, but in fact these substances are probably some of the oldest psychoactive materials known to humans. We can imagine that they might have been discovered by early man, foraging for foodstuffs. Indeed, some would argue that these substances might even have been the catalysts for the earliest philosophies and theologies, once

man had developed language. It is hard to think of Neolithic man wondering about the gods or an afterlife, but rather we'd think they might be more concerned about having enough wood for the winter fires, or enough dried meat and fish, or enough skins to stay warm. But imagine if on one of their hunts they discovered a psychoactive mushroom and ate it. Assuming that their neurochemistry is not so different from our own, we would imagine that they would be transported to a wondrous and unfamiliar realm. Afterwards, they would perhaps wonder, "where was that place?" Or, "who were those beings?" They might never view the world in the same way again.

Within recorded history we know that these substances played a very important role in many early cultures. There are many hymns in the Rig Vedas in worship of *soma*, a psychoactive drug whose identity is lost to antiquity, but which may have been a species of psychedelic mushroom.

In ancient Greece, we find the rituals at the village of Eleusis, practiced every fall for nearly 2000 years, from around 1500 BC until about 400 AD. We know very little about these rituals, because to speak of them would bring a sentence of death. On this slide is a picture of the bowl that was used to dispense a brew called *kykeon* that was ingested during the rituals. We know it contained barley as a central ingredient, along with some mint, but we know very little else. The ritual and all-night ceremony was available to any adult Greek who had not been convicted of murder. There were attendants and singing, and even a special building for the ceremony. Probably every great Greek that you could name had participated in the ceremony, and it appears to have been of great cultural significance. Only a few brief sentences were ever written by one or two participants, and they only convey that the ceremony was very powerful, and that one might see both the beginning and end of time. The best speculation is that the *kykeon* was prepared from ergot-infested rye, and certain strains of ergot produce LSD-like psychoactive alkaloids that might have had very powerful effects on the mind.

On this next slide is a picture of mushrooms used by the Aztec Indians. These mushrooms, called *teonanacatl*, or "god's flesh" were used on many occasions. They are generally referred to today as psilocybin mushrooms, or in the popular culture as magic mushrooms. They were ingested by the Aztecs during celebrations and social events, but also by the shaman to foretell the weather, predict the crop, or to diagnose the cause of illness in some member of the tribe. These mushrooms gave one a connection to the gods, or to an otherworldly realm that was ordinarily invisible.

And on this slide is a picture of the peyote cactus, also used by the Aztecs and known as *peyotyl*. Recent archeological studies have dated samples of this cactus preserved in burial sites to 3,000 BC, showing that the use of this cactus dates back at least 5,000 years. It has effects similar to psilocybin mushrooms. In the early 20th century, the ancient use of this cactus was incorporated along with elements of Christianity into the Native American Church. The church today has on the order of a quarter of a million

members. Dried tops of the cactus are chewed and eaten in all-night services of the church. Although peyote is designated a Schedule I controlled substance by the United States DEA, the Indians have legislative protection for its use. The church has low rates of alcoholism, drug abuse, and divorce, and a recent study by a John Halpern has shown that members of the church suffer no negative neurological or cognitive effects from life-long ingestion of this sacrament as members of the church.

As you can surmise from these examples of the use of psychedelics in a culturally-appropriate way, the earlier definition I presented for this class of drugs really seems quite appropriate. We see these substances used as a central focus for religious rituals, and see them imbued with properties that make them sacred substances. It is easy to imagine that early man would believe that they held the keys to visions of the afterlife, and as ways to talk with the gods, or with departed ancestors.

This next slide shows the structures of the principle types of psychedelics. I recognize that most of you are not chemists, so I won't dwell long here. I would simply point out that all of these substances are relatively simple molecules that have two molecular themes. The peyote cactus contains mescaline, which is the prototype for the phenethylamine structure shown on the left. Psilocybin, and a variety of naturally-occurring psychedelic plant substances are based on the tryptamine structure shown in the middle, and LSD, shown on the right, and the most potent psychedelic, is simply a more complex tryptamine type molecule.

So, as this slide indicates, between 1950 and the mid 1960s, there were more than 1,000 clinical papers discussing 40,000 patients, as well as several international conferences and a number of books concerning psychedelics and their use in psychotherapy. These drugs were an extremely hot research topic and one typically saw glowing reports that psychedelics were the new technology for psychiatry, and the significance of their discovery was often compared with the discovery of atomic energy.

In addition to their impact on psychiatry and psychology, there were a number of studies showing that they might produce genuine mystical experiences, and might lead to a sort of renaissance in religious thought. Indeed, Walter Houston Clark, the eminent religious scholar, has said, *"Millions of Americans, if they are ever to enjoy profound religious experience, will only do so through psychedelic drugs."* Of course, in this international venue, we might say that his comments would apply to everyone, and not just Americans.

But suddenly, everything stopped. Scientific studies of psychedelics completely ended by the early 1970s. In the intervening 35 years there has not been one single approved clinical study of LSD. Not one. From being considered the most promising technology to be discovered for psychiatry in decades, research simply came to a complete halt. Why? Once psychedelics became popular recreational drugs, repressive laws were

quickly passed that also effectively stopped scientific research. The FDA simply refused to approve clinical studies of psychedelics until the mid 1990s, and even after that there has been no approved study of LSD. Not only did the regulations to obtain psychedelics become very onerous, but substances of sufficient quality for clinical studies were no longer available. In addition, researchers who wished to study psychedelics were stigmatized by their peers because of the sensationalized and negative coverage of these drugs by the media. It seemed that the baby had been thrown out with the bath.

Nevertheless, in those intervening years progress has still been made in understanding how these fascinating substances work. What we have learned about their action in the brain is that they probably activate a class of brain serotonin receptor known as the 5-HT_{2A} receptor. The simplest class of drugs, the phenethylamines, activate that receptor as well as the serotonin 5-HT_{2C} receptor. The tryptamines also activate those two receptors, but in addition, also activate the serotonin 5-HT_{1A} receptor. Finally, LSD, which is the most potent and most psychologically profound of the psychedelics activates all three of these serotonin receptors, as well as several other types of serotonin receptors, dopamine receptors, and certain adrenergic receptors. Although we don't fully understand the pharmacology of LSD, it is thought that its high degree of potency is probably related to all the ancillary actions it has on various brain receptors.

Where are serotonin 5-HT_{2A} receptors? This slide shows where the binding sites are, using a radioactive molecule that binds to these sites. The red areas are where the receptor is highly expressed, and it is principally in the outer layer of the brain known as the cortex. The frontal cortex has been called the executive part of the brain, and it is there that sensory information converges and is processed, and where we make sense of our environment. And that is precisely where these receptors are concentrated.

This slide shows areas of the brain that are activated following administration of psilocybin, the active principle in psilocybin mushrooms. These pictures were kindly provided by Dr. Franz Vollenweider. He used a radioactive form of glucose known as FDG. What you see in the brain of the psilocybin subject, compared with a normal brain, are these red areas that represent increased glucose utilization, which represents activation in the prefrontal cortex, as well as some activation in an area known as the thalamus, which is a sort of relay station for incoming sensory information that is then sent on to the cortex for processing, integration, and interpretation.

This next slide has a crude schematic of the wiring diagram of the brain. What you see is that the frontal cortex has all of these lines of communication from a variety of other brain areas. Again, the cortex is where we really make sense of all the information we receive. All of our incoming sensory information except for olfactory input is sent to the cortex for processing. Even so, we are constantly receiving so much information from our environment that there must be some sort of filter or gate to determine which of it is important enough for us to attend to. It is generally thought that this gate lies in the

area known as the thalamus. The thalamus and another area that is wrapped around the thalamus, known as the reticular nucleus of the thalamus, seem to determine what information gets sent to the cortex for processing. So, if you are listening to me speak, your thalamus is saying, "ok pay attention to what Nichols is saying, watch these slides" and that's what you are attending to. If, while I am speaking, someone is walking in back and drops and breaks a glass jar, everyone is suddenly aware of that, and may turn around to look. I might even stop my presentation briefly. The thalamus is telling us to forget about Nichols' talk for the moment, and pay attention to the noise of the breaking glass; attend to that for right now.

Triangular cells called pyramidal cells are the main computational units in the frontal cortex. This is where all the information is integrated together. Psychedelics modify the properties of these cells, making them more sensitive so they respond more easily to lower level signals. In addition, we have these very ancient areas at the top of the brain stem; the locus coeruleus, which produces norepinephrine (noradrenaline); the cells in the raphe nuclei, which secrete serotonin; and the ventral tegmental area that produces dopamine. All of these are involved in vigilance, detecting novelty, and memory and attention. Psychedelics interact with all these areas. They have an effect on raphe cell firing that makes them fire in the same way as when we are dreaming.

The locus coeruleus tells us when something is novel in the environment. The cells there start firing quickly when something novel in the environment occurs. Psychedelics suppress the normal firing of these cells, but in response to anything novel in the environment the response is enhanced, so we can imagine that things that normally would not be perceived as novel might seem very novel or interesting. All these areas either have serotonin 2A receptors that directly affect them, or else they receive signals that are a result of 5-HT_{2A} receptor activation in another area.

Now, if you think about that, and I realize that this is not a neuroanatomy class, and this is maybe way too much, but if you think about it, psychedelic drugs have effects on these very areas, these key areas affecting cognition that determine what gets sent to the frontal cortex and how we actually process and perceive it. It's not too surprising then that psychedelics will have very profound effects on perception, emotion, feelings. In fact, one theory is that at high doses of psychedelics, we actually shut down transmission through the thalamus so we have these processing units, these pyramidal cells in the cortex, highly sensitive and ready to process, but not getting any sensory information from our arms, fingers, or hearing, etc. So they start processing things from our memory and our imagination and create illusions and hallucinations. So that's a very quick sort of overview of how these substances might act.

I should note that there is nothing in the way that psychedelics work that involves the reward pathway that would make the use of these drugs reinforcing or make people self-administer them. People will not administer psychedelics to themselves

repetitively. We cannot train animals to self administer psychedelics. They will self-administer amphetamines, cocaine, methamphetamines, morphine, and even THC from cannabis, but *not* psychedelics. So they represent a completely different picture than the common drugs of abuse that cause so many problems. They do not cause dependence or addiction, and they are actually some of the safest drugs known, in terms of the possibility for damaging body organs.

I'm not going to go through the different signalling pathways that are activated by psychedelics through the 5-HT_{2A} receptor. It is probably possible to activate these receptors with particular types of molecules but not produce an hallucinogenic effect. We actually believe that we may be able to make ligands that would stimulate function in the cortex without causing the common intoxication you see with LSD. We would only know that, however, from human clinical studies, because the animals cannot be trained to detect these differences.

So what would we be interested in? This slide lists some possible ideas for research using psychedelics. First on the list, obviously, are cognitive function and sensory processing. These are the things that psychedelics affect profoundly, and ought to be good tools for study these properties of consciousness.

Obsessive Compulsive Disorder, a very difficult to treat psychiatric disorder is another target. In many anecdotal reports, people who have taken mushrooms, peyote, or LSD have had remission from OCD symptoms, in some cases lasting for years.

Pain and depression in terminal illness is also an obvious area for research. Most people are not aware that one of the most well documented effects of LSD was in the treatment of dying cancer patients. 70-80% of patients treated in a program that included LSD gained some positive benefit from LSD. About 30% had dramatic benefit. By benefit I mean a decreased need for pain medication, decreases in depression measures, and increased mood and quality of life. And that would include relief from intractable pain.

Eating Disorders, Anorexia, and Bulimia are another area where there is a good theoretical basis for assuming psychedelics might be able to provide beneficial effect. With severe anorexia, you have this body image that you are overweight and so don't eat. We believe you may be able to use psychedelics to change body image. This is a very difficult to treat disorder with no good treatments presently available.

Alcohol and Substance Abuse are areas that were probably most widely studied. There are hundreds of papers studying the treatment of alcoholism with LSD. Although the results are inconclusive, a recent meta-analysis by Mary Mangini of all the data indicates some promise. Early studies were not properly designed, they didn't have proper controls, they didn't have proper follow-up, they used the wrong kind of patient selection, etc. But taking this into account, there is still a little bit of signal there. Imagine

if we could treat alcoholism or substance abuse in a program that was successful, that caused savings to society by treating something like alcoholism. This would represent a new approach that is not looked at currently, which was very intensely investigated in the early 50s, but without the kinds of modern clinical approaches that we have today.

Personality Structure and Development: I won't go into that but there is a lot of evidence suggesting that the kind of effect these drugs produce is based on the pre-existing personality, the set and the environment that the patient or subject had.

So, what did I do? Nobody was doing clinical research in this area so I started the Heffter Research Institute in 1993. We have raised US \$1.3 million in private funds since 1993, which is not a lot of money, but it has allowed us to do a lot of pilot studies. We put a fair amount of money into a clinic at the University Hospital in Zurich. Franz Vollenweider is probably the world's leading research expert on psychedelics, principally with psilocybin. He has looked at a number of different things; the effects of MDMA on aspects of decision making; on perceptual rivalry, which involves how the brain chooses which eye to pick up the image from; high level or low level motion perception; these are all cognition aspects. Acute effects in healthy subjects - we have done a number of studies that have shown that psilocybin can safely be given to drug naive subjects. That is a Phase 1 study. A number of these have been completed. Using some of the high tech imaging, fMRI and PET coupled with EEG, low resolution electromagnetic tomography - you have seen those examples already- these could be used along with subjective states questionnaires to really start getting a handle on what happens when people feel and experience certain things. Giving a psychedelic to provoke a change in mood or emotion coupled with PET scanning, or fMRI, some of the new cutting edge technology, we could really start seeing what areas of the brain are activated and making links between neurochemistry, brain anatomy, and mood states. That is interesting to me certainly and a lot of people would like to see things like that happen.

This slide just shows the effect of psilocybin on binocular rivalry, a significant effect. Here is a paper from one of Franz Vollenweider's studies on co-registration of an H₂O PET with a high resolution EEG showing how one can identify the different areas of the brain that are activated through co-registration of these techniques; really high tech stuff that could be done; it has really only been done in just a handful of laboratories of the world today.

So the Heffter Institute funded a pilot study on OCD at the University of Arizona. There were a small number of subjects. We looked at 9 subjects total; these data are from 7 of them. 5 of 7 subjects experienced at least transient improvements of OCD scores; one had remission for at least 5 months. A very interesting signal but too small to make any real conclusions. We need more studies like this to see if the drug really helped, as this is

a very difficult to treat condition. Is there a signal here that is worth pursuing? We think so.

Finally, some recent work with dying patients. So the studies that were have done in the sixties at the Spring Grove hospital with LSD in dying patients were so successful, there were a series of six or seven papers published by the group there that included Stan Grof, Al Kurland, and others. They found that dying patients who had the most dramatic improvement in mood and the most dramatic success were those who had a drug induced mystical experience. The characteristics of these experiences were a sense of unity or oneness, transcendence of time and space, deeply felt positive mood, a sense of awesomeness and reverence, meaningfulness, philosophical insight and ineffability or inability to describe the experience. These are very different effects from methamphetamine or heroin, obviously, this is a different class of substance. Psychedelics can actually a mystical experience. You are dying, it is the end of life, and this experience happens to you and suddenly all your ideas about death change.

So what I've got now is a video of one patient in the study we are supporting now with 24 subjects. This is subject 3, talking about how she felt about the fact that she was dying. She is a terminal diagnosis and this is a fairly short video so let's see if it will play here.

Female subject on video:

"You realise that this is terminal and that this is basically what is going to kill you, and the general progress of the curve of this wasn't very long, so you start to wonder what's going to happen? And your emotional state, your mental state totally turns upside down. You no longer have this life ahead of you that you've planned for. All of a sudden you have a very finite and possibly very short time left, so you are very anxious about the fact that..."

...It becomes a very negative emotional set where you are basically living in fear. Unfortunately, that fear can be, to an extent that it paralyzes the good life that you are living at the moment while you are still healthy, while you are not sure when it is going to come back. It becomes almost overwhelming, like I said, it infringes upon the time that you are enjoying...and so, I was hoping that this study would help, and also with the support of a psychiatric team, would allow me to deal with some of that. To clear it up a little; to find a way to achieve a level of peace within myself..."

End of First Video

Now, that interview was after she had actually done the sessions so she is in a better frame of mind than what she was before the treatment, but she is reflecting back on how she felt as she approached the session. This is a pilot study; she was subject three and we are up to number four now I think, or maybe five. 24 subjects with a crossover placebo design. They receive a placebo and psilocybin, one treatment of each. This is

using the procedure that was developed back in 1956. Eric Kast, an internist in Chicago was comparing the analgesic effects of LSD with opiates, because he had heard that LSD had an analgesic effect. He looked at dying patients and found that during the four hours or so of the acute effects, LSD was as effective as opiates in pain reduction. But he then observed that there was a significant number of his patients that had long term pain relief, two or three weeks later, long after the acute effect of the LSD had worn off. And when he interviewed these patients he found that their attitudes toward death had changed. This was really just the beginning of this whole approach, and this was the one indication that was most widely accepted as useful for LSD.

What we have done is move in that direction now. No one has really been able to use LSD so far. I know Amanda would hope that we see some research started on that particular substance, but it is still kind of taboo, so we used psilocybin, which has similar effects. The subject goes through preparatory sessions with a psychiatrist, talking about family issues, life issues, how she feels about death, her relationship with her husband, so forth and so on, and the actual session itself is one dose, given orally. She listens to evocative, powerful music that would evoke images of spirituality, nature, optimism, and she is wearing eye shades. So, there is no intervention by the psychiatrist; this is a completely internalized session and, with luck, this experience occurs, this visionary experience, which takes away, to some extent, the fear of death and leads to reduction in stress, decreased need for pain medication, and an improved quality of life. So this next video is of her talking about the session and what it meant to her:

Start of second video

“As the session began and as it built up I felt this lump of emotions welling up and firming up almost like an entity. And, I started to cry a little and just to start to feel, oh, it was almost like everything was concentrated a little. And it came up, welling up, and then it started to dissipate and I started to look at it differently and I think that’s the beauty of having, being able to expand your consciousness. Change the way you are feeling about things. Open... I don’t think the drug is the cause of these things. I think it’s a catalyst that allows you to release your own thoughts and feelings from someplace that you’ve bound them very tightly...

And I began to realize that all of this negative fear and the guilt was such a hindrance to the actual positive part of making the most of, and enjoying the healthy time that I’m having...that I, and however long it may be, that I was basically not utilizing it to the best, and enjoying my life because I was so afraid of what wasn’t there yet....

To think how if I could just let go of that and not focus so much on being afraid of what wasn’t here today that I could be more in for today, in the here/now, in the present, and enjoy the time that I had and take it as a gift, that it was something that was so precious and that it didn’t deserve to be clouded by these fears, that there would be plenty of time to be worried about it, to be afraid when something really happened, when the disease manifested itself again and needed to be

dealt with at a different level, but today I wasn't at that level and I was able to really internalize that thought and those feelings. And there was a tremendous feeling of relief and of very... happiness ...and of hope, that this could move on, and go forward, and that it was something I could deal with.

Certainly, it affects the quality of life. Your emotions are a huge part of the quality of your life. But I also really, truly believe that by dealing with your emotional fears and your mental fears that you are freer to take better care of yourself physically to fight the disease. For instance, one of the things about feeling very hopeful and optimistic is I get myself out there and exercise really hard because it makes me physically feel better and I know it physically makes me stronger.

I think it has been an enormously beneficial exercise and I would like to see this become part of the mainstream treatment for stage four cancer... I think it is something that should be available and for many reasons some people may or not choose to take advantage of it, but I can't see any reason why it should not be available as a part of your treatment plan...

I think that the most scary thing for people who would hesitate would be all the fear mongering, mostly by government and religious groups and people who think this is all evil and horrible, and... and it's not! These substances occur in our natural world, people have been using them for thousands of years... It isn't the bogey man. But I think it's very important. I'd like other studies like this to come; honest, open information about all kinds of substances, that people understand that there are enormous benefits. There are certainly some risks. These should all be out in the open for people to evaluate and to choose whether this is something they would feel comfortable with...

End of second video.

The thing I guess I want to point out is that most of you here probably considered psychedelics, LSD, as "not on my radar screen, not a control issue," I think it is one of the travesties of modern psychiatry and neuroscience that more people have not really looked at what has happened to research with psychedelics and tried to move them back into respectable science. I think you'll have to admit that this video is pretty interesting; this is the third patient, and all three patients had dramatic effects. In fact they thought they had lost touch with the second patient. Charlie Grob, the investigator, actually thought she might have died, because these are all patients with very short time in their hands. But he says she called him from, I think, Jamaica and she says, "we are on vacation, we are having a wonderful time and I think I might be in remission." Now I am not going to claim that the drug produces remission, but she became so hopeful and so optimistic that it completely changed her quality of life, and this woman had been depressed. These people get into this study because they are depressed about the fact they are dying. As you saw here, she didn't look too depressed; she was excited, she was hopeful, and she agreed to allow these pictures to be released in a number of

different venues because she says she was so impressed by the treatment that people should know about it.

So I would encourage you, I hope this has brought you up to speed a little on what psychedelics are, and where they came from. Sure, we don't want teenagers using psychedelics; they are powerful mind altering drugs. But in a medical and scientific context I believe they can be extremely powerful for understanding how the brain is connected to the mind, aspects of personality, cognition, treatment of OCD, and in terminal patients for sure, as you just saw, and maybe also in eating disorders. We do not have enough people interested; the Heffter Institute is a very small, resource-limited institute. We have been pushing these studies basically because no one else is doing them. LSD is one of the most powerful psychoactive drugs known to man, with unknown but possibly unbelievable potential. It was considered a breakthrough in psychiatry, yet not a single clinical study in 35 years has been approved or reported. So why is that? It is certainly something to think about.

I would like to thank a lot of students that helped me over the years, a lot of postdoctoral fellows and collaborators.